Imaging in Minor Head Injury

Early complications and late consequences

Marion Smits

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Imaging in Minor Head Injury

Early complications and late consequences

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Acute complicaties en gevolgen op lange termijn

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Aan mijn ouders
Frans en Frieda

CONTENTS

CHAPTER 1

General introduction

HEAD INJURY is traditionally divided into minor, moderate or severe head injury, depending on the patient's presenting level of consciousness as expressed in the Glasgow Coma Scale (GCS) score. The vast majority of patients (>90%) present with a normal or near-normal level of consciousness (GSC score of 13–15) and are thus classified as minor head injury patients (1, 2). With an estimated 60 000 patients annually in the Netherlands, minor head injury forms a major health care and societal burden. Despite being classified as 'minor', the injury is not inconsequential. Consequences of minor head injury can be divided into early, potentially life-threatening complications, and long-term functional disability as well as a wide range of postconcussive complaints.

Early complications of minor head injury

Early complications of minor head injury are infrequent (6%–10%), and include skull fractures, sub- or epidural haematoma and intraparenchymal injury (Figure 1) (2–7). Rarely (0.4%–1.0%), complications are life-threatening and require urgent neurosurgical intervention and therefore rapid and reliable diagnosis (2–7). Skull radiography has been largely abandoned for this indication due to its low sensitivity for the diagnosis of intracranial traumatic lesions (8). Computed Tomography (CT) of the head is currently the imaging modality of choice (5, 9–11), being widely available and providing fast diagnosis with a sensitivity approaching 100% (12).

Given the relatively low incidence of neurocranial traumatic lesions after minor head injury, and particularly the rare occurrence of lesions requiring neurosurgical intervention, the question is whether the liberal use of CT is justified. This is reflected in a wide range of hospital policies and clinical guidelines for the use of CT in the evaluation of minor head injury patients, with some guidelines recommending a lenient use of CT while others advocate a more restrictive approach.

Decision rules

Selection of patients for CT after minor head injury is preferably guided by prediction or decision rules, which are developed in prospectively included patient populations. With prediction rules, an estimate can be made of the patient's risk of neurocranial complications after minor head injury. In decision rules, this risk estimate is then used to decide whether CT is indicated. In recent years, two decision rules for the use of CT in minor head injury have been published, namely the New Orleans Criteria (NOC) and the Canadian CT Head Rule (CCHR), which both by design identify all patients who required neurosurgical intervention of a neurocranial complication after minor head injury (2, 6). Based on internal validation, implementation of these decision rules in the United States was expected to lead to a reduction in CT scans performed for minor head injury of 23% for the NOC and 46% for the CCHR.

Despite the NOC's and CCHR's lack of external validation, both decision rules have already found their implementation in clinical practice in the form of guidelines. The NOC has been used as a basis for the Dutch national guidelines (13), the CCHR for the criteria set out by the National Institute for Clinical Excellence (NICE) in the United Kingdom (14), and both the NOC and CCHR were incorporated in the guidelines set forth by the European Federation of Neurological Societies (15).

As well as lack of external validation, implementation of the NOC and CCHR is further hindered by the fact that both decision rules are applicable only to a limited group of patients, most importantly only patients with a history of loss of consciousness or posttraumatic amnesia. Although the risk

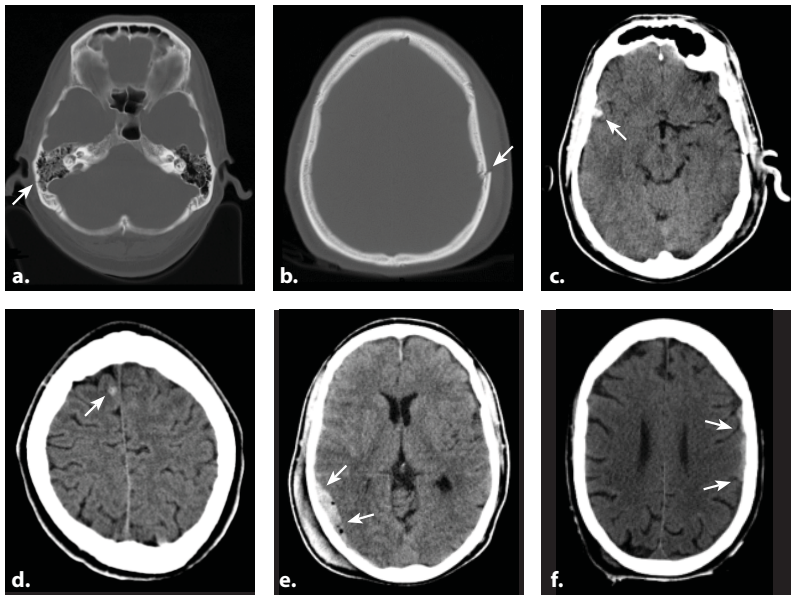

Figure 1. Examples of neurocranial traumatic findings on CT after minor head injury from the CT in Head Injury Patients study. Arrows indicate (a) skull base fracture, (b) depressed skull fracture, (c) haemorrhagic contusion, (d) diffuse axonal injury, (e) epidural haematoma, and (f) subdural haematoma.

of neurocranial complications after head injury in patients presenting with a normal level of consciousness, no history of loss of consciousness, and no posttraumatic amnesia is estimated to be approximately a quarter of the risk in patients with (a history of) an altered level of consciousness or posttraumatic amnesia, neurocranial complications do also occur in the former (16, 17).

Cost-effectiveness of selective CT scanning

Although a reduction of CT scanning would seem to be cost-saving, as was recently reported by Stein et al (18), the selective use of CT, as opposed to scanning all minor head injury patients, introduces the risk of missing minor head injury patients with traumatic complications, despite the decision rules' reported 100% sensitivities. This is due to their wide 95% confidence intervals, which is the result of the low incidence of neurocranial traumatic lesions requiring neurosurgical interventions. Although the risk of missing a patient with a traumatic complication is expected to be small, the consequences in terms of loss of (quality of) life years may be substantial, and may even outweigh the costs saved by selective scanning. In a cost-effectiveness analysis both the impact of the decision rules' sensitivities and specificities and their influence on patient management are taken into account, offering a combined measure of the decision rule's validity and utility.

Long-term outcome

The late consequences of minor head injury consist of functional disability and postconcussive complaints. Generally, minor head injury patients make a full functional

recovery, although it is not uncommon to see patients with minor head injury suffering from long-term sequelae after the injury (19–25). Functional outcome in patients with so-called *complicated* minor head injury, ie, with a neurocranial traumatic complication, has shown to be significantly poorer than in patients without neurocranial traumatic complications after minor head injury (26, 27). Long-term outcome in terms of functional disability or postconcussive symptoms in patients with complicated minor head injury specifically, however, is still largely unknown (25, 27). Also, it seems likely that functional outcome may not be the same for different traumatic CT findings.

Postconcussion syndrome

Even in the absence of neurocranial traumatic findings on CT or even conventional Magnetic Resonance Imaging (MRI), more than 80% of minor head injury patients experience postconcussive complaints in the first week of the injury. These symptoms are generally self-limiting, and, while still present in 30% of patients one month after the injury, they have commonly disappeared after 6 months, only to persist in a small minority of patients (28–31). A minimum of 3 symptoms persisting for at least 3 months after the injury is considered diagnostic of the postconcussion syndrome (32, 33), comprising a wide range of symptoms, such as headache, fatigue, dizziness and cognitive complaints such as memory and attention deficits. The subjective severity of these complaints can often not be objectively confirmed, and taken together with the high base rate of many of these symptoms in the general population as well as the absence of imaging abnormalities, patients are often considered malingerers.

A neuropathological substrate of postconcussion syndrome is still lacking (32, 34), although it has been hypothesised that microstructural damage of the brain, not detectable with conventional imaging techniques, may be responsible, which in turn causes a functional deficit (31, 35–38). Brain plasticity compensating for this functional deficit would explain the only – if any – subtle cognitive deficits found on neuropsychological testing, while memory and attention problems are still perceived and are accompanied with fatigue and headache due to the compensatory brain activity.

Two advanced neuroimaging MRI techniques hold promise to gain evidence to support this hypothesis. With functional MRI (fMRI) brain activation changes can be visualised, while Diffusion Tensor Imaging (DTI) provides a sensitive measure of changes in white matter integrity.

fMRI and DTI

Functional MRI is at present the most commonly used functional neuroimaging technique due to its entirely noninvasive nature. Blood Oxygenation Level Dependent (BOLD) fMRI takes advantage of the tight link between local neuronal activity and blood flow (neurovascular coupling) (39, 40). When neuronal activity increases locally, local blood flow also increases, leading to an increase in oxygenated blood that is disproportionate to the increased need of oxygen for neuronal activity. As a result, local susceptibility effects, caused by the presence of paramagnetic deoxygenated hemoglobin, decrease, leading to a signal increase on T2* weighted images in those brain areas that are active (41, 42). A functional deficit, hypothesised to be underlying postconcussion syndrome, would be expected to become apparent in the two cognitive domains commonly affected, namely working memory and selective attention, as compensatory and/or more dispersed activation (43–46).

Microstructural damage after minor head injury is thought to be due to shearing injury, affecting the deep white matter, particularly at the corticomedullary junction, in the

brainstem and the corpus callosum. Shearing injury may lead to microhaemorrhages, as well as breakdown of white matter integrity. High-resolution gradient recalled echo (HRGRE) T2* weighted sequences are very sensitive to microhaemorrhages (47–50). With DTI white matter integrity can be assessed in vivo. By applying diffusion weighted gradients in multiple directions, the degree of anisotropy in the Brownian motion of water molecules can be measured (51, 52). A high degree of anisotropy of diffusion reflects motion of water molecules favoured in a specific direction, for example parallel to the highly structured white matter fibres. A reduction of anisotropy is considered evidence of microstructural white matter injury, even if the white matter appears normal on conventional MR imaging.

AIMS AND OUTLINE

The purpose of the studies described in this thesis is twofold, focusing on the diagnosis and management of early complications of minor head injury, as well as on the late consequences of minor head injury, in terms of functional outcome after neurocranial traumatic complications and the neuropathological substrate of postconcussion syndrome.

Firstly, we evaluated the use of CT in the acute setting of minor head injury management in our large, multicentre CT in Head Injury Patients (CHIP) study. External validation of the published decision rules and clinical guidelines is described in **chapters 2 and 3** respectively. Since in both previously published decision rules patients without a history of loss of consciousness or posttraumatic amnesia were excluded, while included in our study, we assessed whether loss of consciousness should be considered an independent risk factor for neurocranial complications after minor head injury in **chapter 4**. In **chapter 5** we describe the CHIP prediction rule, developed based on the NOC and CCHR, but more widely applicable than these two previously published prediction rules. Finally, we assessed in a cost-effectiveness analysis described in **chapter 6**, whether selective scanning is more cost-effective than scanning all minor head injury patients.

Secondly, we assessed long-term functional outcome in all patients from the CHIP study who had a neurocranial traumatic lesion on CT upon presentation. These findings are discussed in **chapter 7**, together with an evaluation which CT findings were predictive of poor functional outcome. In a separate prospectively included patient population we explored the neuropathological substrate of postconcussion syndrome using advanced MRI techniques. With fMRI of working memory and selective attention we correlated brain activation patterns with the severity of postconcussive symptoms in **chapter 8**. Microstructural injury, as assessed with DTI and HRGRE T2* weighted imaging in relation to postconcussion syndrome is explored in **chapter 9**.

Finally, in **chapter 10** our findings are summarised and discussed.

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CHAPTER 2

External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury

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Context Two decision rules for indications of computed tomography (CT) in patients with minor head injury, the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC), suggest that CT scanning may be restricted to patients with certain risk factors, which would lead to important reductions in the use of CT scans.

Objective To validate and compare these 2 published decision rules in Dutch patients with head injuries.

Design, setting, and patients A prospective multicenter study conducted between February 11, 2002, and August 31, 2004, in 4 university hospitals in the Netherlands of 3181 consecutive adult patients with minor head injury who presented with a Glasgow Coma Scale (GCS) score of 13 to 14 or with a GCS score of 15 and at least 1 risk factor.

Main outcome measures Primary outcome was any neurocranial traumatic finding on CT scan. Secondary outcomes were neurosurgical intervention and clinically important CT findings. Sensitivity and specificity were estimated for each outcome for the CCHR and the NOC, using both rules as originally derived and also as adapted to apply to an expanded patient population.

Results Of 3181 patients with a GCS score of 13 to 15, neurosurgical intervention was performed in 17 patients (0.5%); neurocranial traumatic CT findings were present in 312 patients (9.8%). Sensitivity for neurosurgical intervention was 100% for both the CCHR and the NOC. The NOC had a higher sensitivity for neurocranial traumatic findings and for clinically important findings (97.7%-99.4%) than did the CCHR (83.4%-87.2%). Specificities were very low for the NOC (3.0%-5.6%) and higher for the CCHR (37.2%-39.7%). The estimated potential reduction in CT scans for patients with minor head injury would be 3.0% for the adapted NOC and 37.3% for the adapted CCHR.

Conclusions For patients with minor head injury and a GCS score of 13 to 15, the CCHR has a lower sensitivity than the NOC for neurocranial traumatic or clinically important CT findings, but would identify all cases requiring neurosurgical intervention, and has greater potential for reducing the use of CT scans.

HEAD INJURY is one of the most common injuries in the Western world with an estimated incidence of hospital treated patients with minor head injury of 100 to 300 per 100 000 population (1). Minor head injury is commonly defined as blunt trauma to the head, after which the patient has lost consciousness for less than 15 minutes or has a short posttraumatic amnesia of less than 1 hour, or both, as well as a normal or minimally altered mental status on presentation (a Glasgow Coma Scale [GCS] score of 13–15) (2, 3).

Intracranial complications of minor head injury are infrequent (6%–21%) but potentially life-threatening and may require neurosurgical intervention in a minority of cases (0.4%–1.0%) (3–8). Neurocranial injury that does not require neurosurgical intervention may still cause significant clinical problems; these patients will usually be kept under close clinical observation. Computed tomography (CT) of the head is the imaging modality of choice for diagnosing neurocranial traumatic lesions, such as skull fractures, epidural and subdural hematomas, and hemorrhagic contusion. In many Western countries, CT is therefore routinely used to evaluate patients with minor head injury for the presence of neurocranial complications.

A study by Haydel et al (7) suggested that CT is only indicated in patients with minor head injury with 1 of 7 risk factors (the New Orleans criteria [NOC]) (Table 1). According to this decision rule, patients without any risk factors would not require CT scanning and implementation of this rule in the United States was estimated to reduce CT scans performed for minor head injury by 23%. A similar study by Stiell et al (3) identified a different set of risk factors, the Canadian CT Head Rule (CCHR) (Table 1). The potential reduction in the number of CT scans by implementing this decision rule was estimated at 46%. Both decision rules had 100% sensitivity for identifying patients with traumatic brain injury, as is desirable according to a survey of emergency physicians, but both rules had low specificities (9).

Proper external validation of these published decision rules is necessary before they can be implemented. Our goal was to externally validate these 2 decision rules, the NOC and the CCHR, in a large multicenter study in the Netherlands.

Table 1. Decision rules for indications for CT scan in patients with minor head injury

Study	Patient population	Indications for CT scan	Reported validity, %*	
			Sensitivity	Specificity
Haydel et al 2000 (7) (NOC)	GCS score of 15, loss of consciousness, no neurological deficit, aged >3 y	Headache, vomiting, seizure, intoxication, short-term memory deficit, aged >60 y, or injury above clavicles	100	24.5
Stiell et al 2001 (3) (CCHR)	GCS score of 13–15, loss of consciousness, no neurological deficit, no seizure, no anticoagulation, aged >16 y	High-risk patients: GCS score <15 at 2 h post-injury, suspected skull fracture, vomiting (≥2 times), aged ≥65 y† Medium-risk patients: retrograde amnesia >30 min, dangerous mechanism (pedestrian versus motor vehicle; ejected from motor vehicle; fall from height >1 m or 5 stairs)‡	98.4	49.6

Abbreviations: CCHR, Canadian CT Head Rule; CT, computed tomography; GCS, Glasgow Coma Scale; NOC, New Orleans Criteria.
* Validity for identifying patients with traumatic CT findings.
† High-risk patients in whom a CT scan is mandatory.
‡ Medium-risk patients in whom a CT scan is recommended but close clinical observation is an alternative.

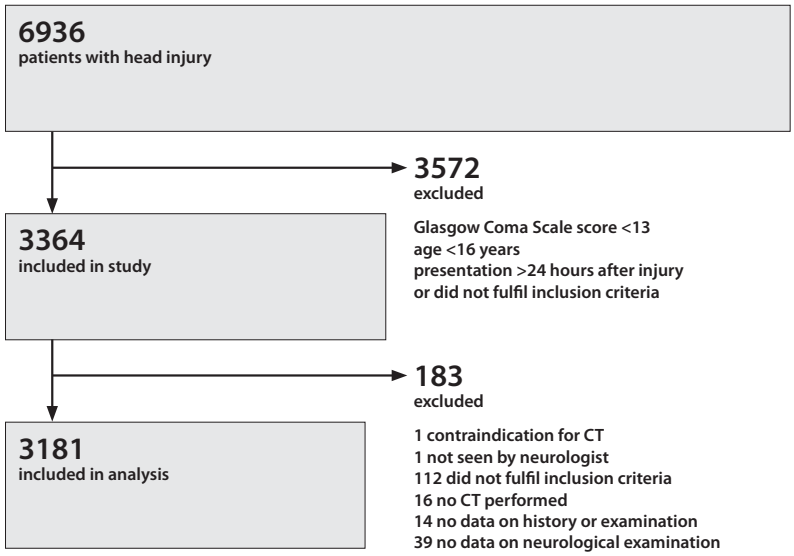

Figure. Flow of patients presenting with head injury. CT indicates computed tomography. The number of patients presenting with head injury (n = 6936) is an estimate based on the proportion of patients included from the total number of trauma patients seen by a neurologist-in-training in the emergency department of the participating center, which included the majority of patients.

METHODS

Patient population

In our prospective multicenter study, data were collected on 3364 consecutively included patients between February 11, 2002, and August 31, 2004, in 4 Dutch university hospitals (Figure). Patients were included if they presented within 24 hours after blunt head injury, were older than 16 years, and had a GCS score of 13 to 14 or had a GCS score of 15 with 1 of the following risk factors: history of loss of consciousness, short-term memory deficit, amnesia for the traumatic event, posttraumatic seizure, vomiting, severe headache, clinical evidence of intoxication with alcohol or drugs, use of anticoagulants or history of coagulopathy, physical evidence of injury above the clavicles, and neurological deficit. Patients were excluded if a CT scan could not be performed due to concurrent injury or if there were contraindications to CT scanning.

After review of our study protocol, patient informed consent was waived by the institutional review board and medical ethical committee, because patients meeting our inclusion criteria routinely undergo a head CT scan according to most local hospital policies, as is recommended in the current Dutch guidelines (10).

Clinical definitions

Patients were considered to have lost consciousness when reported by a witness or by the patient. Loss of consciousness was not considered an obligatory criterion for inclusion in study, as was the case in previously published studies, but rather as

one of the risk factors for neurotraumatic findings. A deficit in short-term memory was defined as a persistent anterograde amnesia. If the patient could not recall the entire traumatic event, this was considered as amnesia for the traumatic event. Posttraumatic seizure was classified as either a witnessed or suspected seizure after the traumatic event. Vomiting included any emesis after the traumatic event. Headache included both diffuse and localized pain. No blood toxicology tests were performed to assess severity of intoxication; presence and severity of intoxication were evaluated clinically, evidenced by slurred speech, alcoholic fetor, or nystagmus. Anticoagulant treatment included only warfarin and not platelet aggregation inhibitors (eg, aspirin, clopidrogel). Presence of coagulopathy was assessed by patient history; no blood coagulation tests were performed. Physical evidence of injury was defined as clinically significant discontinuity of the skin or extensive bruising. Focal neurological deficit was defined as any abnormality on routine clinical neurological examination, indicating a focal cerebral lesion.

Patient assessment

All patients were examined by a neurologist or a neurologist-in-training under the supervision of a neurologist. All included patients underwent head CT scanning following physical examination. CT scanning was performed according to a routine trauma protocol, which consisted of a maximum slice thickness of 5 mm infratentorially and 8 mm supratentorially, without intravenous contrast administration. All scans were interpreted by a neuroradiologist or a trauma radiologist in bone and brain window settings. The reading radiologist was not blinded to the patient's clinical information, because all reading was performed in a clinical setting to evaluate the validity of the decision rules in daily practice.

Data collection

Data were collected on patient and trauma characteristics (age, sex, time of injury and presentation, intoxication, anticoagulant treatment), accompanying symptoms (loss of consciousness, posttraumatic amnesia, posttraumatic seizure, short-term memory deficits, headache, vomiting), as well as on physical and neurological examination, CT findings, and the need for neurosurgical intervention. Selection of items was based on a literature review of published risk factors for intracranial complications after minor head injury. Data on patient history and examination were entered by the examining physician into a database (11) before the patient underwent CT, unless this interfered with the clinical work flow, in which case data were entered after the CT was performed (12). CT findings were added separately by the reading radiologist (H.M.D., D.R.K., P.A.M.H., and H.L.J.T.). Data on neurosurgical intervention were collected by searching the included patients' records in the hospital patient information system.

Outcome measures

Our primary outcome measure was any traumatic finding of the neurocranium on the CT scan. Findings on the CT scan that led to neurosurgical intervention, although more important from a clinical point of view, were considered a secondary outcome, because of their low frequency and potential clinical variability across centers. However, because of their clinical significance, they will be reported first. A neurosurgical intervention was defined as any neurosurgical procedure (craniotomy, intracranial pressure monitoring, elevation of skull fracture, ventricular drainage) within 30 days after the traumatic event. Findings on the CT scan, which we considered to be important

for clinical practice in that the patient would generally be admitted to hospital, were also considered a secondary outcome measure. These were defined as any intracranial traumatic finding on the CT scan, including depressed skull fractures.

Sample size

To reliably validate the published decision models for predicting neurocranial traumatic findings on CT scan, a minimum of 100 events of our primary outcome were needed (13, 14). Given an incidence of traumatic findings on CT of 8% to 10%, at least 1250 patients who fulfilled the inclusion criteria of the original decision rules would need to be included (15).

Data analysis

Patient data entered in the database were assessed by one of the authors (M.S.) for correct patient inclusion and for completeness of the data. Missing data of patients included in the analysis were assumed to be missing at random and imputed based on the available data means to avoid bias. The proportion of imputed missing data was 3.81%, which included both items documented as unknown and items that were not documented. We evaluated our patient population for demographic characteristics, mechanism of injury, traumatic findings, neurosurgical intervention, and occurrence of the risk factors of both decision rules.

We determined the sensitivity and specificity (and 95% confidence intervals [CIs]) for neurosurgical intervention, neurocranial traumatic findings on CT, and clinically important lesions on CT of both decision rules (16). The decision rule was considered positive when at least 1 of the risk factors was present. For the CCHR, in which a distinction is made between high-risk and medium risk criteria, we chose not to use this distinction; therefore, all risk factors were considered equally important.

Table 2. Patient characteristics (n = 3181)

Characteristics	No. (%) of patients
Men	2244 (70.5)
Age, mean (range), y	41.4 (16.0-102.3)
Time to presentation, mean (range), min	93.8 (0.0-1400.0)
Mechanism of injury	
Assault	771 (24.2)
Fall (not from height)	691 (21.7)
Motor vehicle crashes	537 (16.9)
Fall from height*	513 (16.1)
Cyclist versus vehicle	246 (7.7)
Hit head	127 (4.0)
Pedestrian versus vehicle	100 (3.1)
Heavy object on head	79 (2.5)
Ejected from vehicle	65 (2.0)
Other	52 (1.6)
Risk factors	
Signs of injury above clavicles	2612 (82.1)
Loss of consciousness	1951 (61.3)
Headache	1910 (60.0)
Signs of intoxication	1367 (43.0)
Posttraumatic amnesia >30 min	916 (28.8)
Dangerous mechanism of injury†	676 (21.3)
Age >60 y	534 (16.8)
GCS <15 (1 h after presentation)	506 (15.9)
Deficit in short-term memory	475 (14.9)
Age ≥65 y	424 (13.3)
Vomiting	342 (10.8)
Neurological deficit	304 (9.6)
Anticoagulation treatment	218 (6.9)
Clinical signs of skull fracture	66 (2.1)
Posttraumatic seizure	23 (0.7)

Abbreviation: GCS, Glasgow Coma Scale.
* More than 1 meter or 5 stairs.
† Pedestrian hit by motor vehicle, ejected from motor vehicle, or fall from height of more than 1 meter or 5 stairs.

The published decision rules were designed for specific patient populations, which were more restricted than our patient population. We therefore first performed our validation analyses in the subgroup of

patients for whom the decision rule was designed (Table 1); these decision rules are referred to as the original decision rules. We then adjusted the original decision rules for use in our entire study population, which also included patients without a history of loss of consciousness, by adding the exclusion criteria of the original rules as additional risk factors, which are referred to as the adapted decision rules. This means that the adapted NOC decision rule also included the risk factors neurological deficit and a GCS score of 13 or 14, and the adapted CCHR decision rule included the risk factors anticoagulation, posttraumatic seizure, and neurological deficit in addition to the original risk factors. The potential reduction in emergency CT scans was estimated by assuming that if the rule were to be adapted, then a positive result on the rule would be followed by a CT scan and a negative result on the rule would not.

Data were analyzed using SPSS version 12.0 software (SPSS Inc, Chicago, Ill); $P<.05$ was considered statistically significant.

RESULTS

The total number of patients presenting with head injury during our study at the 4 centers was estimated to be 6936 (Figure). A total of 3572 patients were not included because they did not meet the inclusion criteria. Of the 3364 patients originally included in the study, 112 did not meet the inclusion criteria on reassessment and were excluded from further analysis. One patient had a contraindication for CT, 1 was not seen by a neurologist, 16 patients did not have CT performed because of logistical reasons, 14 patients had no available data on patient history, and 39 patients had no available data on neurological examination. These patients were also excluded from further analysis, resulting in 3181 patients in the data analysis.

Patient characteristics are shown in Table 2. A total of 304 patients had neurological deficit, including 64 patients (21%) with lateralized motor weakness, 60 patients (20%) with lateralized sensory disturbances, and 251 patients (83%) with focal neurological deficits. Focal neurological deficits included, among other deficits, pathological reflexes (37%), nystagmus (19%), visual disturbances (9%), and pupil abnormalities (6%). In our study population, relatively few patients had posttraumatic seizure (0.7%), clinical signs of skull fracture (2.1%), or use of anticoagulation (6.9%).

Most patients presented with a normal GCS score of 15 (Table 3). Neurosurgical intervention was required in 17 patients (0.5%), which was performed for epidural hematoma in 8 cases, subdural hematoma in 3 cases, depressed skull fracture in 3 cases, and a combination of extra-axial hematoma and depressed skull fracture in the remaining 3 cases. Neurocranial traumatic lesions on the

Table 3. Neurocranial traumatic CT findings and neurosurgical interventions by patient Glasgow Coma Scale score (GCS) on presentation*

Glasgow Coma Scale score	No. (%) of patients			
	CT		Neurosurgical intervention	Total
	Negative	Positive		
13	114 (75.5)	37 (24.5)	2 (1.3)	151 (4.7)
14	478 (84.2)	90 (15.8)	5 (0.9)	568 (17.9)
15	2277 (92.5)	185 (7.5)	10 (0.4)	2462 (77.4)
Total	2869 (90.2)	312 (9.8)	17 (0.5)	3181 (100)

Abbreviation: CT, computed tomography.
* CT negative indicates no neurocranial traumatic lesions were present and CT positive indicates a neurocranial traumatic lesion was present

CT scan were found in 9.8% of the patients, with the highest proportion of traumatic findings in the category of patients with a GCS score of 13 (24.5%). The most common traumatic finding on the CT scan was a skull fracture (59.6%) (Table 4). Clinically important lesions were present in 243 patients (77.9%). Epidural hematoma was present in 11.2% of patients with traumatic findings; most of these hematomas were small with no or only localized mass displacement (25 of 35 cases) and were likely to be venous in origin in 4 cases. Subdural hematoma was present in 67 patients (21.5%) with traumatic findings on CT, and also was small in most cases with no (42 patients) or minimal (14 patients) mass displacement.

Notably, in 5 (29%) of 17 patients who underwent neurosurgical intervention, no history of loss of consciousness was present. A history of loss of consciousness was also absent in 85 (27%) of 312 patients with neurocranial traumatic CT findings and in 61 (25%) of 243 patients with clinically important CT findings.

For both the NOC and CCHR decision rules, both original and adapted, sensitivity for identifying patients who underwent neurosurgical intervention was 100% (Table 5). Sensitivity for neurocranial traumatic lesions on the CT scan, however, was not 100% for both rules. The adapted NOC reached the highest sensitivity for identifying patients with neurocranial traumatic findings on the CT scan (99.4%; 95% CI, 97.7%–99.8%); the original CCHR had the lowest sensitivity (83.4%; 95% CI, 77.7%–87.9%). Two patients with neurocranial traumatic CT findings were not identified using the adapted NOC rule. One of these patients with a nonhemorrhagic contusion would have been identified by the adapted CCHR because of the presence of prolonged (>30 minutes) posttraumatic amnesia. With the adapted CCHR, 47 patients with traumatic findings would have been missed; 46 of these patients would have been identified with the adapted NOC, because of the presence of external injury above the clavicles other than clinical signs of a skull fracture (41 patients) or headache (5 patients). Traumatic findings on the CT scan in these patients included skull fracture (n = 30), subdural (n = 5) and epidural (n = 2) hematoma, subarachnoid hemorrhage (n = 12), hemorrhagic (n = 11) and nonhemorrhagic (n = 1) contusion, and diffuse axonal injury (n = 2). One patient with diffuse cerebral swelling did not have any risk factors using either the CCHR or NOC decision rules. Sensitivity for clinically important traumatic CT findings was very similar to that for all neurocranial traumatic CT findings for both decision rules.

Specificity for neurosurgical intervention and neurocranial traumatic CT findings was very low for the adapted NOC decision rule but higher for the adapted CCHR decision rule (Table 5). Specificity for clinically

Table 4. Traumatic CT findings (n = 312)*

CT finding	No. (%) of patients
Skull fracture	186 (59.6)
Skull base	82 (26.3)
Depressed	19 (6.1)
Linear	114 (36.5)
Subdural effusion	2 (0.6)
Subdural hematoma	67 (21.5)
Epidural hematoma	35 (11.2)
Subarachnoid hemorrhage	86 (27.6)
Intraparenchymal lesions	142 (45.5)
Hemorrhagic contusion	118 (37.8)
Nonhemorrhagic contusion	15 (4.8)
Diffuse axonal injury	14 (4.5)
Intraventricular hemorrhage	5 (1.6)
Clinically important lesions†	243 (77.9)

Abbreviation: CT, computed tomography.
* Some patients had more than 1 CT finding.
† Defined as any intracranial traumatic CT finding, including depressed skull fractures but excluding isolated linear fractures.

important traumatic CT findings was almost identical to that for all neurocranial traumatic CT findings for both decision rules. The potential reduction in emergency CT scans by using these decision rules would have been higher with the adapted CCHR (37.3%; 95% CI, 35.6%–39.0%) than with the adapted NOC (3.0%; 95% CI, 2.4%–3.6%).

COMMENT

In this multicenter prospective validation study of 2 published decision rules for the use of CT scanning in patients with minor head injury, we found that both the NOC and the CCHR had 100% sensitivity for identifying patients who underwent neurosurgical intervention after minor head injury. This was true for both the original decision rules (when applied to the patient population these rules were designed for) and for the adapted rules applied to our entire study population. Sensitivity for neurocranial traumatic CT lesions or for clinically important lesions, however, was not 100% for both rules. The NOC decision rule had high sensitivity for neurocranial traumatic CT lesions, but the CCHR did not. The difference in sensitivities for neurocranial traumatic CT findings between the 2 decision rules seems to be mainly due to the more stringent use of the risk factor of external injury in the CCHR. In the NOC, this risk factor comprises all external injuries above the clavicles, whereas in the CCHR only external injury indicating a skull (base) fracture is considered a risk factor for neurocranial traumatic CT findings. Specificities for neurocranial traumatic CT findings and for neurosurgical

Table 5. Performance of the original and adapted decision rules for identifying patients with neurosurgical intervention, neurocranial traumatic CT findings, and clinically important CT lesions as well as the potential reduction in CT scans*

	Present†		Absent†		Sensitivity, %	Specificity, %	CT reduction, %
	RF+	RF-	RF+	RF-	(95% Confidence Interval)		
Original NOC (n = 1307)							5.3 (4.2-6.6)
Neurosurgical intervention	2	0	1236	69	100.0 (34.2-100.0)	5.3 (2.5-8.3)	
Neurocranial CT findings	115	2	1123	67	98.3 (94.0-99.5)	5.6 (2.7-8.8)	
Important CT findings	86	2	1152	67	97.7 (92.1-99.4)	5.5 (2.6-8.7)	
Adapted NOC (n = 3181)							3.0 (2.4-3.6)
Neurosurgical intervention	17	0	3070	94	100.0 (81.6-100.0)	3.0 (1.2-4.8)	
Neurocranial CT findings	310	2	2777	92	99.4 (97.7-99.8)	3.2 (1.4-5.2)	
Important CT findings	241	2	2846	92	99.2 (97.1-99.8)	3.1 (1.3-5.1)	
Original CCHR (n = 2028)							37.1 (35.0-39.2)
Neurosurgical intervention	7	0	1269	752	100.0 (64.6-100.0)	37.2 (34.1-40.4)	
Neurocranial CT findings	171	34	1105	718	83.4 (77.7-87.9)	39.4 (36.0-42.8)	
Important CT findings	136	25	1140	727	84.5 (78.1-89.3)	38.9 (35.6-42.3)	
Adapted CCHR (n = 3181)							37.3 (35.6-39.0)
Neurosurgical intervention	17	0	1979	1185	100.0 (81.6-100.0)	37.5 (34.9-40.0)	
Neurocranial CT findings	265	47	1731	1138	85.0 (80.5-88.5)	39.7 (37.0-42.4)	
Important CT findings	212	31	1784	1154	87.2 (82.5-90.9)	39.3 (36.6-42.0)	

Abbreviations: CT, computed tomography; CCHR, Canadian CT Head Rule; NOC, New Orleans Criteria; RF+, at least 1 risk factor: RF-, all risk factors absent.
* Clinically important lesions were defined as any intracranial traumatic CT finding, including depressed skull fractures but excluding isolated linear fracures.
† Presence or absence of neurosurgical intervention and neurocranial CT findings.

intervention were low for the NOC decision rule, and higher for the CCHR but at the cost of a lower sensitivity for traumatic findings on the CT scan.

A single-center prospective study by Ibanez et al (17) included 1101 patients and validated several guidelines and decision rules for minor head injury, including the CCHR and NOC. In this study, as well as in our study, none of the guidelines or decision rules reached a 100% sensitivity for traumatic lesions on the CT scan, with the NOC also reaching a higher sensitivity (95%) than the CCHR (86%). Unfortunately, Ibanez et al (17) reported only sensitivities for relevant acute intracranial CT lesions and not the sensitivities for neurosurgical intervention. Furthermore, it is not clear from the article how the decision rules were validated, especially since that study population was not the same as the patient populations for which these guidelines and decision rules were designed.

The incidence of traumatic CT findings (9.8%) and of subsequent neurosurgical intervention (0.5%) in our study population correspond with findings in previous studies of patients with minor head injury (traumatic findings, 6.4%–21.0%; and neurosurgical intervention, 0.4%–1.0%) (3, 7, 8). Assault as the most common mechanism of injury is remarkable and may be due to the fact that 2 of our participating centers are in 2 large cities in the Netherlands, where crime rates are highest. Another reason may be that we included patients with minor head injury irrespective of loss of consciousness. Assault usually results in less severe injury than motor vehicle crashes or falls, which are the more common mechanisms of injury in similar studies (3).

In our adaptation of the NOC and CCHR decision rules for use in our population, we did not include loss of consciousness as a risk factor, although loss of consciousness is generally regarded as a risk factor for complications after minor head injury. Loss of consciousness is often considered such a strong predictor that its presence usually is considered an obligatory part of the definition of minor head injury. The absence of loss of consciousness, however, does not exclude the possibility of neurocranial lesions, some of which may require neurosurgical intervention, although with a lower incidence than when the patient has lost consciousness (17). Our results emphasize this point, since almost 30% of patients requiring neurosurgical intervention had not lost consciousness. Clearly, certain patients without a history of loss of consciousness after minor head injury are also at risk of serious complications and therefore require a CT scan. By not including loss of consciousness as a risk factor in the adapted NOC and CCHR decision rules and validating them as such, the reported sensitivities and specificities of the adapted decision rules are valid for any patient with minor head injury, irrespective of whether loss of consciousness was present. Our simple adaptation to the 2 published decision rules may not be the optimal strategy, but it was beyond the scope of our study to design an entirely new decision rule. Designing a new decision rule, which is also applicable to patients with minor head injury but without loss of consciousness, may however be better than these simple adaptations to existing decision rules, and will require further research.

A limitation of our study is that we did not use the exact predictors that Stiell et al (3) defined in the derivation of the CCHR. In that study, Stiell et al (3) found that a GCS score of less than 15 at 2 hours after presentation to the emergency department was a risk factor for clinically important brain injury and neurosurgical intervention. In our participating centers, however, most patients underwent CT scanning within 2 hours of presentation. Therefore, we evaluated GCS at 1 hour after presentation instead of after

2 hours. Another predictor for clinically important brain injury according to the CCHR is amnesia preceding the traumatic event (retrograde amnesia) of more than 30 minutes. Our neurologists found it difficult to assess the duration of retrograde amnesia, which makes it an unreliable risk factor. Estimation of posttraumatic or anterograde amnesia is easier and seems to be more reliable. Since posttraumatic amnesia was also significantly associated with brain injury in the study by Stiell et al (3), we chose to use posttraumatic amnesia of more than 30 minutes as a risk factor instead of retrograde amnesia. In addition, the CCHR defined vomiting as involving more than 1 episode of emesis, whereas we defined vomiting as any period of emesis. It seems unlikely that the low sensitivity of the CCHR for traumatic lesions is due to our slight adjustments to the decision rule. If anything, the contrary is more likely since our adjusted predictors regarding the GCS score and vomiting are less restrictive than the CCHR original predictors.

Another limitation is that data on patient history and examination, although documented before the CT scan, were not always entered into the database before the CT scan was performed in those cases when data entry before the CT scan would have interfered with patient management. This may have caused some classification bias. In addition, we did not exclude patients who presented with minor head injury after a seizure and whose physical and neurological examination postictally is difficult to interpret. There is also a theoretical possibility that we may have missed patients undergoing neurosurgical intervention, who were initially discharged from 1 of the participating hospitals, and who later deteriorated and underwent emergency neurosurgical intervention in a different hospital. This is a highly unlikely event since the centers participating in our study are primary regional neurosurgical centers, which would mean that patients who would present to a different hospital than 1 of our participating centers would very likely be transferred to the participating center for neurosurgical intervention.

Despite these limitations, we were able to validate 2 published decision rules for the indications for CT scanning in patients with minor head injury in a large study population and multicenter setting. The NOC, both in its original form and adjusted for use in our entire patient population, reached the highest sensitivity for identifying patients with neurocranial traumatic lesions, but since its specificity was very low, the potential reduction in CT scans by implementing this rule would be much lower than estimated by Haydel et al (3% versus 22%) (7). The potential reduction in CT scans by using the adapted CCHR decision rule in the entire patient population may be considerable (37%). However, the adapted CCHR attained a sensitivity for traumatic CT findings of only 83% to 87%, which may be too low for clinical practice, although the sensitivity for neurosurgical intervention was 100%.

A key clinical question is whether 100% sensitivity is needed for identifying patients with any neurocranial traumatic CT finding. The reason to perform an emergency CT scan in patients with minor head injury is to detect intracranial complications of minor head injury that require neurosurgical intervention or that cause significant clinical problems for which close clinical observation is needed. For this reason, we also validated the decision rules for clinically important lesions, which generally require clinical observation.

Still, the question remains whether all of the patients with a clinically important lesion on the CT scan really did require observation and, consequently, whether a CT scan was really indicated. A CT scan is

certainly indicated in patients with traumatic lesions requiring neurosurgical intervention; however, we feel that focusing solely on neurosurgical intervention may be too restrictive. We therefore think it would also be important to assess the outcomes in terms of costs and effectiveness of head injury to identify those patients who may benefit from an emergency CT scan (18). In this respect, it is important to recognize that if the CT scan is negative and the patient may then be sent home without further clinical observation, this would result in both a gain in effectiveness (less days in hospital for the patient) as well as in cost-savings both for the health care system and society (a CT scan costs less than hospital admission) (19). The magnitude of these effects will need to be ascertained, which can then be used to determine the optimal trade-off between sensitivity and specificity, and may help to formulate an evidence based approach for reducing CT scans in patients with minor head injury.

In summary, based on application of the CCHR and the NOC in 3181 patients, the adapted NOC decision rule appears valid for use in all patients with minor head injury who are 16 years or older and have a GCS score of 13 to 15, irrespective of loss of consciousness. However, the potential reduction in CT scans performed for this indication is extremely low in the clinical context studied. The adapted CCHR has a lower sensitivity for traumatic findings on the CT scan, but would identify all patients requiring neurosurgical intervention. Further research is needed to identify patients with neurocranial injury who do not require neurosurgical intervention but may benefit from emergency CT scanning and to determine the optimal trade-off between sensitivity and specificity for a decision rule for CT scanning in patients with minor head injury based on cost and effectiveness outcomes.

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CT scanning for minor head injury: Letter in reply

JAMA, 2006;295:497-498.

TO THE EDITOR

WE PERFORMED additional analyses to answer Dr Schwam's question about the sensitivity and specificity of the Canadian CT Head Rule (CCHR) for clinically important lesions in patients with a Glasgow Coma Scale (GCS) score of 15, no focal neurological deficit, and no anticoagulation. In our study population, 2104 of the patients fulfilled these criteria, 1473 of whom had a history of loss of consciousness or posttraumatic amnesia. Of these patients, 87 (5.9%) had 1 or more clinically important lesions on CT scan: hemorrhagic contusion (n = 36 [41%]), traumatic subarachnoid hemorrhage (n = 29 [33%]), subdural hematoma (n = 18 [21%]), epidural hematoma (n = 12 [14%]), nonhemorrhagic contusion (n = 7 [8%]), diffuse axonal injury (n = 7 [8%]), depressed skull fracture (n = 3 [3%]), intraventricular hemorrhage (n = 3 [3%]), and subdural effusion (n = 1 [1%]). Additionally, skull base fractures in 17 patients (20%) and linear fractures in 23 patients (26%) were observed in combination with other lesions.

Sensitivity and specificity for clinically important lesions on CT scan for the CCHR were 77.0% (95% confidence interval [CI], 67.1%–84.6%) and 47.8% (95% CI, 43.7%–51.9%), respectively, for the subgroup of 1473 patients. This sensitivity is lower than the sensitivities reported for our original patient population. This is not surprising because the CCHR was originally designed for a wider variety of patients, including those with lower GCS scores. Applying the CCHR to a less severely injured subgroup of patients as specified above, the number of patients with true-positive results decreases more than the number of patients with false-negative results, hence, the lower sensitivity.

Our findings therefore still show a lower sensitivity of the CCHR for clinically important lesions than in the population in which it was internally validated (1). Although Schwam suggests that this difference may be due to our subset of patients all having at least 1 of the New Orleans Criteria (NOC) risk factors, this is not strictly true. We considered loss of consciousness as one of the risk factors and inclusion criteria, and we included all patients with a history of loss of consciousness irrespective of the presence of other risk factors. However, most of our patients did have an NOC risk factor in addition to a history of loss of consciousness, explaining the low specificities of the NOC in our study. This may reflect differences in patient populations visiting emergency departments in our participating centers in the Netherlands versus those in North America. These types of differences indicate why external validation studies are necessary before implementation of decision rules.

Finally, the decision to use the CCHR for the selection of patients requiring CT scan may not only depend on its sensitivity for clinically important findings, as Schwam suggests, but also on the costs and health outcome effects of its implementation.

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CHAPTER 3

Minor head injury: Guidelines for the use of CT – a multicenter validation study

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Purpose To prospectively and externally validate published national and international guidelines for the indications of computed tomography (CT) in patients with a minor head injury.

Materials and methods The study protocol was institutional review board approved. All patients implicitly consented to use of their deidentified data for research purposes. Between February 2002 and August 2004, data were collected in consecutive adult patients with blunt minor head injury (Glasgow Coma Scale score of 13–14 or 15) and a risk factor for neurocranial traumatic complications at presentation at four Dutch university hospitals. Primary outcome was any neurocranial traumatic CT finding. Secondary outcomes were clinically relevant traumatic CT findings and neurosurgical intervention. Sensitivity and specificity of each guideline for all outcomes and the number of patients needed to scan to detect one outcome (ie, the number of patients needed to undergo CT to find one patient with a neurocranial traumatic CT finding, a clinically relevant traumatic CT finding, or a CT finding that required neurosurgical intervention) were estimated.

Results Data were available for 3181 patients. Only the European Federation of Neurological Societies guidelines reached a sensitivity of 100% for all outcomes. Specificity was 0.0%– 0.5%. The Dutch guidelines had the lowest sensitivity (76.5%) for neurosurgical interventions. The best specificities for traumatic CT findings and neurosurgical interventions were reached with the criteria proposed by the United Kingdom National Institute for Clinical Excellence (NICE) (46.1% and 43.6%, respectively), albeit at relatively low sensitivities (82.1% and 94.1%, respectively). The number of patients needed to scan ranged from six to 13 for traumatic CT findings and from 79 to 193 for neurosurgical interventions.

Conclusion All validated guidelines demonstrated a similar trade-off between sensitivity and specificity. The lowest number of patients needed to scan for either of the outcomes was reached with the NICE criteria.

IN THE Western world, the number of patients with a mild head injury treated at a hospital is estimated to be 100–300 per 100 000 persons annually, making it one of the most common injuries seen in emergency departments (1). Minor head injury is usually defined as a blunt injury to the head, after which the patient may briefly lose consciousness, may have short posttraumatic amnesia, or both, and may have a normal or minimally altered mental status at presentation (Glasgow Coma Scale [GCS] score of 13–15) (2, 3). Intracranial complications of minor head injury occur infrequently. The frequency with which complications occur depends on the population, and, in general, complications occur in 6%–10% of patients; however, these complications are potentially life threatening and may require neurosurgical intervention in a minority (0.4%–1.0%) of cases (3–8). A neurocranial injury that does not require neurosurgical intervention may still cause substantial clinical problems. Patients with these injuries will usually be kept under close clinical observation.

Computed tomography (CT) of the head is commonly considered to be the imaging modality of choice for the rapid and reliable diagnosis of neurocranial traumatic lesions, such as skull fractures, epidural and subdural hematomas, and both hemorrhagic and nonhemorrhagic contusions (6, 9–11). Numerous national and international guidelines regarding the use of CT in patients with a minor head injury have been published; some of these guidelines are in part based on published algorithms, such as the New Orleans criteria and the Canadian CT head rule (Table E1) (3, 7). An important goal of implementing such guidelines is to perform CT in only those patients who are at risk of developing complications. This would reduce costs involved with CT scanning and reduce the strain on emergency, neurology, and radiology departments. In each of the guidelines, a distinction is made between low-, medium-, and high-risk patients. In low-risk patients, CT scanning is deemed unnecessary. In the remaining patients, the clinician is given the choice of scanning all medium- and high-risk patients (lenient criteria) or scanning only high-risk patients (strict criteria).

The published guidelines show considerable overlap. Most guidelines consider a history of loss of consciousness, posttraumatic amnesia, suboptimal GCS score, focal neurologic deficit, posttraumatic seizure, vomiting, or coagulopathy as a risk factor. However, there are substantial differences between the guidelines with respect to the definitions of risk factors, as well as to the number, set, or combinations of risk factors for which CT scanning would be indicated. In some guidelines, a lenient use of CT is recommended, while other guidelines advocate a more restrictive approach. Use of guidelines that recommend the restrictive use of CT in patients with a minor head injury leads to a reduced number of CT scans performed for this indication compared with the number of CT scans performed at the recommendation of lenient guidelines and therefore would be preferable to avoid overuse and reduce radiation dose. While the New Orleans criteria and Canadian CT head rule have recently been externally validated, this is not the case for all guidelines (12, 13). It remains unclear whether restrictive guidelines serve to identify at-risk patients as well as do lenient guidelines. Thus, the purpose of our multicenter observational study was to prospectively and externally validate published national and international guidelines for the indications of CT in patients with a minor head injury (12).

MATERIALS AND METHODS

Study group

Between February 11, 2002, and August 31, 2004, data were prospectively collected

for 3364 consecutive patients at four Dutch university hospitals who met our inclusion criteria (presentation within 24 hours after blunt head injury, aged 16 years or older, and GCS score of 13 or 14 at presentation or GCS score of 15 at presentation with at least one of the following risk factors: history of loss of consciousness, short-term memory deficit, amnesia associated with the traumatic event, posttraumatic seizure, vomiting, headache, clinical evidence of intoxication with alcohol or drugs, anticoagulant treatment or history of coagulopathy, external evidence of injury above the clavicles, or neurologic deficit) (Table 1). Patients were excluded if concurrent injuries precluded head CT within 24 hours of the head injury or if contraindications to CT scanning were present. Although there are no generally acknowledged absolute contraindications to CT scanning, pregnancy is sometimes considered a relative contraindication and was therefore considered an exclusion criterion in our study.

Our study was entirely observational and did not influence patient care or pose any risk to the patients. The systematically collected data solely included information that is routinely documented during the work-up of a patient with a minor head injury. In the centers that participated in this study, it is common practice for any patient meeting the inclusion criteria to be seen in the emergency department by a neurologist or neurologist-in-training under the supervision of a neurologist. According to the policies of most Dutch hospitals, including those of the centers that participated in this study, patients with a minor head injury routinely undergo head CT (14). The study protocol was reviewed and approved by the institutional review board and medical ethics committee at each of the participating centers. All patients included in our study implicitly

Table E1. Indications for CT in adult patients with minor head injury

Strict criteria	Lenient criteria
Dutch guidelines (2001; revision in progress) (23)	
GCS = 13–14	GCS = 13–14
Loss of consciousness or PTA *and*	Loss of consciousness
Age >60 years	PTA
External injury above clavicles	
Persistent anterograde amnesia	
Early seizure	
Focal neurologic deficit	
Vomiting	
Persisting headache	
Coagulopathy	
Unclear accident history	
High-energy accident	
History of neurosurgical treatment (shunt)	
Intoxication with alcohol or drugs	
WFNS guidelines (2001; no revision date indicated) (24)	
GCS = 13–14	GCS = 13–14
Age >60 years	Loss of consciousness
Skull fracture	Age >60 years
Neurologic deficit	Skull fracture
Coagulopathy	Amnesia
Pretraumatic seizure	Neurologic deficit
History of neurosurgical treatment	Vomiting
Intoxication with alcohol or drugs	Headache
	Coagulopathy
	Pretraumatic seizure
	History of neurosurgical treatment
	Intoxication with alcohol or drugs

EFNS guidelines (2002; no revision date indicated) (15)

GCS = 13–14	GCS = 13–14
Retrograde amnesia >30 minutes	Loss of consciousness
Age >60 years	PTA
External injury above clavicles	Retrograde amnesia >30 minutes
Continued PTA	Age >60 years
Focal neurologic deficit	External injury above clavicles
Seizure	Continued PTA
Vomiting	Focal neurologic deficit
Severe headache	Seizure
Coagulopathy	Vomiting
Unclear accident history	Severe headache
High-energy accident	Coagulopathy
Intoxication with alcohol or drugs	Unclear accident history
	High-energy accident
	Intoxication with alcohol or drugs

NICE* criteria (2003; revision in progress) (25)

GCS = 13–14 at 2 hours after injury	GCS = 13–14 at 2 hours after injury
Suspected open or depressed skull fracture	Suspected open or depressed skull fracture
Suspected basal skull fracture	Suspected basal skull fracture
Focal neurologic deficit	Retrograde amnesia >30 minutes
Posttraumatic seizure	Focal neurologic deficit
Vomiting, >1 episode	Posttraumatic seizure
Loss of consciousness or amnesia *and*	Vomiting, >1 episode
Age ≥65 years	Loss of consciousness or PTA *and*
Coagulopathy	Age ≥65 years
	Coagulopathy
	Dangerous mechanism of injury

SIGN† guidelines (2000; revision in progress) (26)

GCS = 13–14 at 4 hours after injury	GCS = 13–14 on presentation or at 4 hours after injury
GCS deterioration	GCS deterioration
Suspected skull fracture	Loss of consciousness
Altered behavior	PTA
Focal neurologic deficit	External injury to the skull
Posttraumatic seizure	Suspected skull fracture
Vomiting	Altered behavior
Headache	Focal neurologic deficit
	Posttraumatic seizure
	Vomiting
	Headache
	Unclear history
	Nontrivial mechanism of injury

Scandinavian guidelines (2000; no revision date indicated) (27)

GCS = 13	GCS = 13–14
Loss of consciousness >5 minutes	Loss of consciousness
Radiographically shown skull fracture	Radiographically shown skull fracture
Suspected depressed or basal skull fracture	Suspected depressed or basal skull fracture
Focal neurologic deficit	Focal neurologic deficit
Posttraumatic seizure	Posttraumatic seizure
Coagulopathy	Coagulopathy
Multiple injuries	Multiple injuries
Shunt-treated hydrocephalus	Shunt-treated hydrocephalus

Note – CT is indicated when at least one item (or a combination of items such as specified by the guideline) is present. Strict criteria imply that only high-risk patients are scanned; lenient criteria allow all medium- and high-risk patients to be scanned. PTA = posttraumatic amnesia.

* The lenient criteria of NICE include criteria for both an immediate CT scan and a scan within 8 hours of injury.

† The lenient criteria of the SIGN guidelines include criteria for both CT and skull radiography.

Table 1. Collected patient data

History	Symptoms	Physical examination
Date of birth	Loss of consciousness	External injury (above the clavicles)
Sex	Posttraumatic amnesia	GCS on presentation
Time of injury	Posttraumatic seizure	GCS 1 hour after presentation
Time of presentation	Short-term memory deficit	Motor deficits
Mechanism of injury	Headache	Sensory deficits
Intoxication	Vomiting	Focal neurologic deficits
Anticoagulant treatment		

Note – High-energy accident was derived from the description of trauma mechanism and defined as a fall from a height of more than 1 m or down more than five stairs, pedestrian or cyclist versus vehicle, driver or passenger ejected from vehicle, or any individual involved in a motorized vehicle accident or high-velocity cycling accident. Presence and severity of intoxication were evaluated clinically and evidenced by slurred speech, alcoholic fetor, or nystagmus. Anticoagulant treatment included coumarine derivatives only and not platelet aggregation inhibitors (eg, aspirin or clopidrogel). No blood coagulation tests were performed, and the presence of coagulopathy was assessed by taking patient history. Loss of consciousness was considered to have occurred when it was reported by a witness or the patient. Posttraumatic amnesia was an inability to recall the traumatic event and subsequent events; the duration (in minutes) was estimated. Posttraumatic seizure was classified as a witnessed or suspected seizure after the head injury. Short-term memory deficit was defined as persistent anterograde amnesia. Headache included both diffuse and localized pain. Vomiting was defined as any episode of emesis after the injury. External evidence of injury was defined as extensive bruising or clinically substantial discontinuity of skin. Focal neurologic deficit was any abnormality at routine clinical neurologic examination indicating a focal cerebral lesion.

consented to use of their deidentified data for research purposes.

Data collection

Data were collected digitally with software (OpenSDE; http://www2.eur.nl/fgg/mi/OpenSDE/) that was specifically designed for systematic data collection within a clinical setting (Table 1) (15). The software was installed on desktop computers that were easily accessible to the participating physicians. The neurologist or neurologist-in-training who examined the patient systematically collected data on the patient's history, demographics, and general and neurologic examination findings.

All patients who met the inclusion criteria were referred for head CT. The imaging protocol consisted of acquisition of contiguous sections with a maximum thickness of 5 mm infratentorially and 8 mm supratentorially without intravenous contrast material administration. Images were evaluated with brain and bone window settings. The reading neuroradiologist or trauma radiologist added head CT data to the database.

Guideline selection

We (M.S., D.W.J.D., M.G.M.H.) searched PubMed for national and international guidelines for the use of CT in patients with a minor head injury that were published in English or Dutch since 2000. Guidelines that solely addressed the pediatric population or patients with severe head injury were discarded. Only guidelines that were unambiguous (ie, with clearly defined criteria for indications for CT in a patient with a minor head injury) and either published or freely available on the Internet were considered for evaluation.

Outcome measures

Our primary outcome measure was any traumatic finding in the neurocranium at CT, including any skull or skull base fracture and any intracranial traumatic lesion. A traumatic finding at CT that was considered clinically relevant was considered a secondary outcome measure, as was a traumatic CT finding that subsequently led to neurosurgical intervention. A clinically relevant traumatic finding at CT was defined

as any intracranial finding caused by trauma; this included all neurocranial traumatic CT findings (ie, epidural or subdural hematoma, subarachnoid or intraventricular hemorrhage, intraparenchymatous hemorrhagic or nonhemorrhagic contusion, and depressed skull fracture) except isolated linear skull or skull base fractures (3, 16). A neurosurgical intervention was defined as any neurosurgical procedure (craniotomy, intracranial pressure monitoring, elevation of depressed skull fracture, or ventricular drainage) performed within 30 days after the traumatic event.

Statistical analysis

Three authors (M.S., D.W.J.D., M.G.M.H.) working in consensus performed statistical analysis. Missing data were assumed to be missing at random and were imputed on the basis of the available data to avoid bias when data could not be completed by searching patient records (17–21). For categorical data, values that were missing were replaced with the most common value among patients in whom this value was not missing. For continuous data, values that were missing were replaced with the mean value in patients in whom the value was not missing. The percentage of imputed missing data was 3.8% (6425 of 168 593 items), which included items documented as unknown and items that were not documented. Variables that were most frequently imputed were a history of loss of consciousness (18%, 565 of 3181 items) and posttraumatic amnesia (10%, 325 of 3181 items). The reason for imputation for both a history of loss of consciousness and posttraumatic amnesia was that the variables were reported as unknown (15.2% [484 of 3181 items] and 7.2% [230 of 3181 items], respectively) rather than missing (2.5% [81 of 3181 items] and 3.0% [95 of 3181 items], respectively). Owing to the available variable means and consistent with clinical practice, both were imputed as present.

We evaluated the study group for demographic characteristics, mechanism of injury, traumatic findings at CT, and neurosurgical intervention. To validate the guidelines in the study group, we determined the sensitivity and specificity (and their 95% confidence intervals) of all guidelines for each of the outcome measures. A guideline was considered to be positive when a patient fulfilled at least one of the guideline criteria for a CT scan. The sensitivity of each guideline was calculated by dividing the number of patients in whom the outcome measure was present and the guideline was positive by the total number of patients in whom the outcome measure was present. The specificity of each guideline was calculated by dividing the number of patients in whom the outcome measure was absent and the guideline was negative by the total number of patients in whom the outcome measure was absent. We evaluated sensitivity and specificity separately for both the strict criteria (scanning high-risk patients only) and the lenient criteria (scanning both the high- and medium-risk patient groups) of each guideline.

To address the trade-off between sensitivity and specificity for each guideline, we calculated the percentage of patients who needed to undergo CT and the number of patients needed to scan to detect one outcome (ie, the number of patients needed to be scanned to find one patient with a neurocranial traumatic CT finding, a clinically relevant traumatic CT finding, or a CT finding that required neurosurgical intervention). The percentage of patients who needed to undergo CT was calculated by dividing the number of patients in whom the guideline was positive by the total number of patients. The number of patients needed to scan was calculated for each outcome measure. This number was calculated for each of the guidelines by dividing the number of patients in whom the guideline was positive by the number of patients in whom the

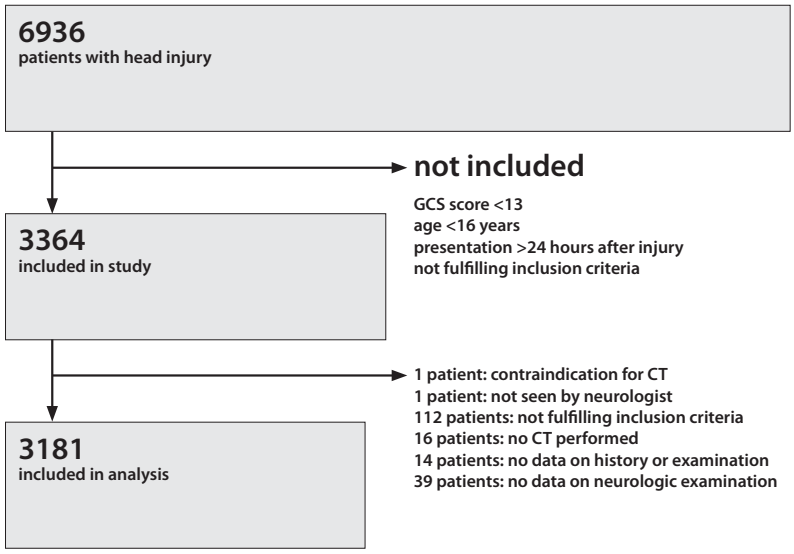

Figure 1. Flowchart of 6936 patients who presented with a head injury. This number is an estimate based on the proportion of patients included in this study from the total number of trauma patients seen by a neurologist or neurologist-in-training in the emergency department of the participating center where the majority of patients were included.

outcome measure was present. Data were analyzed with statistical software (Statistical Package for Social Sciences, version 12.0.1, release 2003; SPSS, Chicago, Ill).

RESULTS

Study group

Data obtained in 3181 patients were analyzed (Figure 1). The majority (n = 2244, 71%) of patients were male, and the mean age was 41.4 years (range, 16–102 years). The median time between injury and presentation to the emergency department was 60 minutes (mean, 94 minutes; range, 0–23.3 hours). At presentation, most patients (n = 2462, 77.4%) had a GCS score of 15; 568 (17.9%) had a GCS score of 14, and 151 (4.7%) had a GCS score of 13.

Neurocranial traumatic lesions were seen at CT in 312 (9.8%) patients (Table 2), with the highest proportion of traumatic findings seen in patients with a GCS score of 13 (37 patients [24.5%]). Neurosurgical intervention was performed in 17 patients (0.5%) for epidural hematoma (n = 8),

Table 2. Traumatic findings at CT

Traumatic findings at CT	No. of patients (n = 312)
Skull fracture	186 (59.6)
Intraparenchymal lesions	142 (45.5)
Traumatic subarachnoid hemorrhage	86 (27.6)
Subdural hematoma	67 (21.5)
Epidural hematoma	35 (11.2)
Intraventricular hemorrhage	5 (1.6)
Intracranial lesions	233 (74.7)

Note – Multiple findings may be present within one patient. Data in parantheses are percentages.

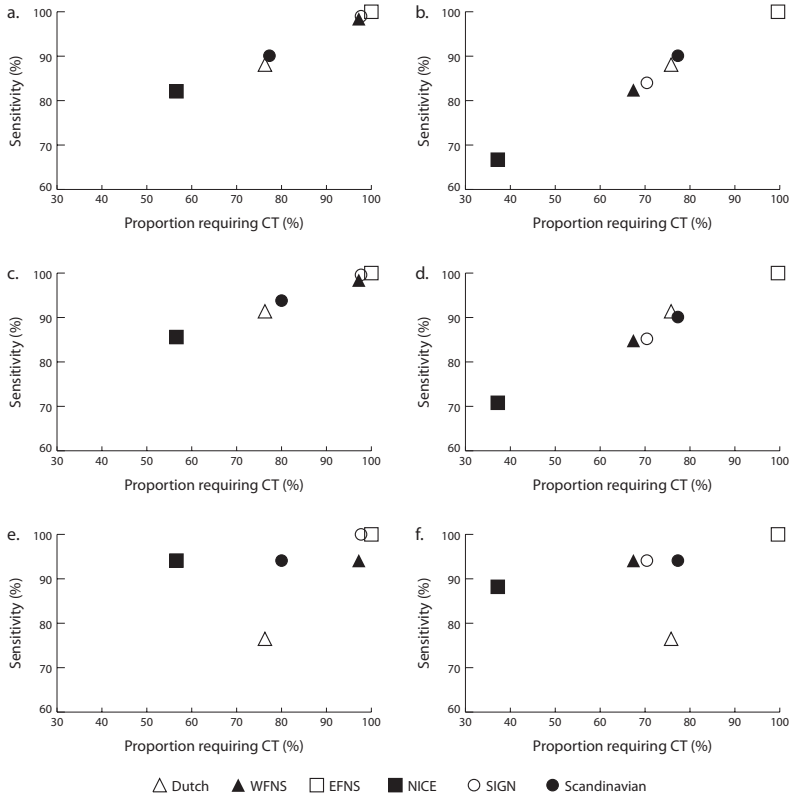

Figure 2. Graphs show the relationship between the proportion of patients in whom CT is required according to each guideline and the sensitivity for (a, b) neurocranial traumatic CT findings, (c, d) clinically relevant traumatic CT findings, and (e, f) neurosurgical intervention for each guideline using lenient (a, c, e) and strict (b, d, f) criteria.

subdural hematoma (n = 3), depressed skull fracture (n = 3), and a combination of extra-axial hematoma and depressed skull fracture (n = 3) (Table 2). In the majority of patients, more than one risk factor was present (Table 3).

Guideline selection

Three national and three international guidelines were identified (Table E1) (14, 22–26). The criteria for the use of CT set forth by the Scottish Intercollegiate Guidelines Network (SIGN) are currently under revision and may be updated in the future; we used the version posted on their Web site at the time of our search (25). The following three guidelines were based on a previously published decision algorithm: the Dutch guidelines on the New Orleans criteria, the criteria proposed by the National Institute for Clinical Excellence (NICE) on the Canadian CT head rule, and the guidelines proposed

Table 3. Presence of risk factors in the entire study group and in patients with a GCS score of 15 at presentation

Risk factor	Entire study group (n = 3181)	Only patients with a GCS score of 15 (n = 2462)
Older than 60 years	534 (16.8)	394 (16.0)
Anticoagulant treatment	218 (6.9)	171 (6.9)
High-energy accident	1457 (45.8)	1113 (45.2)
Dangerous mechanism of injury*	679 (21.3)	506 (20.6)
Loss of consciousness	1951 (61.3)	1419 (57.6)
Headache	1910 (60.0)	1454 (59.1)
PTA lasting longer than 30 minutes	916 (28.8)	510 (20.7)
Vomiting	342 (10.8)	213 (8.6)
Short-term memory deficit	475 (14.9)	195 (7.9)
Posttraumatic seizure	23 (0.7)	16 (0.6)
External injury above clavicles	2612 (82.1)	2008 (81.6)
Clinical signs of skull fracture	66 (2.1)	42 (1.7)
Clinical evidence of intoxication	1367 (43.0)	960 (39.0)
GCS score less than 15 1 hour after presentation	506 (15.9)	50 (2.0)
Neurologic deficit	304 (9.6)	207 (8.4)
More than one risk factor present	3101 (97.5)	2382 (96.8)

Note – Data are number of patients. Data in parentheses are percentages. Multiple risk factors may be present in one patient.
* Dangerous mechanism of injury was defined as pedestrian hit by motor vehicle, passenger or driver ejected from motor vehicle, or fall from a height of more than 1 m or down five stairs. PTA = posttraumatic amnesia.

by the European Federation of Neurological Societies (EFNS) on both the New Orleans criteria and the Canadian CT head rule (3, 7).

Guideline validation

Sensitivity of 100% for both neurocranial and clinically relevant traumatic CT findings, as well as for neurosurgical intervention, was reached with only the EFNS guidelines when either the lenient or the strict criteria were used (Tables E2, E3). According to these guidelines, however, all of the patients with minor head injury included in our study would need to undergo CT (Figure 2; Tables E2, E3). The lowest sensitivity (76.5%) for identifying patients who underwent neurosurgical intervention was reached with the Dutch guidelines and use of either the lenient or the strict criteria. The highest specificities were achieved with the NICE criteria, which, consequently, indicated that only a relatively small percentage (37.2%–56.6%) of all patients with a minor head injury would need to undergo CT (Figure 2; Tables E2, E3).

One patient who required neurosurgical intervention for a subdural hematoma was missed with use of the guidelines proposed by the World Federation of Neurosurgical Societies (WFNS), the NICE criteria, and the SIGN and Scandinavian and Dutch guidelines. This patient did not have a history of loss of consciousness or any other risk factors except for a contusion to the face. Three more patients who required neurosurgical intervention were missed with the Dutch guidelines. All of these patients had several risk factors, including neurologic deficit and clinical evidence of a skull fracture, but no history of loss of consciousness or posttraumatic amnesia.

As expected, the sensitivities for neurocranial and clinically relevant

Table E2. Performance of guidelines and percentage of patients requiring CT on the basis of strict criteria

Guidelines	CT+		CT-		% Sensitivity (95% CI)	% Specificity (95% CI)	% requiring CT (95% CI)
	GL+	GL-	GL+	GL-			
Dutch							75.8 (74.3-77.3)
Neurocranial	275	37	2136	733	88.1 (84.1-91.3)	25.5 (23.2-28.0)	
Clinically relevant	222	21	2189	749	91.4 (87.2-94.3)	25.5 (23.1-27.9)	
Neurosurgical	13	4	2398	766	76.5 (52.7-90.4)	24.2 (22.0-26.5)	
WFNS							67.4 (65.8-69.0)
Neurocranial	257	55	1888	981	82.4 (77.8-86.2)	34.2 (31.6-36.8)	
Clinically relevant	206	37	1939	999	84.8 (79.7-88.7)	34.0 (31.5-36.6)	
Neurosurgical	16	1	2129	1035	94.1 (73.0-99.0)	32.7 (30.3-35.2)	
EFNS							99.6 (99.3-99.7)
Neurocranial	312	0	2855	14	100.0 (98.8-100.0)	0.5 (0.0-2.4)	
Clinically relevant	243	0	2924	14	100.0 (98.4-100.0)	0.5 (0.0-2.4)	
Neurosurgical	17	0	3150	14	100.0 (81.6-100.0)	0.4 (0.0-2.3)	
NICE							37.2 (35.5-38.9)
Neurocranial	208	104	974	1895	66.7 (61.3-71.7)	66.1 (62.9-69.2)	
Clinically relevant	172	71	1010	1928	70.8 (64.8-76.1)	65.6 (62.5-68.7)	
Neurosurgical	15	2	1167	1997	88.2 (65.7-96.7)	63.1 (60.1-66.1)	
SIGN							70.4 (68.8-72.0)
Neurocranial	262	50	1978	891	84.0 (79.5-87.6)	31.1 (28.5-33.6)	
Clinically relevant	207	36	2033	905	85.2 (80.2-89.1)	30.8 (28.3-33.3)	
Neurosurgical	16	1	2224	940	94.1 (73.0-99.0)	29.7 (27.3-32.1)	
Scandinavian							77.6 (76.1-79.0)
Neurocranial	281	31	2186	683	90.1 (86.2-92.9)	23.8 (21.4-26.2)	
Clinically relevant	219	24	2248	690	90.1 (85.7-93.3)	23.5 (21.2-25.9)	
Neurosurgical	16	1	2451	713	94.1 (73.0-99.0)	22.5 (20.3-24.8)	

Note – Strict criteria were used to identify patients with neurocranial traumatic findings at CT, clinically relevant traumatic findings at CT, and findings at CT for which neurosurgical intervention was performed. CT+ indicates a lesion was present; CT– indicates a lesion was absent. The guideline was considered positive (GL+) when at least one of its criteria was present; the guideline was considered negative (GL–) when all of its criteria were absent. Sensitivity was calculated by dividing the number of CT+ patients who were also GL+ by the total number of CT+ patients and multiplying by 100. Specificity was calculated by dividing the number of CT– patients who were also GL– by the total number of CT– patients and multiplying by 100. The percentage of patients requiring CT was calculated by dividing the total number of CT+ and CT– patients who were also GL+ by the total number of patients in the study (n = 3181) and multiplying by 100. CI = confidence interval.

traumatic findings were generally lower when we used the strict criteria rather than the lenient criteria (WFNS guidelines, NICE criteria, SIGN guidelines, and Scandinavian guidelines) (Tables E2, E3). The sensitivities for neurosurgical interventions were the same with use of the strict and lenient criteria for all of the guidelines, except the SIGN and NICE criteria, that showed a decrease in sensitivity (ie, one additional patient who required neurosurgical intervention would have been missed with use of strict instead of lenient criteria) (Tables E2, E3).

Trade-off between sensitivity and specificity

The more restrictive guidelines require scanning only a limited number of patients with a minor head injury; however, the use of these guidelines invariably leads to lower sensitivities than does the use of guidelines

Table E3. Performance of guidelines and percentage of patients requiring CT on the basis of lenient criteria

Guidelines	CT+		CT-		% Sensitivity (95% CI)	% Specificity (95% CI)	% requiring CT (95% CI)
	GL+	GL-	GL+	GL-			
Dutch							76.3 (74.8-77.7)
Neurocranial	275	37	2152	717	88.1 (84.1-91.3)	25.0 (22.6-27.4)	
Clinically relevant	222	21	2205	733	91.4 (87.2-94.3)	24.9 (22.6-27.4)	
Neurosurgical	13	4	2414	750	76.5 (52.7-90.4)	23.7 (21.5-26.0)	
WFNS							97.2 (96.6-97.7)
Neurocranial	307	5	2786	83	98.4 (96.3-99.3)	2.9 (1.0-4.9)	
Clinically relevant	239	4	2854	84	98.4 (95.8-99.4)	2.9 (1.0-4.8)	
Neurosurgical	16	1	3077	87	94.1 (73.0-99.0)	2.7 (1.0-4.6)	
EFNS							100.0 (99.9-100.0)
Neurocranial	312	0	2869	0	100.0 (98.8-100.0)	0.0 (0.0-1.9)	
Clinically relevant	243	0	2938	0	100.0 (98.4-100.0)	0.0 (0.0-1.9)	
Neurosurgical	17	0	3164	0	100.0 (81.6-100.0)	0.0 (0.0-1.8)	
NICE							56.6 (54.9-58.3)
Neurocranial	256	56	1545	1324	82.1 (77.4-85.9)	46.1 (43.3-49.0)	
Clinically relevant	208	35	1593	1345	85.6 (80.6-89.5)	45.8 (43.0-48.6)	
Neurosurgical	16	1	1785	1379	94.1 (73.0-99.0)	43.6 (40.9-46.2)	
SIGN							97.7 (97.1-98.2)
Neurocranial	309	3	2799	70	99.0 (97.2-99.7)	2.4 (0.6-4.4)	
Clinically relevant	242	1	2866	72	99.6 (97.7-99.9)	2.5 (0.6-4.4)	
Neurosurgical	17	0	3091	73	100.0 (81.6-100.0)	2.3 (0.6-4.2)	
Scandinavian							80.2 (78.8-81.5)
Neurocranial	291	21	2260	609	93.3 (89.9-95.6)	21.2 (18.9-23.6)	
Clinically relevant	228	15	2323	615	93.8 (90.1-96.2)	20.9 (18.7-23.3)	
Neurosurgical	16	1	2535	629	94.1 (73.0-99.0)	19.9 (17.7-22.1)	

Note – Lenient criteria were used to identify patients with neurocranial traumatic findings at CT, clinically relevant traumatic findings at CT, and findings at CT for which neurosurgical intervention was performed. CT+ indicates a lesion was present, CT– indicates a lesion was absent. The guideline was considered positive (GL+) when at least one of its criteria was present; the guideline was considered negative (GL–) when all of its criteria were absent. Sensitivity was calculated by dividing the number of CT+ patients who were also GL+ by the total number of CT+ patients and multiplying by 100. Specificity was calculated by dividing the number of CT– patients who were also GL– by the total number of CT– patients and multiplying by 100. The percentage of patients requiring CT was calculated by dividing the total number of CT+ and CT– patients who were also GL+ by the total number of patients in the study (n = 3181) and multiplying by 100. CI = confidence interval.

that recommend that a large number of patients undergo scanning (Figure 2). This trade-off between sensitivity and the number of patients who need to undergo CT was consistent across outcome measures. The number of patients needed to undergo scanning was highest when the EFNS guidelines were followed; with the NICE criteria, the number of patients needed to undergo scanning to detect one patient with a lesion requiring neurosurgical intervention was lowest (79 and 113 patients for strict and lenient criteria, respectively) (Table E4).

DISCUSSION

In our study, only the EFNS guidelines reached 100% sensitivity for the identification of patients with either neurocranial or clinically relevant traumatic findings at

Table E4. Number of patients needed to scan to detect one patient with neurocranial traumatic findings at CT, clinically relevant traumatic findings at CT, or findings at CT that required neurosurgical intervention

Guidelines	Total no. of patients scanned	Neurocranial traumatic CT findings		Clinically relevant traumatic CT findings		Neurosurgical interventions	
		No.	NNS	No.	NNS	No.	NNS
Lenient criteria							
Dutch	2427	275	9	222	11	13	187
WFNS	3093	307	10	239	13	16	193
EFNS	3181	312	10	243	13	17	187
NICE	1801	256	7	208	9	16	113
SIGN	3108	309	10	242	13	17	183
Scandinavian	2551	291	9	228	11	16	159
Strict criteria							
Dutch	2411	275	9	222	11	13	185
WFNS	2145	257	8	206	10	16	134
EFNS	3167	312	10	243	13	17	186
NICE	1182	208	6	172	7	15	79
SIGN	2240	262	9	207	11	16	140
Scandinavian	2467	281	9	219	11	16	154

Note – NNS = No. of patients needed to scan to find one patient with those findings. This number is calculated by dividing the total number of CT scans performed according to the guideline by the total number of patients with each of the outcome measures.

CT and patients needing neurosurgical intervention. Unfortunately, specificity for these guidelines was low. Guidelines with higher specificities, however, showed lower sensitivities for traumatic findings at CT and for neurosurgical intervention. A sensitivity of 100% may not be required for any neurocranial traumatic CT finding, but it is essential for lesions that require neurosurgical intervention. Only the guidelines proposed by the EFNS and the lenient SIGN criteria reached 100% sensitivity for neurosurgical intervention. Guidelines with the worst performance were the Dutch national guidelines; with use of these guidelines, almost 25% (n = 4) of patients requiring neurosurgery would have been missed.

The low sensitivity of the Dutch guidelines for neurosurgical intervention in our study may be explained by the fact that these guidelines are not clear on whether CT is recommended in patients with a normal level of consciousness and without a history of loss of consciousness or posttraumatic amnesia who have another risk factor, such as vomiting or focal neurologic deficit. If the Dutch guidelines are applied strictly, as they were in our study, these patients are classified as having a minimal head injury and may be sent home without any imaging or observation. Three of the patients that underwent neurosurgery would have been missed this way. This explains the low sensitivity of the Dutch guidelines in our study.

In each of the evaluated guidelines, there is the option of scanning all patients at risk of developing complications (lenient criteria) or scanning only high-risk patients (strict criteria). The strict criteria of the guidelines therefore are expected to enable all high-risk patients (ie, those with CT findings that require neurosurgical intervention) to be identified, while patients with other traumatic findings at CT may be missed. For all but the NICE and SIGN criteria, there was indeed no difference in sensitivity for neurosurgical intervention between the strict

and lenient criteria.

Our results largely corroborate findings of the validation study conducted by Ibanez et al (16). In their smaller single-center study, 100% sensitivity for clinically relevant findings at CT was reached with both the WFNS and the EFNS guidelines. Specificities were also low. However, neurosurgical intervention was not considered an outcome measure; therefore, the guidelines were not validated for identification of these high-risk patients. Both the NICE criteria and the WFNS guidelines have also been previously evaluated in a large single-center validation study (5, 27). In their study, Fabbri et al (5, 27) did not strictly adhere to the guidelines and not all patients underwent CT; these conditions may have undermined the validity of their study. Sensitivity for intracranial CT findings and neurosurgical intervention was high (but not 100%) for the WFNS guidelines and the NICE criteria. The NICE criteria reached a slightly lower sensitivity for both outcome measures; however, in line with our findings, these criteria had much higher specificities than the WFNS guidelines.

In all of the guidelines, a similar trade-off was seen between sensitivity and specificity. There was also a corresponding trade-off between sensitivity and the proportion of patients in whom CT was indicated according to each of the guidelines. The EFNS guidelines had the highest sensitivities, lowest specificities, and highest proportion of patients who required CT, whereas the NICE criteria had the highest specificities and the lowest proportion of patients who required CT but at the cost of lower sensitivities. Overall, this trade-off was consistent across outcome measures and was reflected in the number of CT scans needed to detect any of the outcomes, which was highest for the EFNS guidelines and lowest for the NICE criteria. Thus, none of the guidelines was obviously superior to any of the others.

The question is, what do we need to aim for? It is desirable for a guideline to enable the identification of all patients with CT findings who require neurosurgical intervention. The importance of identifying other traumatic lesions at CT, however, depends on the effect of management decisions on the patient's clinical outcome. CT scanning is the only reliable way to rule out serious intracranial complications, while observation performs badly as a diagnostic tool and may lead to a less-than-optimal outcome since intervention subsequent to deterioration is delayed (28, 29). CT findings generally affect clinical management (eg, the decision between discharge or clinical observation); however, since a patient's condition only occasionally deteriorates during observation, it is difficult – if not impossible – to assess whether observation, and therefore CT scanning, really affected the patient's clinical outcome. This would imply that a sensitivity of 100% for traumatic findings at CT may not be necessary, but then the question of what sensitivity would be desirable would remain. The number of patients needed to scan to detect one outcome may be used as a first approximation of the trade-off between sensitivity and specificity, and it is useful in the identification of poorly performing guidelines. One way to further deal with this dilemma is to perform a cost-effectiveness analysis (30). A cost-effectiveness analysis will enable one to take into account the effect of the guidelines' sensitivities and specificities and their influence on patient care, offering a combined measure of a guideline's validity and utility. We intend to perform this analysis for each of the evaluated guidelines in a follow-up study to determine whether any guideline is superior in terms of both cost and effectiveness.

Our study had a number of limitations. First, our inclusion criteria coincided with the criteria proposed in the EFNS guidelines. This is evident from the extremely low specificity we found. A further limitation of

our study was that some of the criteria from the guidelines were not exactly the same as the data we collected in our study; however, this was inherent to the observational nature of our study. The risk factor of high-energy accident was not separately defined, and we determined its presence by using the description of trauma mechanism. Since we then defined high-energy accident to include various broad categories, this lack of specification probably did not have a large effect on the sensitivities of the guidelines, but it may have had some negative influence on the reported specificities. Previous neurosurgery and shunt placement were not formally recorded, nor was altered behavior; therefore, these risk factors could not be used as criteria for one of the guidelines. The same was true for pretraumatic seizure, although this risk factor was again derived from the trauma mechanism description. Furthermore, only the presence and duration of posttraumatic amnesia (but not retrograde amnesia) were assessed at the participating centers. We find that retrograde amnesia is difficult to assess clinically; therefore, it is not a reliable parameter in daily clinical practice, as opposed to posttraumatic amnesia, which is easier to evaluate. Thus, in the evaluation of guidelines that propose retrograde amnesia as a risk factor, we used posttraumatic amnesia as a risk factor instead. Since the relative risks of retrograde and posttraumatic amnesia have been shown to be similar, it does not seem likely that this had a substantial influence on our results (3, 31).

Another limitation is that we validated only those guidelines that were published in English (because they are widely accessible) or Dutch (because our study was performed in the Netherlands). A final limitation of our study is the theoretical possibility that we may have missed patients with clinically important traumatic CT findings or who required neurosurgical intervention who were not (initially) referred to a neurologist and consequently did not undergo CT scanning. Although we acknowledge this possibility, we believe this is unlikely to have happened in many cases because the centers that participated in this study were primary regional trauma and neurosurgical centers in which a neurologist or neurologist-in-training was always present and the threshold for referral was low. To our knowledge, only one of more than 3000 patients in our study group had not been seen by a neurologist. Consequently, this patient was not included in the data analysis.

In conclusion, all of the validated guidelines show a trade-off between sensitivity and specificity and a corresponding trade-off between sensitivity and the proportion of patients who require CT scanning according to the guideline in the identification of patients with traumatic findings at CT, as well as in the identification of patients who require neurosurgical intervention for a complication after a minor head injury. The choice of which guideline to use will depend largely on the objective of implementing a guideline. If the objective is to not miss any patients with a traumatic finding at CT, basically all patients with minor head injury will need to undergo CT, as recommended in the EFNS guidelines. If, however, the objective is to reduce the number of CT scans performed to evaluate minor head injuries (eg, to reduce workload or because of limited availability) and one is willing to accept the risk of misdiagnosing the occasional patient who presents with minor symptoms, the NICE criteria have a high potential to reduce the number of CT scans performed while still having a reasonable sensitivity for the identification of patients with traumatic brain injury and those who require neurosurgical intervention. The final choice of a guideline and its implementation depend on the objective and on cost and effectiveness considerations of the consequences of implementation.

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A history of loss of consciousness or posttraumatic amnesia in minor head injury: 'conditio sine qua non' or one of the risk factors?

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Objective A history of loss of consciousness (LOC) or posttraumatic amnesia (PTA) is commonly considered a prerequisite for minor head injury (MHI), although neurocranial complications also occur when LOC or PTA are absent, particularly in the presence of other risk factors. The purpose of this study was to evaluate whether known risk factors for complications after MHI in the absence of LOC or PTA have the same predictive value as when LOC or PTA are present.

Methods A prospective multicentre study was performed in four university hospitals between February 2002 and August 2004 of consecutive blunt head injury patients (>16 years) presenting with a normal level of consciousness and a risk factor. Outcome measures were any neurocranial traumatic CT finding and neurosurgical intervention. Common odds ratios (OR) were estimated for each of the risk factors and tested for homogeneity.

Results 2462 patients were included: 1708 with and 754 without LOC/PTA. Neurocranial traumatic findings on CT were present in 7.5% and were more common when LOC or PTA was present (8.7%). Neurosurgical intervention was required in 0.4%, irrespective of the presence of LOC or PTA. ORs were comparable across the two subgroups ($p > 0.05$), except for clinical evidence of a skull fracture, with high ORs both when LOC or PTA was present (OR = 37; 95% CI, 17 to 80) or absent (OR = 6.9; 95% CI, 1.8 to 27). LOC and PTA had significant ORs of 1.9 (95% CI, 1.0 to 2.7) and 1.7 (95% CI, 1.3 to 2.3), respectively.

Conclusion Known risk factors have comparable ORs in MHI patients with or without LOC or PTA. MHI patients without LOC or PTA need to be explicitly considered in clinical guidelines.

HEAD INJURY is one of the most common injuries seen in emergency departments, minor head injury (MHI) accounting for 90%–95% of cases (1, 2). In a minority of patients, MHI is associated with neurocranial complications (6%–20%). Neurosurgical intervention is rarely required (0.2%–3.1%) and mortality is low (0.04%–0.29%) (1, 3–11). Definitions of MHI vary considerably, most commonly constituting blunt injury to the head and a normal to minimally altered level of consciousness on presentation (Glasgow Coma Scale [GCS] score = 13–15) (2, 13). Loss of consciousness (LOC) and/or posttraumatic amnesia (PTA) are short, with a maximum duration of 15 and 60 min, respectively. Traditionally, a history of LOC or PTA is considered a 'conditio sine qua non' for MHI (14, 15). The risk of neurocranial complications after head injury in patients presenting with a normal level of consciousness, no history of LOC and no PTA (ie, MHI without LOC or PTA) is estimated to be approximately a quarter of the risk in patients with (a history of) an altered level of consciousness or PTA (ie, MHI with LOC or PTA) (2, 16). Consequently, MHI patients without LOC or PTA are commonly discharged without any imaging, observation or clinical evaluation by a neurologist. (7, 18).

While this approach is probably justified for most MHI patients without LOC or PTA, some may have risk factors other than an altered level of consciousness, history of LOC or PTA that may increase their risk of neurocranial complications (16, 19, 20). In MHI patients with LOC or PTA, risk factors for neurocranial complications have been well established, and these are commonly used as an indication for performing a head CT (8, 14, 21, 22). Arguably, these risk factors may also indicate the need for head CT in MHI patients without LOC or PTA, as is indeed recommended in some clinical guidelines for the use of CT in head injury (1, 14, 23, 24). However, since in MHI patients without LOC or PTA the prior probability of neurocranial complications is lower than in MHI patients with LOC or PTA, this approach may not be optimal. Also, the predictive values of risk factors derived from study populations of MHI patients with LOC or PTA may be biased by the presence of a history of LOC and/or PTA. Using the same risk factors for both MHI patient groups, irrespective of a history of LOC or PTA, as indications for CT may therefore lead to unnecessary CT scanning. On the other hand, CT scanning may be indicated in a selected group of MHI patients without LOC or PTA who are at increased risk of neurocranial complications, to reach a rapid and reliable diagnosis.

The purpose of the present study was to evaluate whether known risk factors for neurocranial complications after MHI with LOC or PTA have the same predictive value after MHI without LOC or PTA.

PATIENTS AND METHODS

Study population

Data were collected in four Dutch university hospitals on 3364 consecutively included patients (Figure 1). Patients were included if they presented within 24 h after blunt head injury, were aged 16 years or older, had a GCS score of 13 or 14 on presentation to the emergency department or had a GCS score of 15 with at least one of the following risk factors: history of LOC, short-term memory deficit, amnesia for the traumatic event, posttraumatic seizure, vomiting, headache, clinical evidence of intoxication with alcohol or drugs, anticoagulant treatment or history of coagulopathy, external evidence of injury above the clavicles, or neurological deficit. Patients were excluded if there were contraindications for CT scanning or if CT

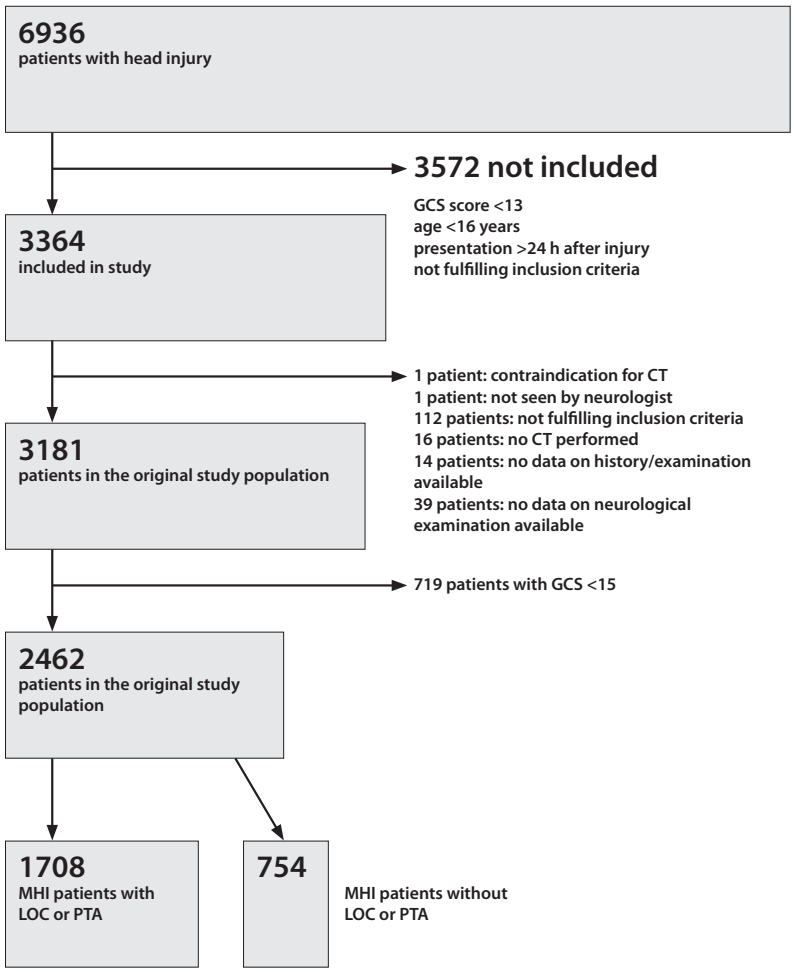

Figure 1. Flowchart of the study population. The number of patients presenting with head injury (6936) is an estimate based on the proportion of patients included out of the total number of trauma patients seen by a neurologist(-in-training) in the emergency department of the participating centre that included the majority of patients.

of the head could not be performed because of concurrent injuries.

For the present study, patients with a GCS score of 15 on presentation were selected from the total study population. This study population was further divided into two groups: patients without a history of LOC or PTA (MHI without LOC or PTA) and those with a history of LOC or PTA (MHI with LOC or PTA). Patient informed consent was

waived by the Institutional Review Board and Medical Ethical Committee, after review of the study protocol, as patients meeting our inclusion criteria routinely undergo a head CT according to most local hospital policies and the EFNS guidelines (1).

Patient assessment

All included patients were examined by a neurologist or by a neurologist-in-training under the supervision of a neurologist, after which all patients underwent a head CT, according to a routine trauma protocol. This consisted of a maximum slice thickness of 5 mm infra- and 8 mm supratentorially, without intravenous contrast administration. All scans were evaluated by a neuroradiologist or a trauma radiologist in bone and brain window settings. Data were collected on patient demographics, history of injury, presence of risk factors, GCS scores on and 1 h after presentation to the emergency department, as well as on CT findings.

Risk factor selection

Selection of risk factors was based on two published prediction rules for the use of CT in MHI, namely the New Orleans Criteria and the Canadian CT Head Rule (CCHR) (8, 9). These were age, headache, vomiting, intoxication, persistent anterograde amnesia, PTA, injury above the clavicles (including clinical signs of skull or basal skull fracture), GCS <15 at 2 h post-injury and dangerous trauma mechanism (pedestrian versus motor vehicle, fall from height, ejected from motor vehicle). Additional risk factors commonly used in clinical guidelines for the management of MHI were also assessed (1, 14, 17, 18, 23–25).

Definitions

A history of LOC was considered to be present when reported by a witness or by the patient. Amnesia for the traumatic event and PTA were defined as the inability to recall the traumatic event and subsequent events; its duration (in min) was estimated by the treating physician. Persistent anterograde amnesia was defined as the patient's inability to capture and retain any new information in memory. Posttraumatic seizure was classified as either a witnessed or suspected seizure having occurred after the head injury. Vomiting constituted any episode of emesis after the injury. Headache included both diffuse and localised pain. Presence and severity of intoxication with alcohol or drugs were evaluated clinically, evidenced by slurred speech, alcoholic foetor or nystagmus. Anticoagulant treatment included coumarine derivatives only and not platelet aggregation inhibitors (eg, aspirin, clopidrogel); no blood coagulation tests were performed and the presence of coagulopathy was assessed by patient history. External evidence of injury consisted of extensive bruising or clinically significant discontinuity of skin; injury suspect of a fracture was classified as clinical signs of skull or facial fracture, whereas other injuries such as contusions, lacerations or abrasions were classified as skull or facial contusion. Focal neurological deficit was defined as any abnormality on routine clinical neurological examination indicating a focal cerebral lesion. High energy accident was derived from the description of the trauma mechanism and defined as: a fall from height (>1 m or >5 stairs), pedestrian or cyclist versus vehicle, ejected from vehicle, any motorised vehicle accident or high velocity cycling accident. Pretraumatic seizure was also derived from the description of the trauma mechanism.

Outcome measures

Our primary outcome measure was any traumatic finding of the neurocranium on CT. A traumatic finding on CT that was considered clinically relevant was a secondary outcome measure, as was a traumatic CT finding that subsequently led to neurosurgical

intervention. A clinically relevant finding on CT was defined as any intracranial finding due to trauma, including depressed skull fracture (ie, any neurocranial traumatic finding on CT except for an isolated linear skull fracture) (9, 26). A neurosurgical intervention was defined as any neurosurgical procedure (craniotomy, intracranial pressure monitoring, elevation of depressed skull fracture, ventricular drainage) within 30 days after the traumatic event.

Data analysis

Missing patient data included in the analysis were assumed to be missing at random and imputed based on the available data means to avoid bias (27). The proportion of imputed missing data was 3.6%, which included both items documented as unknown and items that were not documented.

We evaluated our patient population for demographic characteristics, mechanism of injury, traumatic findings on CT and for neurosurgical intervention. Differences between the two subgroups (MHI with versus MHI without LOC or PTA) were tested for significance using an independent sample t test for continuous variables and the Pearson's χ^2 test for nominal variables. A p value <0.05 was considered statistically significant.

To assess the association of each of the risk factors with the primary outcome measure, a common odds ratio (OR) was estimated using the stratified Mantel-Haenszel statistic for categorical variables and univariable logistic regression analysis for continuous variables. Homogeneity of the OR across the two subgroups was assessed with the Breslow-Day statistic (p <0.05 considered as an

Table 1. Demographic characteristics and neurocranial traumatic CT findings

	MHI with LOC or PTA (n = 1708), n (%)	MHI without LOC or PTA (n = 754), n (%)	P value
Demographics			
Age in years, mean (range)	40.2 (16.0-94.2)	42.2 (16.2-102)	0.020
Male gender	1160 (67.9)	531 (70.4)	0.117
Traumatic CT findings	148 (8.67)	37 (4.91)	0.001
Skull fracture	82 (4.80)	28 (3.71)	0.229
Skull base fracture	37 (2.17)	8 (1.06)	0.059
Depressed skull fracture	7 (0.41)	4 (0.53)	0.679
Linear skull fracture	49 (2.87)	15 (1.99)	0.206
Subdural effusion	1 (0.06)	1 (0.13)	0.552
Subdural haematoma	29 (1.70)	8 (1.06)	0.231
Epidural haematoma	15 (0.88)	2 (0.27)	0.090
Traumatic subarachnoid haemorrhage	38 (2.22)	7 (0.93)	0.027
Intraparenchymal contusion	65 (3.81)	8 (1.06)	0.000
Haemorrhagic	51 (2.99)	7 (0.93)	0.002
Nonhaemorrhagic	7 (0.41)	1 (0.13)	0.265
Diffuse axonal injury*	7 (0.41)	0 (0.00)	0.078
Intraventricular haemorrhage	3 (0.18)	0 (0.00)	0.250
Neurosurgical intervention	6 (0.35)	4 (0.53)	0.519
Intracranial CT findings only	114 (6.67)	21 (2.79)	0.000

LOC, loss of consciousness; MHI, minor head injury; PTA, posttraumatic amnesia.
Multiple findings may be present in one patient. P values were calculated with the independent sample t test for continuous variables and Pearson's χ^2 test for nominal variables.
* Diffuse axonal injury was defined as multiple, small, focal traumatic lesions in the typical locations of shearing injury (lobar white matter at the grey–white matter junction, corpus callosum, brainstem).

Table 2. Indications for neurosurgical intervention

	MHI with LOC or PTA (n = 6), n (%)	MHI without LOC or PTA (n = 4), n (%)
Isolated depressed skull fracture	-	1 (25)
Epidural hematoma	4 (67)	1 (25)
Isolated	1 (17)	1 (25)
In combination with subdural hematoma	1 (17)	-
In combination with depressed skull fracture	2 (33)	-
Subdural hematoma	3 (50)	2 (50)
Isolated	1 (17)	2 (50)
In combination with epidural hematoma	1 (17)	-
In combination with depressed skull fracture	1 (17)	-

LOC, loss of consciousness; MHI, minor head injury; PTA. posttraumatic amnesia.

indication of heterogeneity) for categorical variables (28). For continuous variables, the crude OR, as estimated with univariable logistic regression analysis, was compared with the OR adjusted for the presence of LOC or PTA. A difference of >10% between the crude and adjusted ORs was considered an indication of heterogeneity (29).

Data were analysed using SPSS v12.0 software.

RESULTS

Between 11 February 2002 and 31 August 2004, an estimated 6936 patients presented with head injury to the emergency departments of the participating centres. A total of 3572 patients were not included because they did not meet the inclusion criteria of our study. Of the 3364 patients originally included in the study, 183 were excluded from further analysis for various reasons (Figure 1). A further 719 patients presented with a GCS score of 13 or 14, leaving 2462 patients to be included in the analysis (Figure 1). These included 1708 MHI patients with LOC or PTA, and 754 MHI patients without LOC or PTA. Patient characteristics are summarised in Table 1.

Mean patient age was 40.8 years, MHI patients with LOC or PTA being slightly younger (40.2 years) than MHI patients without LOC or PTA (42.2 years; p = 0.02). Patients presented to the emergency department at an average of 97 min after the injury. The duration between the time of injury and presentation to the emergency department was not different for the two subgroups (99 min for MHI patients with versus 93 min for MHI patients without LOC or PTA, respectively; p = 0.42). The majority of patients were male (68.7%), which was not different between the two subgroups (67.9% of MHI patients with and 70.4% of MHI patients without LOC or PTA; p = 0.22) (Table 1).

Neurocranial traumatic findings on CT were present in 185 patients (7.5%) and were more common in MHI patients with than in MHI patients without LOC or PTA (148 patients (8.7%) versus 37 patients (4.9%); p = 0.001). Neurosurgical intervention was required in 10 patients (0.4%) and was just as frequently needed in MHI patients with as in MHI patients without LOC or PTA (six patients [0.4%] and four patients [0.5%], respectively; p = 0.52) (Table 1).

Indications for neurosurgery included isolated depressed skull fracture (n = 1), epidural haematoma (n = 4), subdural haematoma (n = 4) and a combination of epidural and subdural haematoma (n = 1) (Table 2).

Table 3. Univariable analysis of common risk factors for neurocranial traumatic findings on CT

Variable	MHI with LOC or PTA n (%)	MHI without LOC or PTA, n (%)	OR (95% CI)	P value	P value for heterogeneity
Trauma mechanism					
Pedestrian/cyclist versus vehicle	196 (11)	67 (8.9)	2.3 (1.6-3.4)	0.000	0.215
Fall from (some) height*	442 (26)	147 (19)	1.7 (1.2-2.3)	0.002	0.877
Ejected from vehicle	34 (2.0)	17 (2.3)	1.7 (0.7-4.0)	0.234	0.717
Symptoms					
Persistent anterograde amnesia†	174 (10)	21 (2.8)	1.1 (0.6-1.8)	0.806	0.257
Vomiting	166 (10)	65 (8.6)	2.5 (1.6-3.6)	0.000	0.844
PTA, average duration (min)	18.3	0.0	1.7 (1.3-2.3)‡	0.000	n/a
Loss of consciousness	1419 (83)	0 (0.0)	1.9 (1.3-2.6)	0.000	n/a
Headache					
Diffuse	719 (42)	286 (38)	1.1 (0.8-1.5)	0.467	0.447
Localised	275 (16)	160 (21)	1.3 (0.9-1.9)	0.199	0.107
Post-traumatic seizure	13 (0.8)	3 (0.8)	2.7 (0.8-9.8)	0.122	0.487
External evidence of injury					
Signs of skull fracture	35 (2.0)	12 (1.6)	25 (13-47)	0.000	0.028
Contusion of the skull	591 (35)	329 (44)	2.1 (1.6-2.9)	0.000	0.063
Signs of facial fracture	120 (7.0)	68 (9.0)	2.0 (1.3-3.2)	0.003	0.253
Contusion of face	874 (51)	400 (53)	1.0 (0.8-1.4)	0.922	0.638
Multiple injuries	373 (22)	173 (23)	1.8 (1.3-2.5)	0.000	0.814
Neurological examination					
Neurological deficit	146 (8.5)	61 (8.1)	1.8 (1.1-2.8)	0.011	0.230
GCS score deterioration at 1 h	40 (2.3)	10 (1.3)	3.9 (2.0-7.6)	0.000	0.723
Miscellaneous					
Age, y	40.2	42.2	1.2 (1.1-1.3)§	0.000	n/a
Use of anticoagulant therapy	35 (2.0)	33 (4.4)	2.2 (1.0-4.5)	0.038	0.370
Intoxication					
Mild	151 (8.8)	91 (12)	0.8 (0.4-1.3)	0.355	0.712
Moderate	279 (16)	145 (19)	0.6 (0.4-0.9)	0.023	0.372
Severe	177 (10)	52 (6.9)	1.0 (0.6-1.7)	0.977	0.258

GCS, Glasgow Coma Scale; LOC, loss of consciousness; MHI, minor head injury; n/a, not applicable; OR, odds ratio; PTA, posttraumatic amnesia.
Shown are the prevalence of the risk factors, Mantel–Haenszel odds ratios (OR), p values of the ORs and p values for heterogeneity of the ORs across the two subgroups according to the Breslow–Day statistic.
* Fall from (some) height included falls from any elevation.
† Persistent anterograde amnesia was defined as the inability to capture and retain any new information in memory.
‡ Per 60 min of PTA.
§ Per 10 years.

Univariable analysis of the associations for each of the risk factors with a neurocranial traumatic finding on CT is shown in Table 3.

Risk factors indicating a significantly increased risk of neurocranial traumatic CT findings were pedestrian/cyclist versus vehicle, fall from (some) height, vomiting, PTA, a history of LOC, clinical signs of a skull or facial fracture, skull contusion, the presence of multiple injuries, focal neurological deficit, GCS score deterioration, anticoagulant treatment and increased age.

Clinical evidence of intoxication, however, indicated a reduced risk of neurocranial traumatic findings on CT. ORs were comparable across the two subgroups of MHI patients with or without LOC or PTA, which was demonstrated by homogeneity according to the Breslow-Day statistic: all p values for heterogeneity were larger than 0.05, except for clinical evidence of a skull fracture. The difference between the crude and adjusted ORs for age was 1%, indicating homogeneity of the ORs across the two subgroups. Although the ORs for signs of a skull fracture were different for the two subgroups – namely 37 (95% CI, 17 to 80) for MHI patients with and 6.9 (95% CI, 1.8 to 27) for MHI patients without LOC or PTA – they both indicated a substantial and significantly increased risk of neurocranial traumatic findings on CT in both subgroups and the 95% CI overlapped considerably. Clinical evidence of a skull fracture predicted a skull fracture on CT in 71.4% (25/35) of MHI patients with and 25.0% (3/12) of MHI patients without LOC or PTA. In contrast, clinical evidence of a skull fracture was indicative of a depressed skull fracture on CT in only 8.6% (3/35) of MHI patients with and 16.7% (2/12) of MHI patients without LOC or PTA.

DISCUSSION

Our findings indicate that known risk factors for neurocranial complications after MHI have comparable ORs for patients with or without a history of LOC or PTA. The implication of this finding is twofold. Firstly, patients without a history of LOC or PTA are at risk of neurocranial complications after MHI, even occasionally requiring neurosurgical intervention. Neurosurgical intervention was in fact required just as often in patients with as in patients without LOC or PTA after MHI. Secondly, a history of LOC or PTA should be considered as one of the risk factors for neurocranial complications, and not as a 'conditio sine qua non' for MHI.

A history of LOC or PTA is commonly used as a means of triaging MHI patients for referral to a neurologist/neurosurgeon, or for imaging or observation (15, 30). In many clinical guidelines for the management of MHI patients, it is recommended that patients without LOC or PTA, who have a normal level of consciousness on presentation and have no focal neurological deficit, are discharged without imaging or observation (16, 17). Our findings suggest that this approach is not justified if other known risk factors are present. The incidence of neurocranial traumatic findings on CT, however, was found to be lower in MHI patients without than in those with a history of LOC or PTA. Simply extending existing clinical guidelines to MHI patients without LOC or PTA therefore may lead to an unnecessary increase in CT scanning for MHI. Some clinical guidelines do recommend CT scanning of MHI patients with a risk factor, irrespective of a history of LOC or PTA (1, 14, 23). In a previous validation study, we demonstrated that these guidelines have a very high sensitivity for identifying patients with neurocranial traumatic findings on CT, but also that specificity is extremely low, indicating that many patients are probably scanned unnecessarily (31). In contrast with these guidelines, therefore, decision algorithms will need to be developed that may be implemented in clinical guidelines in which patients without a history of LOC or PTA are explicitly considered (32).

We have reported ORs for variables that are commonly considered risk factors for complications after MHI, based on neurocranial traumatic findings on CT. In a meta-analysis of 35 papers containing more than 83 000 patients, Dunning et al reported relative risks for risk factors for intracranial injury in adults with MHI (25).

As the incidence of the outcome of interest is relatively low, ORs and relative risks are similar and may be compared (33). For most of the risk factors we assessed, ORs were similar to the reported relative risks. For the variables posttraumatic seizure and intoxication, the ORs we observed were lower than those reported. For posttraumatic seizure, we estimated an OR of 2.7 which was not found to be statistically significant, whereas Dunning et al reported a relative risk of 6.4. Very few patients in our study population (n = 13) had a posttraumatic seizure, which may explain why the OR for this variable did not reach statistical significance. The reported relative risk of 6.4 does, however, fall within the 95% CI of our estimate, suggesting that the risk estimates are comparable. Clinical evidence of intoxication, however, was not associated with an increased risk of neurocranial complications in the present study, whereas a relative risk of 1.8 was reported by Dunning et al. As a large proportion of our study population was intoxicated, we cannot assign this difference in risk estimates to lack of data. The study populations included in the meta-analysis, however, had patients with GCS scores of 13–15, while all of our patients had a maximal GCS score on presentation. Clinically evident intoxication is often associated with a submaximal GCS score, which automatically places these patients in a high risk category (14). Reported risks related to intoxication may therefore be associated with GCS scores, rather than with the intoxication itself. In their large study for the development of the CCHR, Stiell et al also failed to find an increased risk of intoxication (9). They found that an unreliable neurological examination due to suspected intoxication was neither reliable nor discriminating and stated that the CCHR would be effective regardless of possible intoxication.

We found a very high predictive value for clinical evidence of a skull fracture, which was much higher for patients with than for patients without a history of LOC or PTA after MHI. This may indicate an interaction between the severity of the injury, as evidenced by the presence of LOC or PTA. In contrast, clinical evidence of a skull fracture was more often indicative of a depressed skull fracture on CT in MHI patients without than in MHI patients with LOC or PTA. This may be a result of selection bias, introduced by the fact that MHI patients without LOC or PTA required the presence of at least one risk factor to be included in our study; MHI patients with LOC or PTA were included irrespective of the presence of any risk factors other than LOC or PTA. One could argue that the need for neurosurgical intervention would be obvious if a depressed skull fracture were already clinically evident, and that the significance of the predictive value of this risk factor may be limited. However, in only a minority of patients with clinical evidence of a skull fracture was a depressed skull fracture actually present on CT. In the majority of patients with clinical signs of skull fracture, CT demonstrated a linear fracture. The association of a linear skull fracture and the development of extra-axial haematomas has been well established (16, 20, 34). Clinical evidence of a skull fracture, therefore, may not only be regarded as indicative of a (depressed) skull fracture, but also needs to be considered as a risk factor for other important intracranial complications.

LOC and PTA were associated with ORs of 1.9 and 1.7, respectively. These risk estimates are in line with those reported previously (25, 35). The risk factors we assessed were not affected by the presence or absence of LOC or PTA. We therefore propose to use the variables LOC and PTA as another two risk factors for neurocranial complications, rather than using them as a means of triaging MHI patients. This is best

achieved with a prediction rule, in which the presence of one or multiple risk factors may be used to estimate the patient's risk of neurocranial complications (32). This risk assessment may then be used to decide on further management, such as clinical observation or CT scanning, that may further be based on analysis of the costs and effectiveness of several of these management strategies (36).

The main limitation of our study was that MHI patients without LOC or PTA and without any further risk factors were not included, which may have biased the predictive values of the risk factors studied. This is inherent in our study design, in which we were bound by the currently implemented clinical guidelines for the use of CT in the Netherlands, that only indicate CT in patients without LOC or PTA if at least one other risk factor is present. The second limitation of our study was that we did not consider actual health outcomes, but limited our outcome measures to neurocranial complications and neurosurgical intervention. The relationship between neurocranial complications on CT and functional outcome is complex. For the purpose of our study, however, we feel that our pragmatic approach of only considering neurocranial traumatic CT findings and neurosurgical interventions as outcomes was sufficient.

Conclusion

Neurocranial complications after MHI, including those requiring neurosurgical intervention, occur both in patients with and in those without a history of LOC or PTA. Therefore, MHI patients without a history of LOC or PTA also need to be carefully evaluated and may also need imaging or clinical observation. Clinical guidelines for the management of MHI patients need to explicitly consider these patients without a history of loss LOC or PTA after MHI.

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CHAPTER 5

Predicting intracranial traumatic findings on Computed Tomography in patients with minor head injury: The CHIP prediction rule

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Background Prediction rules for patients with minor head injury suggest that the use of computed tomography (CT) may be limited to certain patients at risk for intracranial complications. These rules apply only to patients with a history of loss of consciousness, which is frequently absent.

Objective To develop a prediction rule for the use of CT in patients with minor head injury, regardless of the presence or absence of a history of loss of consciousness.

Design Prospective, observational study.

Setting Four university hospitals in the Netherlands that participated in the CT in Head Injury Patients (CHIP) study.

Patients Consecutive adult patients with minor head injury (≥16 years of age) with a Glasgow Coma Scale (GCS) score of 13 to 14 or with a GCS score of 15 and at least 1 risk factor.

Measurements Outcomes were any intracranial traumatic CT finding and neurosurgical intervention. The authors performed logistic regression analysis by using variables from existing prediction rules and guidelines, with internal validation by using bootstrapping.

Results 3181 patients were included (February 2002 to August 2004): 243 (7.6%) had intracranial traumatic CT findings and 17 (0.5%) underwent neurosurgical intervention. A detailed prediction rule was developed from which a simple rule was derived. Sensitivity of both rules was 100% for neurosurgical interventions, with an associated specificity of 23% to 30%. For intracranial traumatic CT findings, sensitivity and specificity were 94% to 96% and 25% to 32%, respectively. Potential CT reduction by implementing the prediction rule was 23% to 30%. Internal validation showed slight optimism for the model's performance.

Limitation External validation of the prediction model will be required.

Conclusion The authors propose the highly sensitive CHIP prediction rule for the selective use of CT in patients with minor head injury with or without loss of consciousness.

MINOR HEAD injury is one of the most common injuries seen in western emergency departments, with an estimated incidence of 100 to 300 per 100 000 people (1). Patients with minor head injury include those with blunt injury to the head who have a normal or minimally altered level of consciousness on presentation in the emergency department, that is, a Glasgow Coma Scale (GCS) score of 13 to 15, and a maximum loss of consciousness of 15 minutes, posttraumatic amnesia for 60 minutes, or both (2).

Intracranial complications after minor head injury are infrequent but commonly require in-hospital observation and occasionally require neurosurgical intervention (3, 4). The imaging procedure of choice for reliable, rapid diagnosis of intracranial complications is computed tomography (CT) (5, 6). Because most patients with minor head injury do not show traumatic abnormalities on CT, it seems inefficient to scan all patients with minor head injury to exclude intracranial complications. Of the published prediction rules for the selective use of CT in patients with minor head injury, the New Orleans Criteria (NOC) and the Canadian CT Head Rule (CCHR) have been externally validated (7–9). Researchers in internal and external validation studies have shown that both rules identify 100% of patients requiring neurosurgical intervention and most patients with traumatic intracranial findings on CT (3, 10–12). The external validation studies, however, yielded lower specificities than the development studies (10, 12). The originally reported specificities were probably too optimistic because of their partial derivation from data sets that were also used for the model development (13). Also, in both studies researchers included only a subset of patients with minor head injury. Most notably, researchers developed the NOC and the CCHR for patients with minor head injury who have a history of loss of consciousness or amnesia, which many of these patients presenting to emergency departments do not have. Generalizability of the NOC and the CCHR is therefore limited.

We aimed to develop a widely applicable and easy-to-implement prediction rule for the selective use of CT in all patients with minor head injury with or without a history of loss of consciousness. To avoid optimism for the model's performance, we used penalty factors and internal validation by using bootstrapping procedures to attain more realistic predictions of the model's performance in an external patient population (13).

METHODS

Patients

We prospectively collected data on consecutive patients in 4 university hospitals in the Netherlands that were participating in the CT in Head Injury Patients (CHIP) study (Figure 1) (14). Inclusion criteria included initial presentation within 24 hours of blunt injury to the head, a minimum age of 16 years, and a GCS score of 13 to 14 or a GCS score of 15, with at least 1 of the following risk factors: history of loss of consciousness, short-term memory deficit, amnesia for the traumatic event, posttraumatic seizure, vomiting, severe headache, clinical evidence of intoxication with alcohol or drugs, use of anticoagulants or history of coagulopathy, external evidence of injury above the clavicles, and neurologic deficit. Exclusion criteria were transfer from another hospital, contraindications for CT, or concurrent injuries precluding a head CT at presentation.

A neurologist or a neurologist-in-training under telephone supervision of a neurologist examined patients, after which a head CT was performed as soon as possible, in accordance

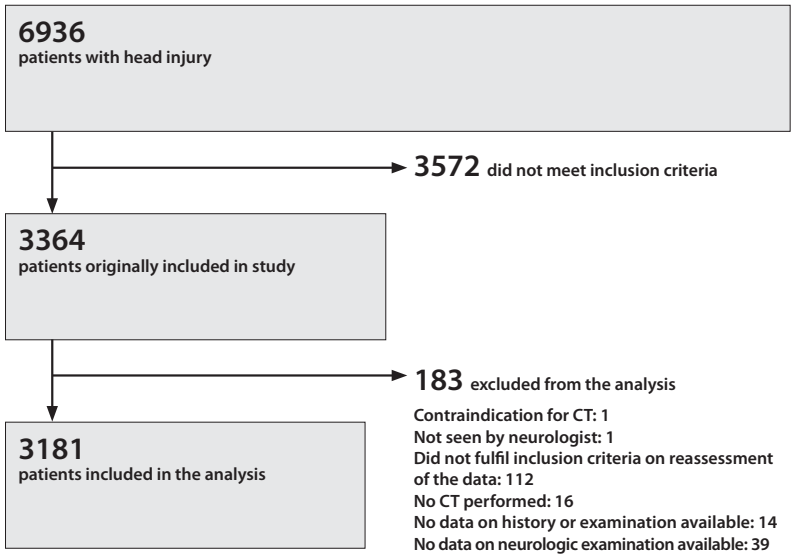

Figure 1. Study flow diagram. The number of patients presenting with head injury is an estimate based on the proportion of patients included out of the total number of trauma patients seen by a neurologist or neurologist-in-training in the emergency department of the participating center that included most patients. CT = computed tomography.

with the current Dutch guidelines (15). We performed head CT according to a routine trauma protocol, with a maximum slice thickness of 5 mm infratentorially and 8 mm supratentorially, without intravenous contrast administration. A neuroradiologist or a trauma radiologist (9 in total, not blinded to the patients' history and clinical findings) interpreted scans in brain and bone window settings.

The institutional review board waived patient informed consent after review of our study protocol because current Dutch guidelines and European Federation of Neurological Societies' guidelines recommend routine head CT for patients meeting our inclusion criteria (15, 16).

Definitions

We considered a patient to have a history of loss of consciousness when a witness or the patient reported it. We defined short-term memory deficit as persistent anterograde amnesia. We deemed amnesia present for the traumatic event if the patient could not recall the entire traumatic event. We defined posttraumatic seizure as a seizure witnessed or suspected after the injury and vomiting as an episode of emesis after the traumatic event. We classified headache as being either diffuse or localized. We evaluated the presence and severity of intoxication clinically by evidence of slurred speech, alcoholic fetor, or nystagmus; we did not perform routine blood toxicology tests. Anticoagulant treatment included only coumarin derivatives. We scored the use of platelet aggregation inhibitors (for example, aspirin and clopidrogel), but we did not consider it to be a risk factor. We assessed noniatrogenic coagulopathy, which we considered a risk factor, by patient history, but we did not perform routine blood coagulation tests. We defined external evidence

of injury as clinically significant discontinuity of the skin or extensive bruising. We classified injury suspect of a fracture as clinical signs of fracture, whereas we classified other injuries, such as contusions, lacerations, or abrasions, as contusion. We defined focal neurologic deficit as any abnormality on routine clinical neurologic examination that indicated a focal cerebral lesion.

Data collection

We collected data on patient and trauma characteristics, symptoms, and risk factors; physical and neurologic examination; CT findings; and neurosurgical intervention. Examining physicians entered data on patient history and examination into a database (OpenSDE, Erasmus MC – University Medical Center Rotterdam, Rotterdam, the Netherlands) before the patient underwent CT. If this interfered with their clinical workflow, they entered the data after the CT (17). The reading radiologist added the CT findings. We collected data on neurosurgical intervention, additional CT scans performed, and the clinical outcomes of patients by searching the hospital's patient information system.

Outcome measures

Our primary outcome measure for this analysis was any intracranial traumatic finding on CT, which included all neurocranial traumatic findings except for isolated linear skull fractures. A secondary outcome measure was neurosurgical intervention contingent to initial CT. We defined neurosurgical intervention as any neurosurgical procedure (craniotomy, intracranial pressure monitoring, elevation of skull fracture, or ventricular drainage) within 30 days of the traumatic event.

Risk factors

We selected all of the risk factors from the NOC and the CCHR (7, 9): age, headache, vomiting, intoxication, persistent anterograde amnesia, retrograde amnesia more than 30 minutes, injury above the clavicles (including clinical signs of skull or basal skull fracture), GCS score less than 15 at 2 hours postinjury, and dangerous trauma mechanism (pedestrian versus vehicle, fall from height, and ejected from motor vehicle). We tested other risk factors from clinical guidelines for the use of CT in minor head injury (15, 16, 18–21) for additional effects. We combined the variables cyclist versus vehicle and pedestrian versus vehicle into 1 variable (pedestrian or cyclist versus vehicle) for statistical analysis because they are similar trauma mechanisms.

Statistical analysis

We based sample size on an estimated 25 variables for multivariable logistic regression analysis. For reliable analysis, we required at least 10 events of the primary outcome measure per variable, that is, 250 events for 25 variables (22). Given an incidence of traumatic findings on CT of 8% to 10%, we needed to include 3125 patients.

We assumed that missing data were missing at random, and we imputed them on the basis of the available data means to avoid bias (23–27). The proportion of imputed data was 3.8%, which included items documented as unknown and items that were not documented. Of all cases, 1956 (62%) were complete. Loss of consciousness and posttraumatic amnesia had the highest proportion of missing or unknown data (18% and 10%, respectively). We imputed both as present on the basis of the available variable means and as consistent with clinical practice. We used the entire data set, after missing value imputation, for all analyses.

We evaluated the study sample for demographic characteristics, mechanism of injury, traumatic findings, neurosurgical intervention, GCS scores, and the presence of risk factors.

We tested associations of each risk factor

with the primary outcome measure using chi-square tests for nominal variables, the Mann–Whitney U test for ordinal variables, and the unpaired 2-tailed t-test for continuous variables by using SPSS software, version 12.0 (SPSS Inc., Chicago, Illinois). We calculated odds ratios with the Nagelkerke R^2 to compare the predictive strengths of the variables (28).

We used restricted cubic spline functions to assess the linearity of effect for continuous variables (29). We selected variables for the final prediction model on the basis of the statistical and clinical criteria. We used multivariable logistic regression with backward stepwise selection with a P value greater than 0.05 for removal of variables, but we forced variables that we considered to have great clinical relevance back into the model. We assessed additional risk factors from clinical guidelines for possible additional effects. We entered separately methodological variables that we considered to be clinically irrelevant into the final model to assess unexpected effects. We did not examine interaction terms but relied on the main effects of the predictors (22). We calculated odds ratios based on the model's regression coefficients to optimize the estimated effects of each variable in the study population.

To improve the model's predictions for future similar patient populations, we estimated the final model's regression coefficients by using penalized maximum likelihood procedures (13, 30). We determined the penalty factor by optimizing Akaike information criterion (31).

Performance

We calculated a linear predictor as the sum of each penalized β-coefficient multiplied by the corresponding variables' values. We constructed receiver-operating characteristic (ROC) curves for both outcome measures by using this linear predictor. We defined a cutoff score for a CT scan indication as the point at which sensitivity for neurosurgical intervention was 100% at maximum specificity because this identifies all very high-risk patients, that is, those requiring neurosurgical intervention. Using this cutoff score, we calculated the sensitivity and specificity (and their 95% CIs) for both outcome measures and potential CT scan reduction due to implementing this model (32). We refer to this prediction model as the detailed prediction model.

We also constructed a simple prediction model from the detailed model. We identified major and minor risk factors on the basis of the rounded, penalized β-coefficients and 100% sensitivity for neurosurgical intervention. For the simple prediction

Table 1. Patient characteristics*

Characteristic	Value	GCS score of 15, n (%)	GCS score of 14, n (%)	GCS score of 13, n (%)
Mean patient age (range), y	41 (16-102)			
Men, n (%)	2246 (70.5)			
Median duration to presentation (range), h	1 (0-23.3)			
Intracranial traumatic CT findings				
Absent		2327 (94.5)	491 (86.4)	120 (79.5)
Present		135 (5.5)	77 (13.6)	31 (20.5)
Neurosurgical intervention				
Absent		2452 (99.6)	563 (99.1)	149 (98.7)
Present		10 (0.4)	5 (0.9)	2 (1.3)

* CT = computed tomography; GCS = Glasgow Coma Scale.

model, we categorized continuous variables at suitable cutoff values. We calculated ROC curves and sensitivities and specificities (and their 95% CIs) for both outcome measures (32).

Internal validation

We assessed internal validity with a bootstrapping procedure for a realistic estimate of the performance of both prediction models in similar future patients. We repeated the entire modeling process, including variable selection and optimum penalty factor search, in 200 samples drawn with replacement from the original sample. We determined the performances of the selected prediction model and the simple rule that were developed from each bootstrap sample in the original sample (30, 33). Performance measures included the average area under the ROC curve, sensitivity and specificity for both outcome measures, and CT reduction at 100% sensitivity for neurosurgical interventions within each bootstrap sample. We validated this by using Harrell's Design library and S-PLUS software, version 6.0 (Insightful Inc., Seattle, Washington).

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RESULTS

Between 11 February 2002 and 31 August 2004, an estimated 6936 patients with head injury presented to the emergency departments of the participating centers. We did not include 3572 of these patients because they did not meet the inclusion criteria. Of the 3364 patients originally included in the study, we excluded 183 from further analysis for various reasons (Figure 1), leaving 3181 patients for the data analysis.

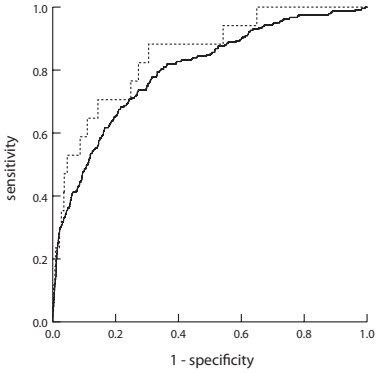

Figure 2. Receiver-operating characteristic (ROC) curves of the detailed prediction model. The dashed line represents the ROC curve for neurosurgical interventions (area under the curve, 0.85 [95% CI, 0.76 to 0.94]), and the solid line represents the ROC curve for intracranial traumatic CT findings (area under the curve, 0.80 [95% CI, 0.77 to 0.83]).

Table 1 shows patient characteristics. We found intracranial traumatic findings on CT in 243 (7.6%) patients. These findings included depressed skull fractures (19 [7.8%] cases), acute subdural (67 [28%] cases) and epidural (35 [14%] cases) hematomas, traumatic subarachnoid hemorrhage (86 [35%] cases), intraparenchymal lesions (142 [58%] cases) consisting mostly of hemorrhagic contusions (118 [49%] cases), and linear (67 [28%] cases) and skull base fractures (53 [22%] cases) in combination with intracranial lesions. Twelve neurosurgeons performed a neurosurgical intervention in 17 patients for epidural hematoma (n = 8), acute subdural hematoma (n = 3), depressed skull fracture (n = 3), and extra-axial hematoma with a depressed skull fracture (n = 3). The procedures consisted

Appendix Table 1. Univariable analysis of variables that were entered into the multivariable logistic regression analysis*

Variable	Patients with an intracranial traumatic finding on CT (n = 243)	Odds Ratio (95% CI)	P value	Nagelkerke R^2
Age, y	48.2	1.2 (1.1-1.3)†	0.000	0.025
Trauma mechanism , n (%)			0.000	0.022
Other	102 (5)	1.0 (reference)		
Pedestrian or cyclist versus vehicle	51 (15)	3.2 (2.2-4.5)		
Fall from any elevation	82 (10)	2.2 (1.6-2.9)		
Ejected from vehicle	8 (12)	2.6 (1.2-5.6)		
Symptoms				
Persistent anterograde amnesia, n (%)	72 (15)	2.7 (2.0-3.6)	0.000	0.028
Vomiting, n (%)	55 (16)	2.7 (2.0-3.7)	0.000	0.023
PTA, duration, min	75	1.7 (1.4-2.0) ‡	0.000	0.032
Loss of consciousness, n (%)	182 (9)	2.0 (1.5-2.7)	0.000	0.016
Headache, n (%)			0.058	0.004
No	84 (6)	1.0 (reference)		
Diffuse	120 (9)	1.4 (1.1-1.9)		
Localized	39 (7)	1.1 (0.7-1.7)		
Posttraumatic seizure, n (%)	5 (22)	3.4 (1.3-9.3)	0.001	0.003
External evidence of injury, n (%)				
Signs of skull fracture	36 (49)	14 (8.4-22)	0.000	0.070
Contusion of the skull	140 (12)	2.4 (1.8-3.1)	0.000	0.030
Signs of facial fracture	24 (10)	1.3 (0.9-2.1)	0.193	0.001
Contusion of the face	118 (7)	0.8 (0.7-1.1)	0.194	0.001
Neurologic examination				
Mean inverse GCS score upon presentation (15 – GCS score)	0.57	2.3 (1.9-2.7)	0.000	0.048
Neurologic deficit, n (%)	42 (14)	2.1 (1.5-3.1)	0.000	0.012
Change in GCS score at 1 h	-0.04	0.8 (0.7-1.0)	0.009	0.004
Use of anticoagulant therapy, n (%)	13 (16)	2.3 (1.3-4.3)	0.005	0.005
Intoxication, n (%)			0.002	0.002
No	164 (9)	1.0 (reference)		
Mild	18 (6)	0.7 (0.4-1.2)		
Moderate	22 (4)	0.4 (0.3-0.7)		
Severe	39 (9)	1.1 (0.7-1.5)		

* For continuous variables, the mean for patients with an intracranial finding on CT is shown.
CT = computed tomography; GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia.
† Per 10 y.
‡ Per 60 min of PTA.

of removing the extra-axial clot (n = 13) and repairing the depressed skull fracture (n = 4). Despite neurosurgical intervention, 1 patient died due to epidural hematoma. Thirteen patients had good clinical outcomes (full recovery or minor disability), and 3 patients had moderate clinical outcomes.

Physicians did not treat the remaining 59 patients with subdural or epidural hematoma or depressed fracture neurosurgically but

Table 2. Prediction model and rule for the identification of intracranial traumatic computed tomography findings in patients with minor head injury based on multivariable logistic regression analysis*

Variable	Odds Ratio (95% CI)†	β-coefficient‡
Signs of skull fracture	10 (5.9-18)	2.3
GCS score of 13 on presentation	3.9 (2.4-6.6)	1.3
GCS score of 14 on presentation	2.1 (1.4-2.9)	0.7
Persistent anterograde amnesia	1.5 (1.1-2.2)	0.4
Contusion of the skull	1.8 (1.3-2.4)	0.6
Vomiting	2.4 (1.7-3.5)	0.8
Patient age – 16 per 10 y	1.2 (1.1-1.3)	0.2
Posttraumatic amnesia of 2 to <4 h	1.6 (0.6-4.5)	0.4
Posttraumatic amnesia ≥4 h	7.5 (1.5-37)	0.6
Loss of consciousness	1.8 (1.3-2.5)	0.6
Neurologic deficit	1.5 (1.0-2.3)	0.4
Fall from any elevation	1.7 (1.2-2.4)	0.5
Use of anticoagulant therapy	2.4 (1.2-4.6)	0.8
Change in GCS score (1 h after presentation)	0.7 (0.6-0.9)	-0.3
Pedestrian or cyclist versus vehicle	3.6 (2.4-5.3)	1.1
Ejected from vehicle	3.1 (1.3-7.2)	0.8
Posttraumatic seizure	2.3 (0.7-8.2)	0.8
Adjustment for prior probability		
2.5%		-1.2
5.0%		-0.4
7.5%		0.0
10.0%		0.3
12.5%		0.6
15.0%		0.8

* Prediction rule: To determine the need for a CT scan, the coefficients of the risk factors that are present (for continuous variables multiplied by the value of the variable) need to be added. If the sum score is ≥1.1, a CT scan is indicated. The predicted probability of an intracranial traumatic finding on CT adjusted for the prior probability in the patient population equals: $1/(1+e^{-(-4.6 + \text{score} + \text{adjustment for prior})})$. In our study population, the prior probability of an intracranial traumatic finding on CT was 7.5%, which was based on a case-mix, adjusted estimate. The adjustment factor was then calculated for other prior probabilities that were arbitrarily chosen (that is, 2.5%, 5.0%, 10.0%, 12.5%, and 15.0%).
CT = computed tomography; GCS = Glasgow Coma Scale.
† Odds ratios are based on standard maximum likelihood estimation.
‡ Penalized estimation was used for the β-coefficients to improve predictions in future patients with minor head injury (30).

hospitalized most (n = 54 [92%]) for clinical observation, during which time the patients remained neurologically stable. Three elderly patients (81 to 82 years of age) exhibited rapid clinical deterioration and extensive intracranial traumatic CT findings, and the attending neurosurgeon considered intervention to be of no avail. All 3 patients died.

One hundred twelve patients received additional CT scans: 81 (72%) to follow a traumatic lesion (intracranial or linear fracture) seen on the initial CT; 3 for non-trauma-related indications (tumor or stroke); 2 for changes in behavior, showing only on the second CT subarachnoid hemorrhage in 1 patient and hypodense lesions consistent with diffuse axonal injury in the other; and 26 for various reasons (for example, headache or dizziness), for which the second

Appendix Table 2. Performance of the detailed and simple prediction model*

Model	Score ≥1.1	Score <1.1	Risk factor present†	Risk factors absent‡	Sensitivity (95% CI), %	Specificity (95% CI), %	CT reduction (95% CI), %
Detailed prediction model							30 (29-32)
Neurosurgical intervention required	17	0			100 (82-100)	30 (28-33)	
No neurosurgical intervention required	2207	957					
Intracranial traumatic CT findings present	229	14			94 (91-97)	32 (30-35)	
Intracranial traumatic CT findings not present	1995	943					
Simple prediction model							23 (22-25)
Neurosurgical intervention required			17	0	100 (82-100)	23 (21-26)	
No neurosurgical intervention required			2422	742			
Intracranial traumatic CT findings present			234	9	96 (93-98)	25 (23-27)	
Intracranial traumatic CT findings not present			2205	733			

* CT = computed tomography.
† A minimum of 1 major or 2 minor risk factors are present.
‡ No major risk factors and ≤1 minor risk factor are present.

CT was negative. Two cases of a dubious intraparenchymal contusion presented on the initial CT; in both cases, the results of the second CT were negative.

Appendix Table 1 shows results from the univariable analysis. The continuous variables of posttraumatic amnesia, age, and GCS scores showed a reasonably linear association with the probability of intracranial traumatic findings on CT (primary outcome measure). Compared with patients without intracranial traumatic findings on CT, patients with intracranial traumatic CT findings had a longer mean posttraumatic amnesia (75 versus 17 minutes), were older (48 versus 41 years of age), had lower mean GCS scores on presentation (14.4 versus 14.8), and more often showed a deterioration of GCS score after 1 hour (0.04-point deterioration versus 0.10-point improvement).

We considered all variables shown in Appendix Table 1 in the multivariable analysis

Table 3. Specificities, potential computed tomography reduction, and cutoff scores at several sensitivities for intracranial traumatic computed tomography findings (detailed prediction model)*

Sensitivity for intracranial traumatic CT findings, %	Specificity for intracranial traumatic CT findings (95% CI), %	Reduction in CT use (95% CI), %	Prediction rule cutoff score
90	40 (37-43)	38 (36-40)	1.26†
92.5	37 (35-40)	35 (33-37)	1.19
95	30 (27-32)	28 (26-29)	1.03
97.5	22 (19-24)	20 (19-22)	0.84
100	0.6 (0.0-2.5)	0.5 (0.3-0.9)	0.05

* CT = computed tomography.
† At this cutoff score, sensitivity for neurosurgical intervention decreases to 94% from 100%. Above the cutoff score, CT is indicated.

(Table 2). The variables of posttraumatic seizure and persistent anterograde amnesia were not statistically significant, but we retained them in the final model because of their clinical importance.

We entered separately each additional risk factor from clinical guidelines for minor head injury into the model, but none showed a significant additional effect (odds ratio for high-energy accident, 0.99 [P = 0.97]; odds ratio for unclear trauma mechanism, 1.38 [P = 0.47]; odds ratio for pretraumatic seizure, 0.39 [P = 0.21]; and odds ratio for multiple injuries, 1.24 [P = 0.20]). The methodological variables, which did not show any significant effects, were the moment of data entry (before or after the CT was performed) (P = 0.43) and the participating center (P = 0.32).

Figure 2 shows ROC curves of the detailed prediction model. At a linear predictor score of 1.1, sensitivity was 100% for neurosurgical interventions and specificity was 30% (Appendix Table 2; Figure 2). At this cutoff score, the prediction model missed 14 patients with intracranial traumatic CT findings (sensitivity, 94%). These 14 patients had 19 intracranial non-neurosurgical traumatic CT findings: 1 depressed skull fracture, 4 acute subdural hematomas (all minimal with no mass effect), 8 traumatic subarachnoid hemorrhages, 6 intraparenchymal lesions (5 of which were hemorrhagic contusions), and 4 linear and 3 skull base fractures with additional lesions. The prediction model missed no patient with an epidural hematoma. Physicians admitted 12 (86%) of these patients for clinical observation, and none died. We knew the clinical outcome for 10 patients, and all patients had a good recovery except for 1 who had a minor disability due to an orbital fracture.

Specificities were 30% for neurosurgical interventions and 32% for intracranial CT findings (Appendix Table 2; Figure 2). Sensitivity for intracranial traumatic findings on CT reached 100% at a score of 0.05, but specificity was only 0.6% (Table 3). Internal validation of the detailed prediction model using bootstrapping procedures indicated optimism for the area under the ROC curve, which we expected to decrease from 0.85 to 0.83 for neurosurgical interventions and from 0.80 to 0.78 for intracranial traumatic CT findings. We expected 100% sensitivity for neurosurgical interventions in 58% of the bootstrap repetitions.

The simple prediction model consisted of 10 major and 8 minor risk factors (Table 4). In the presence of at least 1 major or 2 minor

Table 4. Simple prediction model for intracranial traumatic computed tomography findings in patients with minor head injury*

A CT is indicated in the presence of 1 major criterion
Pedestrian or cyclist versus vehicle
Ejected from vehicle
Vomiting
Posttraumatic amnesia ≥4 h
Clinical signs of skull fracture†
GCS score <15
GCS deterioration ≥2 points (1 h after presentation)
Use of anticoagulant therapy
Posttraumatic seizure
Age ≥60 y
A CT is indicated in the presence of at least 2 minor criteria
Fall from any elevation
Persistent anterograde amnesia‡
Posttraumatic amnesia of 2 to <4 h
Contusion of the skull
Neurologic deficit
Loss of consciousness
GCS deterioration of 1 point (1 h after presentation)
Age 40-60 y

* CT = computed tomography; GCS = Glasgow Coma Scale.
† Any injury that suggests a skull fracture, such as palpable discontinuity of the skull, leakage of cerebrospinal fluid, 'raccoon eye' bruising, and bleeding from the ear.
‡ Persistent anterograde amnesia is any deficit of short-term memory.

risk factors, sensitivity for neurosurgical interventions was 100%, with a specificity of 23% (Appendix Table 2). This model would have missed 9 patients with 13 intracranial traumatic lesions on CT (sensitivity, 96%). These intracranial non-neurosurgical traumatic CT findings included 1 depressed skull fracture, 3 acute subdural hematomas (all minimal with no mass effect), 4 traumatic subarachnoid hemorrhages, 5 intraparenchymal lesions (4 of which were hemorrhagic contusions), and 7 linear and 3 skull base fractures with additional lesions. The simple model missed no patient with an epidural hematoma. Specificity of the simple model for intracranial traumatic lesions was 25% (Appendix Table 2). Potential reduction in CT scans with this simple model (23%) was lower than that with the detailed model (30%), although sensitivity for intracranial traumatic CT findings was slightly higher in the simple model (96% versus 94%).

Internal validation of the simple prediction model using bootstrapping procedures

Table 5. Comparison of the 2 previously published prediction rules (New Orleans Criteria and Canadian CT Head Rule), additional risk factors from various guidelines, and the CT in Head Injury Patients prediction rule for use of computed tomography in patients with minor head injury*

Risk factor	NOC	CCHR	CHIP†
Headache	Major	-	-
Vomiting	Major	Major (≥2 episodes)	Major
Posttraumatic seizure	Major	Excluded	Major
Intoxication	Major	-	-
Persistent anterograde amnesia	Major	-	Minor
Age	Major (>60 y)	Major (≥65 y)	Major (≥60 y) or minor (40-60 y)
Clinical signs of skull fracture	Major	Major	Major
Contusion of the skull	Major	-	Minor
Signs of facial fracture	Major	-	-
Contusion of the face	Major	-	-
GCS score deterioration	-	Major	Major (≥2 points) or minor (1 point)
Pedestrian versus vehicle	-	Minor	Major (also cyclist)
Ejected from vehicle	-	Minor	Major
Fall from height	-	Minor	Minor
Prolonged posttraumatic amnesia	-	Minor (>30 min)	Major (≥4 h) or minor (2 to <4 h)
GCS score <15 at presentation	Excluded	-	Major
Loss of consciousness	Inclusion	Inclusion	Minor
Neurologic deficit	Excluded	Excluded	Minor
Anticoagulation therapy	-	Excluded	Major
High-energy trauma	-	-	-
Multiple injuries	-	-	-
Pretraumatic seizure	-	-	-
Unclear trauma mechanism	-	-	-

* Dash indicates that the variable is not a risk factor in the model.
Excluded = risk factor was not assessed in the development of the prediction rule because patients with this risk factor were excluded from the study; Inclusion = risk factor was not assessed in the development of the prediction rule because it was used as an inclusion criterion for the study; major = risk factor is present in the prediction rule as a major criterion; minor = risk factor is present in the prediction rule as a minor criterion.
CCHR = Canadian CT Head Rule; CHIP = CT in Head Injury Patients; GCS = Glasgow Coma Scale; NOC = New Orleans Criteria.
† Applies to both the detailed and the simple rule.

indicated a small optimism for the area under the ROC curve, which we expected to decrease from 0.84 to 0.82 for neurosurgical interventions and from 0.79 to 0.77 for intracranial traumatic CT findings. Using a minimum of 1 major or 2 minor risk factors as a CT indication, we expected 100% sensitivity for neurosurgical interventions in 56% of the bootstrap repetitions (average sensitivity, 96%). When we used only 1 minor risk factor as a CT indication, the model reached 100% sensitivity for neurosurgical interventions in 76% of samples, but at this score the potential CT reduction decreased to 5.8% (95% CI, 5.0% to 6.7%).

DISCUSSION

The highly sensitive CHIP prediction rule for the use of CT is applicable to most patients with minor head injury, including patients without loss of consciousness or posttraumatic amnesia. We present a detailed prediction rule and a simplified prediction rule. The latter is easier to use in a clinical setting, but some information is lost, which is demonstrated by a slightly lower specificity. The former is more complicated, although it is easy to implement in digital patient file systems or to consult online (available at http://www.marionsmits.net/chip-prediction-rule). It has several advantages, including that no information is lost, prior probabilities of intracranial traumatic CT findings may be considered, and thresholds may be varied. Researchers have already published 2 high-quality prediction rules for the use of CT in patients with minor head injury, the NOC and the CCHR (7, 9). They are highly sensitive to intracranial traumatic CT findings and neurosurgical interventions. We propose a third prediction rule for the selective use of CT in patients with minor head injury, the CHIP prediction rule that is more widely applicable than either the NOC or the CCHR, provides more realistic predictions, and is internally validated. It may greatly reduce the number of CTs for the indication of minor head injury compared with scanning all patients with minor head injury (16, 18, 19). The actual CT reduction will, however, depend on current clinical practice and adherence to the prediction rule.

Researchers developed the NOC and the CCHR in a more restricted population of patients with minor head injury, comprising only 41% to 64% of our study population (10). Unlike the CHIP prediction rule, both previously published rules require that the patient has a history of loss of consciousness or amnesia and normal findings on neurologic examination. Because of these restrictions, generalizability of these prediction rules is limited. The CHIP prediction rule is more widely applicable and is consequently easier to incorporate into clinical guidelines.

In developing our prediction rule, we first selected risk factors that were shown to have a predictive effect in the NOC and the CCHR. We tested additional risk factors in clinical guidelines, but they were not useful in selecting patients for CT. The CHIP prediction rule clearly provides a compromise between the NOC and CCHR rules (Table 5). It contains the same risk factors as the CCHR and some additional risk factors from the NOC. The remaining risk factors in the CHIP prediction rule are related to the patient selection criteria of the NOC and CCHR. Loss of consciousness is only a minor risk factor in our model, despite it often being considered a critical risk factor in patients with minor head injury (34). This may be explained by our inclusion criteria, which required the presence of an additional risk factor if a patient had no history of loss of consciousness (18, 35). The effect of loss of consciousness is thus diminished by an a priori increased risk due to the presence of another risk factor.

We reduced the model's optimism by

penalizing the regression coefficients to make realistic and reproducible predictions in future similar patients with minor head injury. This results in a more conservative, but also more realistic, estimate of the model's performance. In the development of the NOC and the CCHR, researchers did not perform this penalization, which may explain the lower-than-expected performance in external validation studies (10, 12).

Finally, we validated our prediction rule internally by using a bootstrapping procedure (30, 33). Overall performance (area under the ROC curve) was only marginally lower than that of the original model. Because our prediction model is similar to existing prediction rules, does not seem to be too optimistic, and shows only marginal deterioration of performance in internal validation, we feel that our model is robust and its predictions are realistic.

We chose our indication for CT threshold such that sensitivity for neurosurgical interventions was 100% because we required our model to identify all very high-risk patients. Sensitivity for intracranial traumatic CT findings was somewhat lower, and the question is whether this sensitivity would be acceptable for clinical use. It is difficult to speculate on the clinical outcome of patients who would have been missed if triaged on the basis of the prediction rule. All potentially missed patients in our study population had relatively minor CT findings and required no intervention, suggesting that triaging on the basis of the prediction rule would not have had adverse clinical consequences in terms of clinical outcome. One may argue that a sensitivity of 100% is also required for intracranial traumatic CT findings, but this causes specificity to decrease dramatically. Internal validation suggests that 100% sensitivity for neurosurgical interventions may be a too optimistic expectation in future patients. If definitely no patients with intracranial traumatic CT findings or requiring neurosurgical intervention may be missed, all patients will need to be scanned and a prediction rule will be superfluous. The decision about which threshold to use (that is, the minimum desired sensitivity) should ideally be based on an analysis of the costs and benefits of scanning (36).

Increasingly, physicians use prediction rules as decision rules, that is, they now frequently use predicted probabilities of an outcome in the decision-making process (37). Although we suggest that the CHIP prediction rule may be used as an aid to decide whether to perform a CT, this is valid only under the assumption that accurate predictions improve clinical decisions. Even then, a prediction rule can be used only as a decision-support system because it can only complement, never replace, clinical judgment (37, 38). If clinical suspicion is high, a CT scan is indicated regardless of the prediction rule.

Our study has some limitations. First, although the overall proportion of missing or unknown variables was low, the proportion of patients with at least 1 unknown variable was relatively high. This was mostly because of the difficulty of reliably obtaining a history of loss of consciousness and posttraumatic amnesia, which is a well-known problem in clinical practice. If unknown, these 2 risk factors are assumed to be present, which is how we imputed missing values in our data set and is consistent with clinical practice. A further limitation of our study is that we determined the variables of high-energy accident and pretraumatic seizure on the basis of the description of the trauma mechanism. We included these variables in the univariable analysis because they are commonly considered to be risk factors in the various guidelines for the use of CT in patients with minor head injury. They are not, however, considered to be risk factors in the NOC and the CCHR, and our analysis confirms that they are not relevant after other variables are considered in a multivariable analysis. The lack of toxicology testing is another limitation because we did not obtain objective information on the toxicologic status of patients. However,

toxicology screening in a busy emergency department to triage patients would reduce the clinical usefulness of a prediction rule. A further minor limitation is that only university hospitals participated, which may have induced selection bias. Three of the participating hospitals are large inner-city hospitals, and all 4 serve a large, general patient population. To reduce bias, we excluded patients transferred from other hospitals. The final and most important limitation of our study is the lack of external validation. Although we performed internal validation, the model should still be validated in a separate, preferably multicenter, study to assess its generalizability and its effect (38).

We propose the highly sensitive CHIP prediction rule for the use of CT in patients with minor head injury. The rule is applicable to a large proportion of patients with minor head injury presenting to the emergency department. It may greatly reduce the number of CTs performed for this indication, and it identifies almost all patients requiring neurosurgical intervention and most patients with an intracranial traumatic finding on CT.

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CHAPTER 6

Cost-effectiveness of Computed Tomography in minor head injury

submitted

Background Prediction rules can be used to select patients for CT after minor head injury (MHI). We assessed the cost-effectiveness of selective CT strategies, compared with CT in all patients.

Methods We evaluated 5 strategies: CT in all MHI patients; selective CT according to the New Orleans Criteria (NOC), Canadian CT Head Rule (CCHR) or CT in Head Injury Patients (CHIP) rule; and no CT (reference). We used a decision tree for the short-term, and a Markov model for the long-term costs and effectiveness. Outcome measures were first-year and lifetime costs, quality adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER). The model's robustness was tested against varying the model parameters across their 95% confidence intervals in n-way and probabilistic sensitivity analysis. Also, value of information (VOI) analysis was performed.

Results Selective CT according to the CCHR or CHIP rule could lead to substantial US cost-savings (US$ 120 million respectively US$ 71 million). At prediction rules' sensitivities below 97% to identify patients requiring neurosurgery, CT in all patients was cost-effective. Sensitivity analyses demonstrated that the CHIP rule was most likely to be cost-effective. VOI analysis demonstrated an expected value of perfect information of US$ 7 billion, mainly due to uncertainty in long-term functional outcome.

Conclusions Selecting MHI patients for CT is cost-effective, provided that the sensitivity to identify patients requiring neurosurgery is extremely high. More research is needed to increase certainty on long-term functional outcome after MHI. Until such time, CT in all patients is also justified.

INCREASINGLY, HEAD Computed Tomography (CT) in minor head injury (MHI) patients is used routinely for rapid and reliable diagnosis of traumatic complications (1). Although such traumatic complications are relatively infrequent after MHI (6%–10%), they may require neurosurgery (0.4%–1.0%) (2–4). MHI is defined as blunt head injury with a presenting Glasgow Coma Scale (GCS) score of 13–15. Due to its high population incidence (100–300/100 000) (5) it poses a substantial economic burden on healthcare and society.

CT is less costly than and equally effective as clinical observation for the management of MHI patients (6–8). Prediction rules could reduce the use of head CT in MHI patients by selecting patients at risk of traumatic complications for CT (9). The published prediction rules New Orleans Criteria (NOC) (3), Canadian CT Head Rule (CCHR) (4) and CT in Head Injury Patients (CHIP) rule (10) (Table 1) are all 100% sensitive for traumatic complications requiring neurosurgery. Both the NOC and CCHR have been externally validated (11, 12), and the CHIP rule is an adaptation of these two rules based on external validation findings. The rules could reduce the use of CT by up to 37% (11, 12), which would seem to be cost-saving (13). The selective use of CT, however, introduces the risk of missing patients with traumatic complications, as the prediction rules' sensitivities have wide 95% confidence intervals (CIs) (11, 12). Although this risk is expected to be small, the consequences in terms of loss of (quality of) life years may be substantial, potentially outweighing the cost savings of selective CT use.

Our purpose was to assess the cost-effectiveness of selective CT strategies, taking the uncertainty of the prediction rules' sensitivities into account, compared with the routine use of CT in all MHI patients. Furthermore, we evaluated whether further research to reduce uncertainty would be required and justified.

MATERIALS AND METHODS

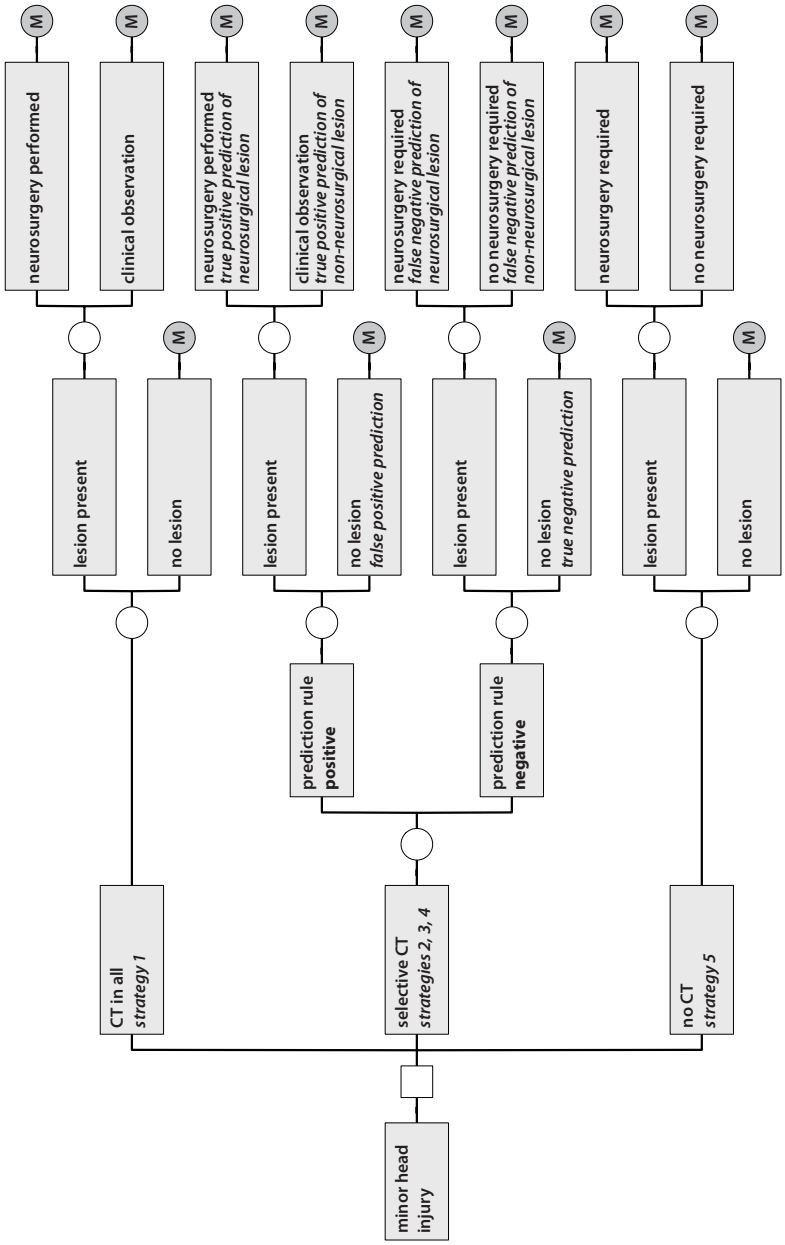
Study population

Data were used from the CT in Head Injury Patients (CHIP) study, in which data on 3364 consecutive MHI patients (GCS = 13–14 or GCS = 15 with at least one risk factor) were collected prospectively in 4 Dutch university hospitals between 2002 and 2004 (10, 11). All patients underwent head CT, and data on clinical course and follow-up were retrieved from medical records of all patients with intracranial traumatic findings (14). Long-term functional outcome (Glasgow Outcome Scale [GOS]) (15) and quality of life (EuroQOL-5D) (16, 17) were assessed by telephone in a subset of these patients (14). The Internal Review Board approved the study, and written informed consent was obtained from all interviewed patients.

Decision model

We developed a decision model to evaluate the use of CT in MHI (Figure 1). The strategies considered were: 1, CT in all MHI patients; 2, selective CT according to NOC; 3, selective CT according to CCHR; 4, selective CT according to the CHIP rule; and 5, no CT (reference strategy). Short-term costs were modeled with a decision tree, and a Markov model was used to assess long-term (≥1 year after the injury) costs and effectiveness in quality adjusted life years (QALYs). All evaluations started after clinical assessment in the emergency department.

The Markov model (1 year cycle length) consisted of 4 health states: 1, death (GOS = 1); 2, severe disability (GOS = 3); 3, minor disability (GOS = 4); 4, full recovery (GOS = 5). Vegetative state (GOS = 2) was not modeled, as it is very rare after MHI (18–22), and patients infrequently survive the first year (23). Functional outcome was assumed stable after 1 year (20, 24); thus, after the first year, there were no transitions between the health


minor head injury
CT in all strategy 1
selective CT strategies 2, 3, 4
no CT strategy 5
prediction rule positive
prediction rule negative
lesion present
no lesion
lesion present
no lesion false positive prediction
lesion present
no lesion true negative prediction
lesion present
no lesion
neurosurgery performed
clinical observation
neurosurgery performed true positive prediction of neurosurgical lesion
clinical observation true positive prediction of non-neurosurgical lesion
neurosurgery required false negative prediction of neurosurgical lesion
no neurosurgery required false negative prediction of non-neurosurgical lesion
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states, other than from alive to dead.

Data sources and assumptions

We based our model on data from the CHIP study (Tables 1–3; Technical appendices 2–3) (11). We searched the literature (PubMed, English language only) for data not available from the CHIP study and for data to be used in the sensitivity analyses. All variables were entered in the model as distributions.

Mortality during the first year was obtained from the CHIP study, and after the first year from the 2005 Dutch vital statistics (25). To account for radiation induced mortality associated with head CT (estimated effective dose, 2 mSv) (26–31) mortality was assumed to be increased by 0.008%, modeled as an increased annual mortality in patients undergoing CT. Annual mortality in severely disabled patients (GOS = 3) was assumed to be relatively increased by 5% (32).

CT was considered 100% sensitive to identify patients with a neurosurgical lesion (7, 33–35).

Patients with missed neurosurgical lesions were assumed to return to the emergency department (by ambulance) and to undergo delayed CT and delayed neurosurgery. Their functional outcome was estimated to be worse than in those correctly identified and treated without delay (Table 2) (36–42).

Patients with missed intracranial traumatic lesions not requiring neurosurgery were assumed to be discharged home without clinical observation, but otherwise to have the same clinical course and recovery as patients correctly identified by the prediction rule. A proportion of these patients was expected to reattend and undergo CT upon reassessment, in cases of prolonged or worsening of complaints. We assumed that this proportion was equal to the proportion of patients in our study population who underwent a repeat CT scan for worsening of symptoms (43).

Patients without intracranial traumatic CT findings were considered to fully recover with maximum quality of life (21, 44).

The EuroQOL-5D (16) results were converted to quality of life utilities (17), and used to calculate QALYs for each of the health states in the Markov model (Table 3). Effectiveness was discounted at 3% per year (45–47).

Cost data

We included direct healthcare and direct non-healthcare costs (Technical appendix 3) (45–47). A cost analysis was performed to estimate the cost of a head CT (48). All other costs were provided by the Dutch Healthcare Insurance Board (49), converted to the year 2006 based on the Dutch consumer price index (25), and reported in 2006 US dollars (US$, 1.256 US$ = 1 euro) (50). All future costs were discounted at 3% per year (45–47).

Outcome measures

We calculated total costs for the first year after the injury, lifetime costs, QALYs,

Figure 1 (facing page). Simplified version of the decision tree. The square indicates a decision node, circles indicate chance nodes, (M) indicates a Markov model.

In the first strategy all patients undergo head CT. CT either does or does not show an intracranial traumatic lesion, which either does or does not require neurosurgery.

In the selective CT strategies (strategies 2, 3, 4), a CT scan is performed only if indicated by the prediction rule (NOC, CCHR or CHIP rule). After performing head CT, patients are identified with an intracranial traumatic lesion (true positive prediction) or without (false positive prediction). True positive patients are either admitted for clinical observation (non-neurosurgical lesion) or to undergo neurosurgery (neurosurgical lesion). If CT is not indicated according to the prediction rule, patients are discharged home without observation, some of whom incorrectly (false negative prediction), depending on the prediction rules' sensitivities (Table 1).

Strategy 5 serves as a hypothetical reference strategy, in which all patients are discharged home without CT, either with or without a (neurosurgical) intracranial traumatic lesion.

the incremental cost effectiveness ratio (ICER), and the gain in net health benefit (NHB) compared with the reference strategy. The willingness-to-pay threshold was assumed to be US$ 75 000 per QALY gained.

Base case analysis

Data analysis was performed from a societal perspective with a lifetime horizon, using DATA TreeAge Pro 2007 Suite (TreeAge Software Inc, Williamstown, MA, USA).

Table 1. The proportion of patients in whom the prediction rules were positive, the diagnostic odds ratios, sensitivities and specificities for the identification of patients with a traumatic intracranial lesion, as determined in our study population

	NOC	CCHR	CHIP rule
Proportion positive, point estimate (95% CI)	0.97 (0.96-0.98)	0.63 (0.61-0.64)	0.70 (0.49-0.88)
Diagnostic odds ratio, point estimate (95% CI)	3.9 (0.95-15.9)	4.4 (3.0-6.5)	7.7 (4.5-13.3)
Sensitivity for lesion on CT, point estimate (95% CI)	0.99 (0.98-1.00)	0.87 (0.83-0.91)	0.94 (0.91-0.97)
Specificity for lesion on CT, point estimate (95% CI)	0.03 (0.03-0.04)*	0.39 (0.37-0.41)*	0.32 (0.30-0.34)*
Sensitivity for lesion requiring neurosurgery, point estimate (95% CI)	1.00 (0.98-1.00)†	1.00 (0.83-1.00)†	1.00 (0.91-1.00)†
Source	(11)	(11)	(10)
Criteria for CT	Headache, vomiting, seizure, intoxication, short-term memory deficit, age >60 y, injury above clavicles	High-risk patients: GCS score <15 at 2 h post-injury, suspected skull fracture, vomiting (≥2 times), age ≥65 y Medium-risk patients: retrograde amnesia >30 min, dangerous trauma mechanism‡	Major criteria: pedestrian or cyclist versus vehicle, ejected from vehicle, vomiting, posttraumatic amnesia ≥4 h, clinical signs of skull fracture, GCS score <15, GCS deterioration ≥2 points (1 h after presentation), anticoagulant therapy, posttraumatic seizure, age ≥60 y Minor criteria: fall from any elevation, persistent anterograde amnesia, posttraumatic amnesia 2-4 h, contusion of the skull, neurologic deficit, loss of consciousness, GCS deterioration of 1 point (1 h after presentation), age 40-60 y§

NOC = New Orleans Criteria; CCHR = Canadian CT Head Rule; CHIP = CT in Head Injury Patients; CI = confidence interval.

All variables were entered into the model as beta distributions, except for the diagnostic odds ratio, which was entered as a lognormal distribution.

Lesion on CT was defined as any intracranial traumatic finding on CT, including depressed skull fracture, but excluding isolated linear skull fracture.

* In the model, specificity was modeled as a function of sensitivity and the diagnostic odds ratio to reflect the inverse relationship between sensitivity and specificity in the (probabilistic) sensitivity analyses.

† The 95% CIs reported in the literature are wider than used in the model. In studies evaluating clinical prediction rules for selective CT, any intracranial traumatic lesion on CT is considered a proxy for a lesion requiring neurosurgery, because the latter is such a rare event. Therefore, in the (probabilistic) sensitivity analyses we linked the sensitivity for any intracranial traumatic lesion and for neurosurgical lesions (through proportional odds ratios, Technical appendix 1) allowing them to change simultaneously. We modeled the sensitivity for lesions requiring neurosurgery to be at least the sensitivity for any intracranial traumatic lesion. In a secondary analysis we repeated the (probabilistic) sensitivity analysis allowing the two sensitivities to vary independently.

‡ In high-risk patients a CT scan is deemed mandatory; in medium-risk patients a CT scan is recommended but close clinical observation is an alternative.

§ A CT is indicated in the presence of 1 major or 2 minor criteria.

In the base case analysis we evaluated 10 000 41-year-old males with MHI, representative of the typical patient in the CHIP study. The prior probability of a non-neurosurgical intracranial traumatic lesion was 7.6%, and that of an intracranial traumatic lesion requiring neurosurgery 0.5% (11, 14).

Sensitivity analysis

We repeated our analysis using the United Kingdom and Dutch recommendations for cost-effectiveness modeling. The UK recommendations include a healthcare perspective, which compared to the base case analysis implied excluding time costs, and discounting both future costs and effectiveness at 3.5% (51, 52). The Dutch recommendations include a societal perspective, with patient time costs and productivity losses (friction costs) taken into account, and discounting of future costs and effectiveness at 4% and 1.5% respectively (53).

Using one-way sensitivity analyses we assessed the impact of varying each parameter across its 95% CI. The impact of outcome after delayed diagnosis of a neurosurgical traumatic lesion was assessed by varying the proportion of patients with poor outcome (GOS = 1–4) from 0.4 (which is the proportion of poor outcome if a neurosurgical lesion is correctly identified) to 1.0 (ie, all patients with delayed diagnosis

Table 2. Probability of long-term functional outcome (≥1 year after the injury) according to the Glasgow Outcome Scale, as determined in our own study population

Outcome after 1 year	Non-neurosurgical traumatic intracranial lesion	Identified neurosurgical lesion	Missed neurosurgical lesion
GOS = 1 (dead), point estimate (95% CI)	0.04 (0.02-0.07)	0.06 (0.00-0.20)	0.29 (0.01-0.76)*
GOS = 3 (severe disability), point estimate (95% CI)	0.01 (0.00-0.06)	0.00 (0.00-0.00)	0.10 (0.00-0.68)*
GOS = 4 (moderate disability), point estimate (95% CI)	0.31 (0.21-0.44)	0.31 (0.02-0.76)	0.22 (0.00-0.73)*
GOS = 5 (full recovery), point estimate (95% CI)	0.64 (0.54-0.77)	0.63 (0.19-0.95)	0.39 (0.05-0.82)*
Source	(14)	(14)	(14, 42)

GOS = Glasgow Outcome Scale; CI = confidence interval.

All variables were entered into the model as beta distributions. Data on outcome 1 year after the injury according to GOS were available on 92 patients (4 with a neurosurgical lesion).

* Estimates of probability of outcome after delayed diagnosis of a neurosurgical lesion were based on our estimates for an identified neurosurgical lesion, and adjusted for delay in diagnosis based on data by Cordobes et al (42), by calculating the ratio between delayed diagnosis and correct identification of a neurosurgical lesion for each outcome.

Table 3. Quality of life estimates, as determined in our own study population

Outcome	Quality of Life point estimate	95% CI	Distribution	Source
GOS = 1	0.00	-	-	CHIP study
GOS = 3	0.15	0.06-0.28	beta	CHIP study
GOS = 4	0.51	0.39-0.63	beta	CHIP study
GOS = 5	0.88	0.74-0.97	beta	CHIP study
Well (no lesion on CT)	1.00	-	-	(21, 44)

CI = confidence interval.

Quality of life data were available on 87 patients (14). GOS = 2 (vegetative state) was not observed in the CHIP study and therefore not modeled.

of a neurosurgical lesion have poor outcome). The distribution of GOS states in patients with poor outcome was kept constant. We also assessed the impact of age (range, 20–60 years), cost of a CT scan (range, US$ 50–250), and increased radiation induced mortality to account for repeat CT scans and age of exposure (range, 0.008%–0.8%). To assess the impact of bias towards missing patients with a non-neurosurgical traumatic lesion we repeated the analysis assuming equal costs whether a non-neurosurgical traumatic lesion was correctly identified or left undiagnosed.

Using two-way sensitivity analyses, we varied the prediction rules' sensitivities to identify patients requiring neurosurgery in combination with important parameters, namely the proportion of patients with poor outcome after delayed diagnosis of a neurosurgical traumatic lesion, age, cost of a CT scan, and radiation induced mortality.

In a three-way sensitivity analysis, we varied the prediction rules' sensitivity for identifying patients requiring neurosurgery, age, and radiation induced mortality.

Finally, we performed probabilistic sensitivity analyses, using two alternative modeling approaches (Technical appendix 1), drawing from all variable distributions (Technical appendix 2–3) using Monte Carlo simulation of 10 000 samples. We calculated

Table 4. Estimates of the total costs, survival, and effectiveness for the first year after the injury

	Total costs (US$)	Survival (%)	Effectiveness (QALY)
CT scan performed (ie, positive prediction rule)			
No lesion present *(false positive prediction)*	138	99.9	1.00
Non-neurosurgical lesion present *(true positive prediction)*	18 890	96.2	0.72
Neurosurgical lesion present *(true positive prediction)*	35 322	94.1	0.71
No CT scan performed (ie, negative prediction rule)			
No lesion present *(true negative prediction)*	0	99.9	1.00
Non-neurosurgical lesion present *(false negative prediction)*	10 108	96.2	0.72
Neurosurgical lesion present *(false negative prediction)*	44 509	71.0	0.47

US$ = US dollar; QALY = quality adjusted life year.

The difference in costs between patients with a neurosurgical lesion who had not initially undergone CT and those with a neurosurgical lesion who had undergone CT were due to return to hospital by ambulance (US$ 588), re-assessment in the emergency department (US$ 138), an increased proportion admitted for intensive care observation for an average of 5 days (100% versus 59%, US$ 2234/day), as well as an increased proportion (10% versus 6%) of patients being discharged from hospital to a nursing home as a result of poorer outcome for the duration of the rest of the year (US$ 274/day for 353 days).

The difference in costs between patients with a non-neurosurgical lesion who were scanned versus those that were not scanned was due to the reduced number of CT scans performed (100% versus 32%, US$ 77/CT scan), and the fact that patients in whom a non-neurosurgical traumatic lesion was detected (with CT) were admitted for clinical observation: 84% in a normal ward (US$ 539/day) for an average of 7 days, and 16% in intensive care (US$ 2234/day) for an average of 5 days and an additional 14 days in a normal ward. Patients who were not scanned, and consequently in whom a non-neurosurgical lesion was not identified, were not admitted, but discharged home. Only 20% of these patients were seen for outpatient follow-up, while all patients with an identified traumatic lesion had an average of 2 outpatient follow-up visits (US$ 104/visit).

No costs were involved in patients without a traumatic lesion who were not scanned, while the cost of the CT scan, including time costs, was the only cost contributing to the total costs for those without a traumatic lesion who underwent CT.

the probability that performing CT in all patients was cost-effective compared to the selective use of CT (for each of the prediction rules) for varying willingness-to-pay thresholds using acceptability curves. Expected value of perfect information (EVPI; simulation with 20 000 samples), the population EVPI (US population, 5 years, discount rate of 3%), and the partial EVPI (2-level simulation with 500×500 samples) were determined to assess the value of performing further research in order to decrease uncertainty related to the model's parameters (54, 55).

RESULTS

Study population and parameter estimates

Data on 3181 of 3364 patients were included in the CHIP study (11, 14). CT showed an intracranial traumatic finding in 243 patients (7.6%), 17 of whom underwent neurosurgery (ie, had a neurosurgical lesion) (Technical appendix 2). Parameter estimates, costs, and outcome data from the CHIP study are summarized in Tables 1–3 and Technical appendices 2–3.

First year costs and outcome

Total costs in the first year after the injury were highest for patients with a neurosurgical lesion who had not initially undergone CT (US$ 44 509; Table 4). For patients with a non-neurosurgical lesion, total costs in the first year were lower for patients in whom no CT scan was performed (US$ 10 108; Table 4) than for those who were scanned (US$ 18 890; Table 4). Outcome one year after the injury was worst in patients with a neurosurgical lesion who had not undergone CT, as a result of delayed diagnosis and surgery (71% survival, 0.47 QALY; Table 4). Outcome in patients with a non-neurosurgical lesion was the same whether CT was performed or not (96% survival, 0.72 QALY; Table 4).

Base case analysis

In the base case analysis, all CT strategies were almost equally effective (22.464 QALYs; Table 5). The differences were negligible,

Table 5. Base case analysis (cohort analysis)

Strategy	Cost (US$)	Effectiveness (QALY)	ICER (US$/QALY gained)	Gain in NHB*	Cost-savings (US$)†
No CT[ref]	9703	22.43444	dominated	0	n/a
CCHR	8800	22.46393	superior	0.0415	120 million
CHIP	8854	22.46395	3 million	0.0408	71 million
NOC	8923	22.46391	dominated	0.0399	9 million
CT in all	8933	22.46390	dominated	0.0397	0

US$ = US dollar; QALY = quality adjusted life year; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; Ref = reference strategy; N/a = not applicable; CCHR = Canadian CT Head Rule; CHIP = CT in Head Injury Patients; NOC = New Orleans Criteria.

The ICER is calculated as the incremental difference in cost divided by the incremental difference in QALY. Compared with the CCHR, the CHIP rule is US$ 54 more expensive, and 0.00002 QALY is gained, thus the ICER of CHIP compared with CCHR is 54/0.00002 = US$ 3 million per QALY gained. A strategy is dominated if another strategy is equally or more effective and less costly. A strategy is superior if it is the least costly compared with all other strategies, and (near) equally effective.

* Gain in NHB compared with the reference strategy (no CT) is calculated as the difference in effectiveness of a strategy with the reference strategy – (difference in cost of a strategy with the reference strategy/willingness-to-pay threshold) and using a willingness-to-pay threshold of US$ 75 000/QALY.

† Cost-savings: potential annual cost-saving compared with CT in all patients for an estimated 900 000 patients presenting annually in the US with minor head injury. The estimated incidence of minor head injury patients in the US is derived from an incidence of 300/100 000 (5) and the US population of 300 million.

because they result from poorer outcome in patients with a missed neurosurgical lesion, while the CT strategies were assumed not to misclassify patients in addition to neurosurgical lesions being very rare. Of the CT strategies, CCHR was the least costly (lifetime costs US$ 8800; Table 5), and thus the most cost-effective (Table 5). Any of the prediction rules would lead to cost-savings compared to CT in all patients, but the cost-savings with CCHR and the CHIP rule were substantially greater than with NOC.

Sensitivity analysis

Repeating the analysis according to the UK and the Dutch recommendations for cost-effectiveness analysis again demonstrated that selective CT was cost-saving and that the CCHR and CHIP rule provided substantially higher cost-savings than NOC.

Varying all parameters across their 95% CIs in one-way sensitivity analyses did not affect the model outcome, except for varying the prediction rules' sensitivities to identify patients requiring neurosurgery. At sensitivities below 97%, CT in all patients was more cost-effective with an ICER below the willingness-to-pay threshold. At sensitivities below 91%, CT in all patients became dominant, being both less costly and more effective than all other strategies.

The model outcome was not affected by varying the proportion of patients with poor outcome after delayed neurosurgery, age, cost of a CT, or increased radiation induced mortality. Assuming equal costs whether a non-neurosurgical traumatic lesion was correctly identified or left undiagnosed did not affect the outcomes substantially. Variation of these parameters in two- and three-way sensitivity analyses and using alternative modeling approaches (Technical appendix 1) demonstrated that the threshold sensitivity for identifying patients requiring neurosurgery ranged from 91% to 99% depending on the combination of parameter values.

Probabilistic sensitivity analysis demonstrated that the probability that selective CT was cost-effective compared to CT in all patients was 0.51–0.64 depending on the willingness-to-pay threshold. Selective CT according to the CHIP rule was most likely to be cost-effective.

Value of information analysis showed an EVPI for further research of US$ 1759 per patient, which for the entire US population (300 million) over a period of 5 years amounts to US$ 7 billion. Partial EVPI calculations demonstrated that this was mainly due to uncertainty in the long-term functional outcomes (US$ 1703 per patient), which was in turn largely due to uncertainty in the outcome of patients with a non-neurosurgical lesion (US$ 1498 per patient) and to a lesser extent of patients with a neurosurgical lesion (US$ 187 per patient).

DISCUSSION

Using CCHR to select patients for CT after MHI is most cost-effective and can lead to annual US cost-savings of US$ 120 million. This finding, however, is only valid under the assumption that this prediction rule is highly sensitive for the identification of patients requiring neurosurgery. At lower sensitivities cost-savings are less, and at sensitivities below 91%–99% CT in all patients is cost-effective compared with selective CT. Furthermore, uncertainty concerning long-term functional outcome after MHI currently precludes a definitive decision on whether selective CT is more cost-effective than CT in all MHI patients. Value of information analysis demonstrated that further research is warranted to reduce uncertainty regarding long-term functional outcome after MHI.

Stein et al (13) also found CCHR to be more cost-effective than CT in all patients, skull radiography, clinical observation or no treatment. Other selective CT strategies,

such as NOC or the CHIP rule, were not modeled. In the present study, we confirmed that selecting patients for CT based on a prediction rule is cost-effective, with CCHR yielding the largest cost-savings. With the CCHR, the best distinction between patients requiring neurosurgery versus those who do not is made. As identification of non-neurosurgical lesions increases the use of resources without a gain in effectiveness, while identification of neurosurgical lesions averts costs and loss of (quality of) life, it was not surprising that CCHR was found to be the most cost-effective strategy in the base-case analysis.

Selective CT strategies, however, introduce the risk of misclassification, and consequently missing patients requiring neurosurgery. Previous cost-effectiveness studies have left this issue unaddressed (13, 56). We found that selective CT had a probability of only 51%–64% to be cost-effective compared with CT in all MHI patients. Furthermore, CT in all patients was the most cost-effective strategy when sensitivities for identifying patients requiring neurosurgery were below 91%–99%. So, even though a neurosurgical traumatic lesion after MHI is very rare, CT in all MHI patients is more cost-effective than missing even a small proportion of these patients, as delayed diagnosis of patients requiring neurosurgery presumably leads to poorer outcome, incurring higher costs due to disability and loss of quality of life. Due to the rare occurrence of neurosurgical lesions after MHI, 95% CIs for the prediction rules' sensitivities for such lesions are wide, with lower limits well below 90% (11, 12). Given this rare occurrence of neurosurgical lesions, the prediction rules were originally designed considering any intracranial traumatic lesion on CT as a proxy for a lesion requiring neurosurgery. The sensitivity for neurosurgical lesions, therefore, would not be lower than the overall sensitivity for any intracranial traumatic lesion. CCHR's lower limit of the 95% CI for sensitivity for intracranial traumatic lesions is well below 90%, yielding a real possibility that CCHR is less cost-effective than CT in all MHI patients, despite its large potential for cost-savings. The CHIP rule also yields considerable annual cost-savings (US$ 71 million), and is more likely to be cost-effective, given its 95% CI lower limit for sensitivity of intracranial traumatic lesions of 91%. This was confirmed in our probabilistic sensitivity analysis. An additional advantage of the CHIP rule is its wide applicability since it also applies to patients without a history of posttraumatic amnesia or loss of consciousness.

Our model was based on several assumptions. The strength of our study was that we based our model on our own data, leaving only a few parameters to be estimated from the literature. An important parameter was the cost of a CT scan, which we derived from our own hospital data, including only true costs. Our cost estimate for CT is much lower than that reported in previous cost-effectiveness studies, as true costs are lower than the charges and reimbursements used in previous studies, and possibly also by the Dutch setting. All costs included in the model were true costs, proportionate to the cost of a CT scan, and lower than those reported in other studies. In the sensitivity analyses, there was no effect of increasing the cost of a CT scan.

The most important uncertain parameters were functional outcome after delayed diagnosis of neurosurgical lesions and after missed diagnosis of a non-neurosurgical traumatic lesion. Data on these outcomes are scarce and unlikely to become available due to obvious medico-ethical issues. Patients with a non-neurosurgical traumatic lesion with a false negative prediction and who were consequently discharged home undiagnosed, were assumed to have the same functional outcome as patients with a true positive prediction, since patients with a diagnosed

non-neurosurgical traumatic lesion in our study underwent no intervention affecting their functional outcome (43). Since patients with an undiagnosed non-neurosurgical traumatic lesion were not admitted, costs were much lower than those for correctly identified patients, who were admitted. Combined with equal functional outcome, this assumption biased our model towards missing these patients, ie, towards the strategy with the lowest sensitivity for identifying these patients, which was CCHR. Sensitivity analysis, however, showed that CCHR was the most cost-effective strategy even if there was no difference in costs between these two groups.

One could argue that functional outcome is not equal between patients with an undiagnosed and a diagnosed non-neurosurgical lesion. Other than clinical observation and outpatient follow-up, no intervention was performed that would influence these patients' outcome. The main indication for clinical observation is early detection of deterioration and subsequent need for neurosurgery. In our model, patients with a lesion that changed from non-neurosurgical to neurosurgical during clinical observation would have been identified by the prediction rules as requiring a CT scan and would not be categorized as non-neurosurgical. Whether clinical observation without subsequent neurosurgery, and outpatient follow-up affects functional outcome is entirely speculative. The uncertainty about long-term functional outcome after MHI was taken into account in the probabilistic sensitivity analysis and was the most important parameter requiring further research in our value of information analysis.

Functional outcome after delayed diagnosis of neurosurgical lesions is generally assumed to be poorer than when timely neurosurgery is performed (36–42), although there is only little and indirect evidence to support this. The outcome estimates for our model were based on the only published study in which the impact of CT on functional outcome in patients with a neurosurgical traumatic lesion was assessed (42). The authors compared patients with extradural hematoma from before the introduction of CT with those after the introduction of CT and found poorer outcome in patients with delayed diagnosis. Although retrospective and relatively old, from the time when CT was introduced, this study provides the most direct evidence for improved functional outcome with early identification of neurosurgical traumatic lesions. Indirect evidence comes from general observational studies of neurosurgical trauma patients (36, 40, 41, 57).

Uncertainty about model parameters represents the main limitation of this study. Most parameters were based on our own study data and were compared to and complemented with findings from literature. We addressed these uncertainties by extensively varying all model parameters in sensitivity analyses. The finding that CCHR was most cost-effective was insensitive to variation of most uncertain parameters, except for the prediction rules' sensitivities as addressed above. With the use of CT, radiation issues are a concern (30), since MHI patients tend to be young, with known increased radiation risks, and may have multiple MHIs in their life requiring repeated CT scans. We therefore included radiation induced mortality in our model, and repeated the analyses assuming extreme increases in radiation related mortality combined with patient age, but found that this did not affect the model outcome.

With CT scanners being widely available and the high pressure of medico-legal issues, many clinicians would welcome a lenient CT strategy. Our study suggests that, given the currently available evidence and the remaining uncertainty concerning long-term functional outcome, CT in all MHI patients

is justified, even when taking radiation issues into account, since selective CT is not unequivocally more cost-effective.

Conclusion

Selective CT based on prediction rules is cost-saving and potentially cost-effective. Out of the 3 prediction rules, the highest annual cost-savings are expected with CCHR, although its sensitivity for identifying patients requiring neurosurgery can be below the threshold at which CT in all MHI patients is cost-effective. The CHIP rule is more sensitive than CCHR, is more likely to be cost-effective, is more widely applicable, and also has the potential of substantial cost-savings. More research is warranted to increase certainty on long-term patient outcome after MHI. Until such time, CT in all MHI patients is also justified.

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TECHNICAL APPENDIX 1

Modeling the inverse relationship between sensitivity and specificity

In the model specificity was expressed as a function of sensitivity and the diagnostic odds ratio (DOR) to reflect the inverse relationship between sensitivity (sens) and specificity (spec) in the (probabilistic) sensitivity analysis according to equation 1:

$$DOR = \frac{TP}{FN} \cdot \frac{TN}{FP}$$

$$DOR = \frac{sens}{1 - sens} \cdot \frac{spec}{1 - spec}$$

$$\frac{1 - spec}{spec} = \frac{sens}{(1 - sens) \cdot DOR}$$

$$1 - spec = \frac{sens}{sens + (1 - sens) \cdot DOR}$$

$$spec = 1 - \frac{sens}{sens + (1 - sens) \cdot DOR}$$

Equation 1. TP = true positive; FN = false negative; TN = true negative; FP = false positive.

The DOR was modeled with a lognormal distribution using equation 2:

$$\ln(DOR) = \ln\left(\frac{TP}{FN} \cdot \frac{TN}{FP}\right)$$

$$se(ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Equation 2. ln = natural logarithm; se = standard error.

Modeling the sensitivity for identifying a neurosurgical lesion

The 95% CIs of sensitivity for identifying a neurosurgical lesion reported in the literature are wide (0.82–1.00), because a lesion requiring neurosurgery is a very rare event and the estimate is based on only a few observations. In studies evaluating clinical prediction rules for selective CT, all intracranial traumatic lesions on CT are generally considered a proxy for lesions requiring neurosurgery, because the latter is so rare.

For the purpose of the (probabilistic) sensitivity analyses, we modeled the sensitivity for identifying neurosurgical lesions using 2 methods:

Method 1: We linked the two sensitivities (through proportional odds ratios [OR]) allowing them to change simultaneously. We modeled the sensitivity for identifying a neurosurgical lesion (sensNSx) to be at least the sensitivity for all intracranial traumatic lesions (sensRULE).

$$\text{ProbToOdds}(\text{sensNSx}) = \text{OR} \cdot \text{ProbToOdds}(\text{sensRULE})$$

Equation 3. With OR = 6 (range, 1-15; distribution, triangular).

Method 2: In a secondary analysis we repeated the (probabilistic) sensitivity analyses allowing the two sensitivities to vary independently comparing selective CT versus CT in all minor head injury patients. The sensitivity for identifying a neurosurgical lesion (sensNSx) was modeled as a triangular distribution with a range from 0.82 to 0.999 and a most likely value of 0.99.

TECHNICAL APPENDIX 2

Probability estimates, as determined in our own study population

Probability	Point estimate	95% CI	Distribution	Source
Lesion on CT	0.08	0.07-0.09	beta	CHIP study
Lesion on CT requiring neurosurgery	0.07	0.04-0.10	beta	CHIP study
Patient presenting out of hours	0.67	0.65-0.69	beta	CHIP study
Additional CT scan with non-neurosurgical lesion	0.32	0.27-0.38	beta	CHIP study
Additional CT scan with neurosurgical lesion	0.71	0.48-0.89	beta	CHIP study
Readmission with non-neurosurgical lesion	0.07	0.04-0.11	beta	CHIP study
Intensive care observation with non-neurosurgical lesion	0.16	0.11-0.21	beta	CHIP study
Intensive care observation with neurosurgical lesion	0.59	0.36-0.80	beta	CHIP study
Normal ward observation with non-neurosurgical lesion	0.84	0.79-0.89	beta	CHIP study
Normal ward observation with neurosurgical lesion	0.41	0.19-0.64	beta	CHIP study
Outpatient follow-up with missed non-neurosurgical lesion	0.20	0.03-0.48	beta	assumption
Physiotherapy with non-neurosurgical lesion	0.24	0.18-0.30	beta	CHIP study
Physiotherapy with neurosurgical lesion	0.08	0.00-0.27	beta	CHIP study
Rehabilitation clinic with non-neurosurgical lesion	0.03	0.01-0.05	beta	CHIP study
Rehabilitation clinic with neurosurgical lesion	0.07	0.00-0.23	beta	CHIP study
Nursing home with non-neurosurgical lesion	0.07	0.04-0.10	beta	CHIP study
Nursing home with identified neurosurgical lesion	0.06	0.00-0.22	beta	CHIP study
Nursing home with missed neurosurgical lesion	0.10	0.06-0.28	beta	CHIP study
Nursing home with GOS = 3	0.80	0.51-0.97	beta	assumption
Nursing care at home with GOS = 3	0.20	0.03-0.49	beta	assumption
Residential home after non-neurosurgical lesion	0.02	0.01-0.04	beta	CHIP study
Residential home after neurosurgical lesion	0.20	0.05-0.43	beta	CHIP study

CI = confidence interval; GOS = Glasgow Outcome Scale.

Lesion on CT was defined as any intracranial traumatic finding on CT, including depressed skull fracture, but excluding isolated linear skull fracture. Neurosurgical lesion was defined as any traumatic lesion on CT requiring neurosurgery within 30 days of the injury.

Data on hospital admission, outpatient follow-up and discharge were available on at least 230 (95%) patients (16 with a neurosurgical lesion).

TECHNICAL APPENDIX 3

Cost calculation parameters

	Point estimate	95% CI	Distribution	Source
Cost (US$)				
1 Emergency ambulance	588	417-811	lognormal	(25)
1 Emergency department visit	185	127-257	lognormal	(25)
1 CT scan	77	38-139	lognormal	(48)
Additional cost of 1 CT scan performed out of hours	11	8-15	lognormal	(48)
1 Neurosurgical procedure	1599	1107-2238	lognormal	(25)
1 Day intensive care observation	2234	1583-3077	lognormal	(25)
1 Day normal ward observation	539	379-732	lognormal	(25)
1 Day nursing home	274	190-384	lognormal	(25)
1 Outpatient visit	104	72-146	lognormal	(25)
Travel for 1 outpatient visit	16	0-93	lognormal	(25)
1 Physiotherapy session	30	21-41	lognormal	(25)
Travel for 1 physiotherapy session	7	0-30	lognormal	(25)
1 Day rehabilitation clinic	446	305-623	lognormal	(25)
1 Day residential home	113	78-158	lognormal	(25)
1 Hour informal care at home	11	8-15	lognormal	(25)
1 Hour nursing care at home	54	38-75	lognormal	(25)
1 Hour support at home	29	20-40	lognormal	(25)
Mean hourly wage male (25-44 y)*	54	38-75	lognormal	(25)
Volume				
Duration (h) of ambulance ride	0.5	0.0-2.6	lognormal	assumption
Duration (h) of CT scan (includes waiting time)	1.0	0.4-2.2	lognormal	assumption
Duration (h) of emergency department visit	1.0	0.1-5.1	lognormal	assumption
Duration (h) of outpatient visit	2.0	0.7-4.5	lognormal	assumption
Duration (h) of physiotherapy session	3.0	0.8-8.1	lognormal	assumption
No. of hours informal care at home with GOS = 4	730	392-1229	lognormal	assumption
No. of hours nursing care at home with GOS = 3	730	392-1229	lognormal	assumption
No. of days of clinical observation with identified non-neurosurgical lesion	9	0-56	gamma	CHIP study
No. of days of clinical observation with neurosurgical lesion	12	0-56	gamma	CHIP study
No. of days intensive care observation with identified non-neurosurgical lesion	5	0-41	gamma	CHIP study
No. of days intensive care observation with neurosurgical lesion	5	0-30	gamma	CHIP study
No. of days normal ward additional to intensive care observation with identified non-neurosurgical lesion	14	0-62	gamma	CHIP study
No. of days normal ward additional to intensive care observation with neurosurgical lesion	8	0-39	gamma	CHIP study
No. of days of normal ward observation with identified non-neurosurgical lesion	7	0-52	gamma	CHIP study

No. of days of normal ward observation with neurosurgical lesion	11	0-59	gamma	CHIP study
No. of days readmitted with non-neurosurgical lesion	6	0-30	gamma	CHIP study
No. of outpatient visits with identified non-neurosurgical lesion	2	0-11	lognormal	CHIP study
No. of outpatient visits with neurosurgical lesion	2	0-29	lognormal	CHIP study
No. of physiotherapy sessions	9	4-17	lognormal	assumption
No. of working hours recovery with no lesion	40	15-89	lognormal	(58)
No. of working hours recovery with non-neurosurgical lesion	350	257-467	lognormal	(59)
No. of working hours recovery with neurosurgical lesion	500	183-1082	lognormal	(59)
No. of days rehabilitation clinic with non-neurosurgical lesion	91	45-162	triangular	assumption
No. of days rehabilitation clinic with neurosurgical lesion	88	45-162	triangular	assumption

US$ = US dollar; CI = confidence interval; GOS = Glasgow Outcome Scale.

* Time costs were based on the mean hourly wage for men aged 25-44 years, and calculated for the working hours the patient spent in hospital, rehabilitation clinic, outpatient follow-up, and physiotherapy.

Non-neurosurgical lesion on CT was defined as any intracranial traumatic finding on CT that didn't require neurosurgery. Neurosurgical lesion was defined as any traumatic lesion on CT requiring neurosurgery within 30 days of the injury.

Data on hospital admission, outpatient follow-up and discharge were available on at least 230 (95%) patients (16 with a neurosurgical lesion).

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Cost-effectiveness of using Computed Tomography (CT) for minor head injury compared with several other management strategies

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TO THE EDITOR

STEIN ET al report on the cost-effectiveness of using computed tomography (CT) for minor head injury compared with several other management strategies (1). They conclude that the selective use of CT in patients with minor head injury according to the Canadian CT Head Rule (CCHR) (2) is the most cost-effective management strategy. However, we think that their analysis is based on several debatable assumptions that may undermine the validity, and consequently, the conclusions of their article.

First, Stein et al claim that CT is only 98% sensitive for the detection of lesions requiring neurosurgical intervention. This figure seems to be based on two studies, referenced in their article (3, 4). The first article indeed reports three cases of neurosurgical intervention with an initial negative CT. However, in all three cases neurosurgical intervention consisted of placement of an intracranial pressure monitor only, and recovery in all three cases was good. As Stein et al specifically state in the Methods section of their article, only intracranial hematomas requiring evacuation were considered surgical lesions, which implies that classifying these three cases as false-negative CT results for neurosurgical lesions is not valid. The second article concerns a retrospective study of patients with minor head injury, in 92% of whom CT was performed. In the Discussion section of this article, the authors mention that 6 of 10 patients requiring neurosurgical intervention had negative findings on early CT, whereas there is no mention of these patients in the Results section and details concerning the type of neurosurgical intervention were not reported. These data can therefore neither be verified nor interpreted. The idea, however, that an early CT may be false-negative for neurosurgical lesions is well recognized, and there are numerous reports on these so-called delayed hematomas. However, the incidence has been shown to be extremely low (<0.02%) (5), indicating that the sensitivity of CT for detection of neurosurgical lesions approaches 100% and CT may therefore be used safely to triage minor head injury patients for clinical observation. Interestingly, Stein et al state precisely this in their discussion, which, in our opinion, contradicts their assumption of a 98% sensitivity of CT for identifying patients requiring neurosurgical intervention.

Second, Stein et al state that admitting all patients for 24-hour clinical observation has no advantage over discharging patients without further screening, whereas observation in the emergency department for 6 hours apparently does have a benefit over each of these strategies in terms of clinical outcome. This seems very contradictory, as it is difficult to understand that 6 hours of clinical observation does, but 24 hours of clinical observation does not have a positive impact on clinical outcome. Moreover, a recent report by Af Geierstam et al (6) indicates that clinical observation performs just as well as early CT scanning in terms of clinical outcome in minor head injury patients, which also is in contrast with the assumption that clinical observation is no better than discharge without further screening.

Finally, the authors conclude that the selective use of CT and performing CT scanning in all patients yield the same number of quality adjusted life years and are therefore equally effective. This is hardly surprising, given that Stein et al assume that the selective use of CT is just as sensitive for identifying patients requiring neurosurgical intervention as when all minor head injury patients are scanned. This assumption, however, is not valid, since external validation studies of the CCHR have shown that the 95% confidence interval of its sensitivity for identifying patients requiring neurosurgical intervention is wide, ranging from 63% to 100% (7, 8). The authors state that, were selective CT to miss 1% of surgical lesions, this strategy would

become slightly less effective than a policy of scanning all patients, but the latter strategy would still be very costly. However, given the wide 95% confidence interval of the CCHR sensitivity, theoretically far more than 1% of patients requiring neurosurgery could be missed with the selective CT strategy. This still leaves the key question unanswered: how many patients can we afford to miss using a selective CT strategy? Can we afford to miss any at all or are the additional costs of scanning all patients with minor head injury justified compared with the gains in survival and quality-of-life?

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CHAPTER 7

Outcome after complicated minor head injury

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Background and purpose Functional outcome in patients with minor head injury with neurocranial traumatic findings on CT is largely unknown. We hypothesized that certain CT findings may be predictive of poor functional outcome.

Materials and methods All patients from the CT in Head Injury Patients (CHIP) study with neurocranial traumatic CT findings were included. The CHIP study is a prospective, multicenter study of consecutive patients, Glasgow Coma Scale (GCS) score of 13–14 or a GCS score of 15 and a risk factor. Primary outcome was functional outcome according to the Glasgow Outcome Scale (GOS). Other outcome measures were the modified Rankin Scale (mRS), the Barthel Index (BI), and number and severity of postconcussive symptoms. The association between CT findings and outcome was assessed by using univariable and multivariable regression analysis.

Results GOS was assessed in 237/312 patients (76%) at an average of 15 months after injury. There was full recovery in 150 patients (63%), moderate disability in 70 (30%), severe disability in 7 (3.0%), and death in 10 (4.2%). Outcome according to the mRS and BI was also favorable in most patients, but 82% of patients had postconcussive symptoms. Evidence of parenchymal damage was the only independent predictor of poor functional outcome (odds ratio = 1.89, P = .022).

Conclusion Patients with neurocranial complications after minor head injury generally make a good functional recovery, but postconcussive symptoms may persist. Evidence of parenchymal damage on CT was predictive of poor functional outcome.

HEAD INJURY is one of the main causes of disability, especially in the younger population. In patients with severe head injury, long-term outcome in terms of disability has been studied extensively and is consequently well documented (1–4). In clinical practice, however, most patients with head injury presenting to emergency departments have sustained minor head injury, which is commonly defined as a presenting Glasgow Coma Scale (GCS) score of 13–15, with or without a brief history of loss of consciousness (maximum of 15 minutes) or posttraumatic amnesia (maximum of 60 minutes) after blunt trauma to the head (5). Generally, these patients make a full functional recovery, though it is not uncommon to see patients with minor head injury with long-term sequelae after the injury (6–12).

With the advent of routine head CT scanning of virtually all patients with head injury, it has become clear that a substantial number (6%–10%) of patients with minor head injury have evidence of neurocranial traumatic complications (13–18). Functional outcome in these patients with so-called 'complicated' minor head injury has been shown to be significantly poorer than that in patients without neurocranial traumatic complications after minor head injury (19, 20). Long-term outcome in terms of functional disability or postconcussive symptoms in patients with complicated minor head injury specifically, however, is still largely unknown (12, 20). Also, outcome may not be the same for different traumatic CT findings. Traumatic findings may range from an isolated linear skull fracture, which is commonly considered to be clinically insignificant and would thus be expected to be associated with favorable functional outcome, to acute extra-axial hematoma requiring neurosurgical intervention, possibly associated with poorer functional outcome and an increased prevalence of posttraumatic complaints (18, 21).

The purpose of our study was to assess functional outcome in terms of disability and postconcussive symptoms in patients with neurocranial complications as established with CT after minor head injury. We hypothesized that certain CT findings may be predictive of poor long-term outcome in these patients with complicated minor head injury.

METHODS

Study population

This follow-up study was an extension of the CT in Head Injury Patients (CHIP) study, in which data were prospectively collected in 4 Dutch university hospitals on 3364 consecutively included patients between February 11, 2002, and August 31, 2004 (Figure 1) (22). Inclusion criteria for the CHIP study were the following: presentation within 24 hours of blunt head injury, 16 years of age or older, a GCS score of 13 or 14 on presentation or a GCS score of 15 and a minimum of 1 risk factor. Risk factors were a history of loss of consciousness, short-term memory deficit, amnesia for the traumatic event, posttraumatic seizure, vomiting, headache, clinical evidence of intoxication with alcohol or drugs, anticoagulant treatment or history of coagulopathy, external evidence of injury above the clavicles, or neurologic deficit. Exclusion criteria were contraindications for CT scanning or concurrent injuries precluding head CT within 24 hours of injury. After assessment by a neurologist or by a neurologist-in-training under supervision of a neurologist, all patients underwent head CT in accordance with local hospital policies and the guidelines set out by the Dutch Neurologic Society and the European Federation of Neurologic Societies (23, 24). Non-contrast-enhanced head CTs were performed in all included patients, by using a maximal section thickness of 5 mm infra-

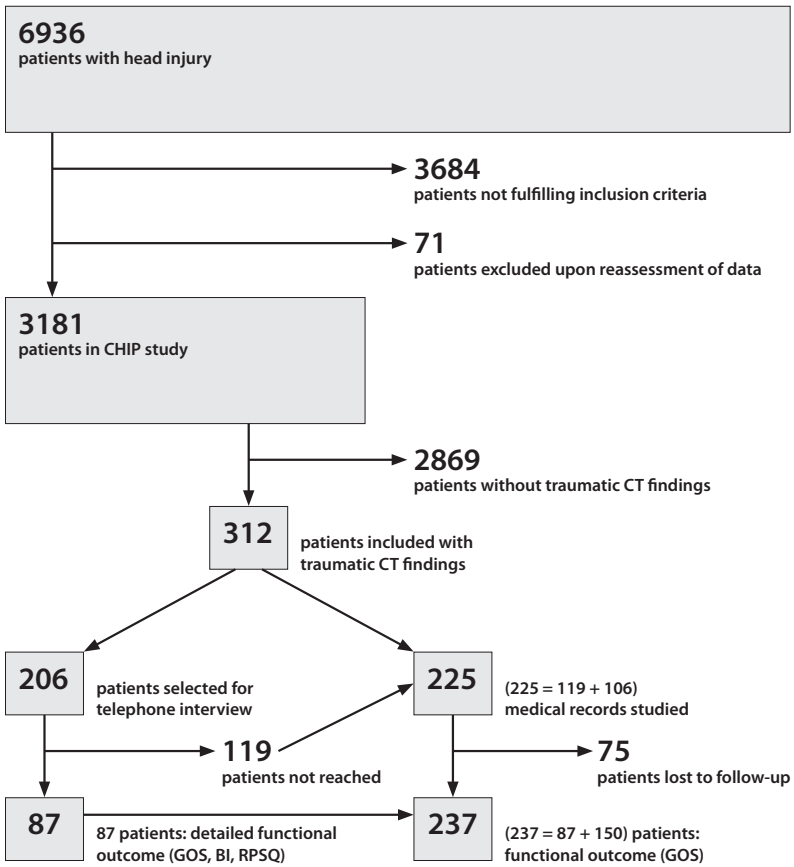

Figure 1. The number of patients presenting with minor head injury (6936) is an estimate based on the proportion of patients included out of the total number of patients with trauma seen by a neurologist or neurologist-in-training in the emergency department of the participating center that included most patients. Of the 3181 patients included in the CHIP study, 2869 did not have any evidence of a neurocranial traumatic finding on CT, leaving 312 patients eligible for inclusion in the current follow-up study.

and 8 mm supratentorially (25, 26). All CT scans were evaluated by a trauma radiologist or neuroradiologist.

For the current follow-up study, all patients with neurocranial traumatic findings on CT were included (Figure 1). The study protocol was approved by the Internal Review Board, and written informed consent was obtained from all patients participating in the assessment of outcome by telephone interview.

Assessment procedure

A detailed assessment of outcome was performed by telephone interview in a large

sample of patients (subpopulation) from our study population. This sample consisted of all included patients in the center in which most patients had been included. In all patients who had been included in the remaining 3 participating centers, as well as in patients who could not be reached for telephone interview, global functional outcome was assessed by careful review of the patients' medical records (27). Every attempt was made to reach all surviving patients from the subpopulation and to obtain their current addresses and telephone numbers from the hospital information system, patients' family doctors, telephone registry, and the local citizens' registry. Patients willing to participate were contacted by telephone, and a structured interview was conducted by a single trained researcher (D.A.v.R.). In patients who were unable to answer the questionnaire, the interview was performed with the patient's relative or care-giver as a proxy.

Mortality

We evaluated all-cause 30-day and disease-specific 1-year mortality in all patients, to avoid errors due to adjudication, which is consistent with the cardiologic and surgical literature. In patients who had died within 1 year, patient records were reviewed to establish whether death was related to the head injury, including remote mortality. In patients who had died of a cause unrelated to head injury, and in patients who had died more than 1 year after the head injury, death was considered not to be related to the head injury. In these patients, functional outcome from before death was derived from the patients' medical records.

Outcome measures

Primary outcome measure was the Glasgow Outcome Scale (GOS), which was assessed in all patients reached for telephone interview or was derived from the patients' medical records. The GOS is a 5-point scale to assess disability after head injury or other neurologic events (27). The clearly defined categories are as follows: 5, full recovery (ie, the resumption of normal life even though there may be minor neurologic or psychological deficits); 4, moderate disability (ie, disabled, but independent in daily life); 3, severe disability (ie, conscious but disabled with the patient being dependent for daily support [for >8 hours per day] due to mental or physical disability); 2, vegetative state (ie, the patient being unresponsive and speechless for weeks or months after the injury); and 1, dead, which included 30-day all-cause mortality and 1-year disease-specific mortality. Although the categories of disability are rather crude and may therefore not be very sensitive to subtle differences or changes in disability, it is the most widely used scale to assess functional outcome after head injury. It has been extensively validated and has been shown to correlate well with other measures of disability (2, 28–30).

In patients reached for telephone interview, a more detailed assessment of functional outcome was made according to the modified Rankin scale (mRS), the Barthel Index (BI), and the Rivermead Postconcussion Symptoms Questionnaire (RPSQ).

The mRS is a 7-point scale that is also used to assess functional disability after neurologic events such as head injury or stroke. It is more sensitive than the GOS for subtle differences in outcome, and ranges from zero (no symptoms) to 6 (death, all-cause 30-day and disease-specific 1-year mortality) (31, 32).

The BI is a 10-item questionnaire of daily functioning, assessing the patient's independence or dependence for each item on a scale from zero (fully dependent) to 2, 3, or 4 (fully independent, maximal score varies per item) (33). It covers the following items: eating, getting dressed, transferring from bed to chair, ambulating, negotiating stairs, managing personal care, bathing,

toileting, and controlling bowel and bladder. A maximal score (score = 20) indicates full independence for all items, whereas a minimal score (score = 0) indicates that the patient is fully dependent for all items.

The RPSQ is a 5-point scale of 16 commonly reported symptoms after head injury, with a high test-retest and inter-rater agreement for the assessment of the presence and severity of postconcussive symptoms (34). Patients are asked to rate the severity for each symptom in comparison with preinjury levels on a scale from zero (no symptoms) to 4 (severe symptoms). Additional symptoms resulting from the head injury may also be recorded and rated. The higher the sum score, the more (severely) symptoms are present after the injury.

Definitions

Neurocranial complications as identified on CT included all traumatic findings of the neurocranium. Intracranial lesions included all neurocranial complications except for isolated linear skull or skull base fractures. Traumatic subarachnoid hemorrhage and epidural and subdural hematomas were recorded as present or absent. Intraparenchymatous contusions included both hemorrhagic and nonhemorrhagic lesions. Diffuse axonal injury was defined as multiple small focal traumatic lesions in the typical locations of shearing injury. Depressed fractures included all fractures of the skull vault in which inward displacement of at least 1 of the bone fragments was seen. Linear skull fractures included all fractures of the skull vault, with no evidence of displacement of bone fragments. Skull base fractures included all fractures of the skull base. If multiple findings were present, the number of findings was recorded. Bilaterally occurring lesions were counted as 2 separate lesions. Diffuse axonal injury was counted as 1 finding. Each intraparenchymatous contusion was counted as 1 finding.

Data analysis

We assessed our study population for patient and clinical characteristics, including the presence of risk factors and findings on physical and neurologic examination, as well as neurocranial traumatic CT findings. We tested differences between the entire study population and the subpopulation for significance ($P < .05$) with respect to patient and clinical characteristics as well as CT findings, by using the independent samples 2-tailed t test for continuous, the Pearson χ^2 test for nominal, and the Mann-Whitney U test for ordinal variables. Similarly, we tested for significant differences ($P < .05$) between the patients who had been reached for the telephone interview and those who could not be reached within the subpopulation. We also assessed potential differences in the distribution of the GOS obtained by telephone interview and the GOS derived from the patients' medical records, with the Mann-Whitney U test ($P < .05$ for significance). All analyses, by using complete cases only, were performed with the Statistical Package for the Social Sciences (Version 12.0, SPSS, Chicago, Ill).

The distribution of functional disability according to the GOS, mRS, and BI was assessed, and the number and severity of postconcussive symptoms according to the RPSQ was recorded. We tested the association of each of the neurocranial traumatic CT findings with disability and symptoms for significance by using the Mann-Whitney U test for ordinal variables (GOS, mRS, and BI) and the independent samples t test for continuous variables (RPSQ). We assessed the association between the number of neurocranial traumatic findings and outcome by using linear regression analysis. A P value $<.05$ was used as a threshold for statistical significance. Results not reaching this level of significance but with a P value <0.10 were considered near significant.

Table 1. Patient characteristics and CT findings in the entire study population and in the subpopulation selected for telephone interview

	Entire population* (n = 312)		Subpopulation (n = 206)				
			Reached (n = 87)		Not reached (n = 119)		
Findings	No.	%	No.	%	No.	%	P value†
Patient							
Mean age‡ (range)	47.2 (17.0-93.3)		50.5 (17.5-86.6)		45.1 (17.7-93.3)		.043
Male sex	238	76	59	68	106	89	.000
Died	22	7.1	0	0	14	12	.001
Intoxication	118	38	33	38	57	48	.154
Clinical							
GCS score = 15	185	59	49	56	71	60	.631
GCS score = 14	90	29	27	31	33	28	.606
GCS score = 13	37	12	11	13	15	13	.993
LOC	227	73	60	69	89	75	.356
PTA	239	77	66	76	90	76	.969
Persistent amnesia	83	27	24	28	26	22	.343
Seizure§	6	1.9	0	0	3	2.5	.136
Headache	212	68	67	77	87	73	.524
Vomiting	69	22	23	26	24	20	.290
Neurologic deficit	48	15	14	16	21	18	.769
Infraclavicular injury	121	23	19	22	27	23	.885
CT							
Intracranial lesions	243	78	63	72	92	77	.421
Linear fracture	114	37	41	47	44	37	.144
Skull base fracture	82	26	29	33	26	22	.066
Depressed fracture	19	6.1	3	3.4	14	12	.032
Subdural hematoma							.033
Mild	58	19	23	26	16	14	
Severe	9	2.9	2	2.3	3	2.6	
Epidural hematoma							.332
Mild	31	9.9	8	9.2	14	12	
Severe	4	1.3	0	0.0	2	1.7	
SAH	86	28	30	34	30	25	.148
Contusion	142	46	28	32	51	43	.120
Diffuse axonal injury	14	4.5	2	2.3	7	5.9	.214

Note – LOC indicates loss of consciousness; PTA, posttraumatic amnesia; SAH, traumatic subarachnoid hemorrhage.
* Multiple symptoms and clinical and CT findings may be present in 1 patient.
† P values <.05 indicate differences between patients who were reached compared with those who were not reached for telephone interview (independent samples t test for continuous, Pearson χ^2 test for nominal, and Mann-Whitney U test for ordinal variables).
‡ Age in years.
§ Posttraumatic seizure.

To assess whether any of the neurocranial traumatic CT findings were independently predictive of long-term outcome according to the primary outcome measure, we performed multivariable logistic regression analysis after dichotomizing GOS into good (GOS = 5) and poor (GOS = 1– 4) outcome (35). We used a stepwise backward procedure by using

Table 2. Postconcussive symptoms as assessed with the RPSQ in 87 patients

Symptom	No or no more (%)	Mild (%)	Moderate (%)	Severe (%)
Headache	68 (78)	2 (2.3)	4 (4.6)	13 (15)
Dizziness	61 (70)	7 (8.0)	6 (6.9)	13 (15)
Nausea	82 (94)	1 (1.1)	1 (1.1)	3 (3.4)
Noise hypersensitivity	80 (92)	2 (2.3)	1 (1.1)	4 (4.6)
Sleep disturbance	65 (75)	6 (6.9)	8 (9.2)	8 (9.2)
Fatigue	52 (60)	8 (9.2)	4 (4.6)	23 (26)
Irritability	63 (72)	7 (8.0)	9 (10)	8 (9.2)
Depression	61 (70)	7 (8.0)	9 (10)	10 (11)
Frustration	66 (76)	6 (6.9)	7 (8.0)	8 (9.2)
Poor memory	54 (62)	7 (8.0)	6 (6.9)	20 (23)
Poor concentration	59 (68)	4 (4.6)	6 (6.9)	18 (21)
Slow thinking	63 (72)	7 (8.0)	5 (5.7)	12 (14)
Blurred vision	72 (83)	5 (5.7)	7 (8.0)	3 (3.4)
Light hypersensitivity	82 (94)	2 (2.3)	1 (1.1)	2 (2.3)
Double vision	79 (91)	5 (5.7)	0 (0.0)	3 (3.4)
Restlessness	79 (91)	3 (3.4)	2 (2.3)	3 (3.4)

Note – RPSQ scores of 0 and 1 indicate no or no more complaints; 2, mild; 3, moderate; 4, severe postconcussive symptoms.

the likelihood ratio criterion with P <.05 for inclusion and P >.10 for removal of variables. To reduce the number of variables (36), we grouped variables that were similar as follows: Epi- and subdural hematoma were combined as extra-axial hematoma; intraparenchymatous contusions and diffuse axonal injury as parenchymal damage; and linear and skull base fractures as nondepressed skull fracture. The other variables entered into the model were traumatic subarachnoid hemorrhage and depressed skull fracture.

RESULTS

Study population

Of the 3181 patients originally included in the CHIP study, 312 had at least 1 neurocranial traumatic finding on CT and were thus included in the current follow-up study (Figure 1).

The subpopulation selected for telephone interview consisted of 206 (66%) patients. There were no significant differences (P <.05) between the subpopulation and the entire study population with respect to patient and clinical characteristics or neurocranial traumatic findings on CT. Telephone interview was successfully performed in 87 (42%) patients at a mean of 2.8 years after the injury (range, 1.7– 4.3 years). No telephone interview was performed in 119 patients for the following reasons: They died (n = 14), lived abroad (n = 8), were homeless or had no permanent address (n = 7), moved without a forwarding address (n = 16), did not speak Dutch (n = 5), refused to participate (n = 23), or had no telephone number available (n = 46). In these 119 patients, as well as in the 106 patients not selected for telephone interview, medical records were reviewed (n = 225) to assess functional outcome according to the GOS (Figure 1).

Patient characteristics are shown in Table 1. Within the subpopulation, patients who were reached for telephone interview were older than those who were not reached and were more commonly female (Table 1). Of the neurocranial traumatic findings on

CT, depressed fracture was seen less and subdural hematoma more frequently in patients who were reached for telephone interview than those who were not reached (Table 1). Overall, there were no differences in the frequency of intracranial traumatic complications on CT. Multiple findings on CT were present in 198 patients (67%; range, 2–16).

Mortality

Twenty-two patients died (7.1%) at an average of 199 days (median, 78 days; range, 0–702 days). All-cause 30-day mortality was 2.9% (n = 9). A further 7 patients died within 1 year of injury, resulting in an all-cause 1-year mortality of 5.1%. In 1 of these patients, death was determined by the investigators to be secondary to complications from the head injury. One-year disease-specific mortality was thus 3.2% (n = 10). The remaining 6 patients died more than 1 year after the head injury.

Functional outcome

GOS data were obtained in 237 of 312 (76%) patients. There was no difference in the distribution of GOS obtained from telephone interview (87 patients, 37%) and GOS derived from medical records (Mann-Whitney U test, P = .173). Mean duration between the latest available follow-up data and time of injury was 15.1 months (median, 3.6 months; range, 0–56 months). Most

Table 3. Mean scores and SDs on the GOS, BI, mRS and RPSQ*

Traumatic CT finding	GOS		BI		mRS		RPSQ	
	Score (SD)	P value	Score (SD)	P value	Score (SD)	P value	Score (SD)	P value
Linear fracture		.820		.433		.419		.619
Absent	4.4 (1.0)		20 (1.2)		1.3 (1.1)		13 (15)	
Present	4.6 (0.7)		19 (2.0)		1.4 (0.9)		15 (12)	
Skull base fracture		.690		.602		.105		.070
Absent	4.5 (0.9)		19 (1.9)		1.2 (1.0)		12 (12)	
Present	4.5 (0.8)		20 (0.6)		1.6 (1.0)		18 (15)	
Depressed fracture		.633		.445		.230		.302
Absent	4.5 (0.9)		19 (1.6)		1.4 (1.0)		14 (13)	
Present	4.6 (0.6)		20 (0.0)		0.7 (1.2)		6 (10)	
Subdural hematoma		.137		.050		.573		.552
Absent	4.5 (0.8)		20 (1.6)		1.3 (1.0)		13 (13)	
Present	4.3 (1.1)		19 (1.5)		1.4 (1.0)		15 (13)	
Epidural hematoma		.200		.705		.313		.054
Absent	4.5 (0.9)		19 (1.7)		1.3 (1.0)		13 (13)	
Present	4.4 (0.8)		20 (0.4)		1.6 (0.9)		23 (16)	
SAH		.330		.238		.502		.681
Absent	4.5 (0.9)		19 (1.9)		1.4 (1.1)		14 (14)	
Present	4.5 (1.0)		20 (0.8)		1.2 (0.7)		13 (12)	
Contusion		.008		.140		.449		.643
Absent	4.7 (0.6)		20 (1.6)		1.3 (1.1)		13 (14)	
Present	4.3 (1.1)		19 (1.5)		1.4 (0.9)		15 (11)	
Diffuse axonal injury		.096		.000		.018		.803
Absent	4.5 (0.9)		20 (1.5)		1.3 (1.0)		14 (13)	
Present	3.8 (1.5)		16 (2.1)		3.5 (0.7)		12 (16)	

Note – SAH indicates traumatic subarachnoid hemorrhage; SD, standard deviation.
* Higher scores on the GOS and BI indicate more favorable outcome, whereas higher scores on mRS and RPSQ indicate poorer outcome and more severe postconcussive complaints, respectively.

patients had a good functional outcome (Figure 2), 150 (63%) patients having made full recovery. Seventy patients (30%) had moderate disability. Severe disability was present in 7 (3.0%) patients, and 10 (4.2%) patients died as a consequence of head injury (9 patients within 30 days and 1 patient within 1 year of head injury).

In the subpopulation, data on mRS were available on 87 surviving patients as well as 3 patients who had died as a result of head injury (all within 30 days of injury). Most patients had no (n = 16, 18%) or minor (n = 43, 48%) symptoms. Minor disability was present in 15 (17%) patients, moderate disability in 10 (11%), and moderately severe disability in 3 (3.3%).

BI could be assessed in 87 patients. Most patients were independent for all activities (n = 73, 84%). All patients were independent with respect to self-care. Dependency was highest for walking stairs, with 4 (4.6%) patients not being able to walk stairs and another 4 (4.6%) needing assistance.

RPSQ data were available on 87 patients (Table 2). Seventy-one (82%) patients had at least 1 postconcussive symptom. If present, symptoms were more frequently moderate to severe than mild. Most frequently reported symptoms were fatigue (40%), depression (30%), dizziness (30%), irritability (28%), sleep disturbances (25%), and cognitive symptoms such as poor memory (38%) and concentration (32%) and slowness of thinking (28%).

Association between neurocranial traumatic CT findings and functional outcome

Patients with diffuse axonal injury had a significantly or near significantly poorer outcome on all functional outcome measures than those without diffuse axonal injury (BI, P = .000; mRS, P = .018; GOS, P = .096; Table 3). Patients with intraparenchymatous lesions had a significantly poorer GOS outcome (P = .008, Table 3), and patients with subdural hematoma had a significantly poorer BI outcome (P = .050, Table 3).

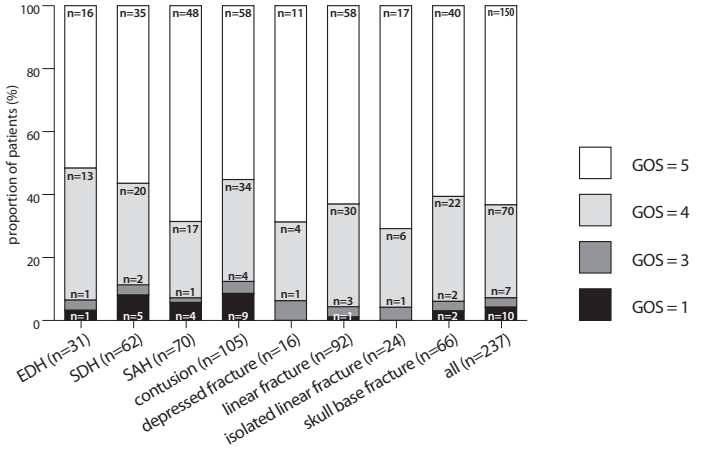

Figure 2. Distribution (percentage) of the Glasgow Outcome Scale (GOS) in patients with epidural hematoma (EDH), subdural hematoma (SDH), traumatic subarachnoid hemorrhage (SAH), intraparenchymatous contusion, depressed fracture, linear fracture, isolated linear fracture, skull base fracture, and in all patients (n = 237). GOS = 1 indicates dead; GOS = 2, vegetative state; GOS = 3, severe disability; GOS = 4, moderate disability; GOS = 5, full recovery.

Patients with epidural hematoma had near significantly more or more severe symptoms than those without epidural hematoma (mean RPSQ score, 23 versus 13, respectively; P = .054; Table 3), as did patients with a skull base fracture (mean RPSQ score 18 versus 12, P = .070; Table 3). No association with outcome was found in patients with traumatic subarachnoid hemorrhage, isolated linear or linear skull fracture, or depressed skull fracture. The number of neurocranial traumatic findings on CT was significantly associated with poorer functional outcome (P = .001) according to GOS and near significantly associated with more or more severe symptoms (P = .069) according to RPSQ.

Multivariable logistic regression analysis to predict outcome in terms of GOS was performed with the independent variables of extra-axial hematoma, parenchymal damage, traumatic subarachnoid hemorrhage, and depressed and non-depressed skull fracture. Evidence of parenchymal damage on CT (which included diffuse axonal injury or intraparenchymatous contusions) was the only independent predictor of poor functional outcome (odds ratio = 1.86; 95% confidence interval, 1.09–3.18; P = .022).

DISCUSSION

In this follow-up study of patients with evidence on CT of neurocranial traumatic complications after minor head injury, we found that most patients made a good functional recovery on long-term assessment. Evidence of parenchymal damage was the only independent factor significantly predictive of poor functional outcome. Despite generally good functional recovery, most of the patients we interviewed had 1 or more postconcussive symptoms.

A limitation of our study was the fact that a substantial number of patients were lost to follow-up. This limitation is inherent to the patient population we studied and the fact that we assessed outcome several years (2– 4 years) after the injury had occurred. Patients with trauma tend to be a young actively employed population that often moves, is difficult to reach, and is less willing to participate than older patients. In our study, most patients who could not be reached had moved without forwarding addresses or had changed telephone numbers. Patients who had been reached were somewhat older and more frequently female, suggesting possible selection bias. Although these differences were statistically significant, patients from both groups were within the same middle-aged range, and in both groups male patients formed the majority. We expect that this difference in demographic characteristics will only have a very small effect on our results. More important, however, the overall frequency of intracranial traumatic findings between the 2 groups was not significantly different, suggesting that the injury severity was comparable for patients who were reached versus those who could not be reached.

A further limitation may be that we included only patients with neurocranial complications and not patients with uncomplicated minor head injury. This makes it impossible to establish whether complicated minor head injury has a poorer outcome than uncomplicated head injury. This question, however, has already been addressed in other studies. Outcome in patients with minor head injury without neurocranial complications is generally known to be good (37), and the additional effort involved in following up these patients in our study would not have been justifiable. Another limitation is that we did not evaluate the effect on outcome of potentially confounding factors, such as multiple injuries due to the injury, premorbid disability, chronic pain, or litigation. Although it would be interesting to include these potential confounders in

the outcome assessment, it would still be difficult to disentangle the effect on outcome of neurocranial complications and those of confounders.

Finally, the fact that some of the data in our study were obtained retrospectively may be considered another limitation. Because there were no differences between the entire study population and the subpopulation or between patients in whom outcome was assessed prospectively or retrospectively, we believe that no significant bias has been introduced by this study design. Because follow-up rates in patients with trauma tend to be low (6, 10, 20), studies with prospectively included patients but retrospectively collected outcome data may be very valuable for these patient populations and may actually introduce less bias than an entirely prospective study with high rates of loss to follow-up (38).

Follow-up studies of patients with traumatic neurocranial complications after minor head injury are in fact scarce. In a recent study by de Andrade et al (39), 266 selected patients' medical records were reviewed to assess GOS after minor head injury in the presence of neurocranial traumatic CT findings. Williams et al (19) prospectively assessed GOS at 6 months after minor head injury in 74 patients with radiographic evidence of neurocranial traumatic complications. In both studies, most patients had made a good functional recovery but outcome was significantly poorer than that in patients without radiographic evidence of neurocranial traumatic complications. In a third study, Fabbri et al (40) reported favorable outcome in most (89%) of 491 patients with minor head injury with neurocranial traumatic CT findings, but not all patients included in their study had undergone CT. Because we assessed outcome in patients with neurocranial traumatic complications from a large cohort of unselected patients with minor head injury who had all undergone CT, our findings are a good reflection of outcome in the general population of patients with complicated minor head injury. Our study confirms these previous findings of a generally favorable functional outcome after complicated minor head injury.

Diffuse axonal injury was significantly associated with higher grades of functional disability on all outcome scales, whereas intraparenchymatous contusions and subdural hematoma were associated with poor outcome according to GOS and BI, respectively. There was also a significant association between the number of neurocranial traumatic findings on CT and poor functional outcome according to the GOS. None of the CT findings were significantly associated with postconcussive symptoms, though a near significant association was found for epidural hematoma and skull base fracture and with the number of neurocranial traumatic findings on CT. Evidence of parenchymal damage (diffuse axonal injury or intraparenchymatous contusions) was found to be the only independent predictor of poor functional outcome, with an odds ratio of 1.9. Most interesting, none of the neurocranial traumatic findings were significantly associated with a better outcome, suggesting that good outcome even for so-called clinically nonsignificant lesions may not be certain. One could argue that the CT imaging protocol we used for this study was relatively insensitive for the detection of small lesions, such as small intraparenchymatous contusions or small amounts of subarachnoid hemorrhage; this insensitivity may have influenced our findings. Potentially, sensitivity could be increased with the acquisition of thinner sections as is now common practice with the advent of multidetector CT scanners, though we are not aware of any published studies formally comparing head CTs of varying section thicknesses in a trauma setting. Even

assuming that thinner sections increase the detection of small intraparenchymatous injury, it is unclear whether this would affect the ability to predict outcome.

Thus far, the relationship between traumatic findings on CT and functional outcome has only been assessed in severely head-injured patients and not as yet in patients with complicated minor head injury. Only in 2 studies were less severely injured patients also included, but no distinction was made between patients with moderate and those with minor head injury (41, 42). In line with our findings, intracranial hematoma and contusions were among the CT findings that were identified as independent predictors of poor outcome in their and previous studies of severely injured patients (41, 43, 44). We dichotomized the GOS classification specifically for our patient population into good (GOS = 5) and poor (GOS <4) outcome, whereas in many studies, good functional outcome also included GOS of 4 (moderate disability) (28). This dichotomization is indeed appropriate for the more severely injured patients, but after minor head injury, patients generally recover fully, and moderate disability would not qualify as a good functional outcome (35).

We used several outcome measures to assess the patients' outcomes. Our primary outcome measure, the GOS, is often criticized for being too crude a measure of functional outcome, in particular for patients with minor head injury. As reported previously and confirmed in the present study, most patients with minor head injury were classified according to the GOS as having made a full recovery, which does not seem to reflect the high rate of symptoms many of these patients still experience. In the subpopulation of patients whom we interviewed, we used the mRS as a more sensitive measure of outcome and were indeed able to distinguish between patients who had fully recovered and those who still had symptoms, though without any disability. The low rate of disability and the high rate of postconcussive symptoms, as assessed by the BI and the RPSQ respectively, support these findings. Although the mRS thus seems to better reflect functional outcome, the absence of disability would generally be considered good functional outcome, with or without the presence of symptoms. The GOS, with its high test-retest and interobserver agreement (2, 28, 29), shows consistent relations with other outcome measures (30) and is also more suitable for reliable outcome assessment in retrospective studies because medical records often do not contain sufficient detail for classification according to the mRS.

In the present follow-up study, we found a very high rate of postconcussive symptoms. Postconcussive symptoms are very common after head injury, especially in the first weeks to months after the injury (6, 7, 11, 12, 45–48). Because many of the reported symptoms, such as headache and fatigue, have a high base rate in the general population, patients with postconcussive symptoms are often considered malingerers, especially when no objective or imaging abnormalities can be found or, as in our study, no relationship between specific imaging findings and postconcussive symptoms can be determined. In a case-control study by Masson et al (11) of patients with head injury versus those with lower limb injury, postconcussive symptoms, except for fatigue, were significantly more often present in patients with the head injury than in those with the lower limb injury. By using the RPSQ, we attempted to control for premorbid levels of symptoms. However, because the injury had occurred on average several years previously, some degree of recall bias was unavoidable. Despite the high reported rates, symptoms generally disappear in most patients after 3–6 months, only persisting in a minority of patients (7, 49). To the best of our knowledge, we are the first to report postconcussive symptoms in patients

with neurocranial traumatic complications after minor head injury. The high rate of symptoms in our patient population suggests that patients with minor head injury with neurocranial complications are at high risk of persistence of symptoms for years after the injury.

Conclusion

Patients with neurocranial traumatic complications after minor head injury generally make a good functional recovery, though postconcussive symptoms may persist for many years after the injury. Evidence of parenchymal damage on CT was predictive of poor functional outcome.

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CHAPTER 8

Postconcussion syndrome after minor head injury: Brain activation of working memory and attention

submitted

After minor head injury postconcussive symptoms (PCS) such as memory and attention deficits frequently occur, while conventional imaging and neuropsychological tests are generally normal. A neuropathological substrate for PCS is still lacking, although it has been hypothesised that PCS are caused by microstructural damage to the brain due to shearing injury, which is not detectable with conventional imaging, and may be responsible for a functional deficit. The purpose of this study was to correlate functional MRI brain activation of working memory and selective attention with PCS.

Twenty-nine minor head injury patients and 12 healthy controls were scanned at 3T. The mean participant age was 29.4 years (range, 18–50); 26 participants were male. Stimulation paradigms were the n-back task and the Counting Stroop task to engage working memory and selective attention, respectively. Functional data analysis consisted of second level regression group analyses, correlating brain activation patterns with the severity of PCS as evaluated with the Rivermead Postconcussion Symptoms Questionnaire (RPSQ). Median RPSQ score was 10 (range, 0–46).

No association was found between the severity of PCS and brain activation related to selective attention. At minimal working memory load, increased activation was seen in patients with greater severity of PCS in brain areas involved in vigilance, as well as in the working memory network, providing evidence of an elevated resting state of the working memory network in patients exhibiting PCS. With an increase of working memory load, differential activation was more pronounced in patients reporting a greater severity of PCS. Furthermore, at high, as well as differential, working memory load, activation associated with PCS was seen in areas outside the working memory network, namely the parahippocampal gyrus and the posterior cingulate gyrus, indicating that these regions may subserve strategies for dealing with very high working memory demands, possibly when the working memory network itself is exhausted.

The recruitment of these additional brain areas may be considered a reflection of the brain's plasticity in response to – microstructural – injury. These observations suggest a causal relationship and potentially represent a manifestation of a neuropathological correlate of the postconcussion syndrome.

HEAD INJURY is a major health and societal burden, with an estimated incidence of 235 patients per 100 000 in Europe (1). The vast majority of head injury patients present with a – near – normal level of consciousness (Glasgow Coma Scale [GCS] score of 13–15) and are considered to be minor head injury patients (2–4). Despite being classified as minor, more than 80% of these head injury patients experience postconcussive symptoms in the first week after the injury. Symptoms are generally self-limiting, and, while still present in 30% of patients one month after the injury, have commonly disappeared after 6 months, only to persist in a small minority of patients (5–8).

Postconcussive symptoms comprise a wide variety of somatic, psychological, and cognitive complaints such as headache, fatigue, depression, and memory and attention deficits (5, 9–11). The presence of a minimum of three symptoms for at least three months after the injury is used as a criterion for the diagnosis of the postconcussion syndrome (11, 12), for which a neuropathological substrate is still lacking (11, 13). With conventional imaging techniques of the brain, such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), generally no structural abnormalities are found (14, 15).

Despite the subjective severity of complaints in these patients, neuropsychological tests are also usually normal. If abnormal, deficits tend to be subtle, and are most commonly found in the cognitive domains of working memory and selective attention (16–18). Working memory refers to the cognitive process during which a limited amount of information is kept in memory for a brief period of time for further cognitive manipulation. A common task to engage working memory is the n-back task, during which at least five areas of the brain have shown to be involved, namely the dorso- and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area (19–23). Selective attention concerns the process of directing attention towards a specific stimulus, and is traditionally tested with the Stroop colour word task, in which the difference in response time for a neutral stimulus (inducing an automatic response) and response time for an interference stimulus (inducing a response for which interfering information needs to be ignored) is considered a measure of selective attention (24). Brain areas involved in the processing of selective attention are the dorsolateral prefrontal cortex and the supplementary motor area, as well as the anterior cingulate cortex (25, 26).

It has been hypothesised that postconcussive symptoms are caused by microstructural damage to the brain due to shearing injury, which is not detectable with conventional imaging, and may be responsible for a functional deficit (8, 14, 27–29). A compensatory mechanism of the brain could explain the discrepancy between the subjective severity of cognitive complaints and – near – normal findings on neuropsychological testing (30). Previous functional MRI (fMRI) studies of minor head injury patients have indeed shown altered patterns of activation during the performance of working memory tasks (31–34), consisting of reports of both increased (31, 32) and decreased (33) activation in the dorsolateral prefrontal cortex and increased activation in the posterior parietal area (31, 32) during an n-back task, as well as more dispersed activation and the recruitment of brain regions in the contralateral hemisphere during a paced auditory serial addition task (34). Meanwhile, it is conceivable that a more global change in brain activity after minor head injury occurs, and that previously reported findings are not task-specific. An association of brain activation with postconcussive symptoms has as yet not

been assessed.

In the present study, we used fMRI to correlate postconcussive symptoms after minor head injury with neural correlates of the two cognitive domains commonly affected, ie, working memory and selective attention. We also assessed whether postconcussive symptoms were associated with brain activation during a simple, non-cognitive finger tapping task.

METHODS

Study population

Patients were prospectively and consecutively included if they met the following inclusion criteria: aged 18 to 50 years, 1 month after presentation to our emergency department with blunt head trauma, a GCS score of 13 to 15, a normal neurological examination, and normal Computed Tomography (CT) of the head performed within 24 hours of injury. Additionally, minor head injury patients from our CT in Head Injury Patients (CHIP) study (35, 36) with chronic postconcussive symptoms were asked to participate. All patients with chronic postconcussive symptoms had a neurocranial traumatic finding on CT performed within 24 hours of the injury. As a control group, healthy volunteers were recruited from the included patients' peers and family where possible, and additionally from hospital co-workers.

Head injury patients and controls were excluded if they had a history of neurological or psychiatric disease, had previous head injury, used prescription medication other than oral contraceptives, or had contraindications for MR imaging.

The study protocol was approved by the institutional review board and written informed consent was obtained from all participants.

Participant characteristics

General demographical data were collected from all participants. Educational level was classified as follows: 1, primary education only; 2, lower-level secondary education; 3, middle-level secondary education; 4, higher-level secondary or post-secondary education. All participants underwent general neurological examination and testing of crude cognitive function by means of the Mini Mental Status Examination (MMSE) (37).

In the head injury patients, the number and severity of postconcussive symptoms was assessed by means of the Rivermead Postconcussion Symptoms Questionnaire (RPSQ) (38). The RPSQ is a 5 point-scale of 16 symptoms that are common after head injury, and has a high test-retest and interrater agreement for the assessment of the presence and severity of postconcussive symptoms (7, 38). Patients rate severity of each symptom in comparison with pre-injury levels on a scale from 0 (no symptoms) to 4 (severe symptoms), thus adjusting for the high base-rate of (some of these) symptoms in the general population. Additional symptoms may be recorded and rated similarly. The higher the sum score, the more (severely) symptoms are present after the injury.

MRI acquisition protocol

Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, WI, US). An 8-channel head coil was used for reception of the signal. For anatomical reference a high-resolution three dimensional (3D) Inversion Recovery (IR) Fast Spoiled Gradient Echo (FSPGR) T1 weighted image was acquired, with the following pulse sequence parameters: repetition time (TR)/echo time (TE)/inversion time (TI) 10.7/2.2/300 ms; flip angle 18°; acquisition matrix 416×256; field of view (FOV) 250×175 mm^2; 192 slices with a slice

thickness of 1.6 mm and 0.8 mm overlap; acquisition time 4:57 minutes. For functional imaging, a single shot T2* weighted gradient echo echo-planar imaging (EPI) sequence sensitive to Blood Oxygenation Level Dependent contrast was used (TE 30 ms; flip angle 75°; acquisition matrix 64×96; FOV 220×220 mm^2, slice thickness 3.5 mm). TR, number of slices and acquisition time varied according to the stimulation paradigm: for the finger tapping task TR was 3000 ms, number of slices 39, and acquisition time 4:15 minutes; for the n-back task TR was 2500 ms, number of slices 32, and acquisition time 6:43 minutes; for the Stroop task TR was 2000 ms, number of slices 26, and acquisition time 6:10 minutes. All functional imaging data acquisitions included 5 dummy scans that were discarded from further analysis.

Functional MRI stimulation paradigms

All tasks were presented using Presentation v9.81 software (Neurobehavioral Systems Inc, Albany, CA, US) installed on a desktop PC, which was dedicated for stimulus presentation. External triggering by the MR system ensured synchronisation of the stimulus paradigms with the imaging data acquisition and precise recording of task performance and response times through fibre optic button response pads. Auditory tasks were presented binaurally through an MR compatible headphone system; visual tasks were presented in near-darkness using a projector and a back-projection screen that was visible with a mirror mounted on the head coil. All tasks were designed according to a blocked design with 30 s block duration.

Finger tapping

The first task was a self-paced finger tapping task of the right hand only, consisting of 8 blocks (4:00 min) of alternating active (right-hand finger tapping) and rest (no finger tapping) conditions. Simple instructions indicating the start of the active and rest conditions were presented auditorily.

N-back task: working memory and vigilance

We used the n-back task to engage continuous attention (vigilance) and verbal working memory. Four different conditions with increasing levels of working memory load were presented: 1, rest; 2, 0-back; 3, 1-back; 4, 2-back. Stimuli consisted of auditorily presented numbers (0–9), one stimulus presented every 3 s. Simple auditory instructions indicated the start of each condition. Participants responded by pressing a response button with the right thumb. During the rest condition, no stimuli were presented and the participant was instructed to do nothing. During the 0-back condition, participants were instructed to press the response button whenever the number "0" was presented. During the 1-back condition, a response was required when the presented number matched the previous one. During the 2-back condition, a response was required when the presented number matched the number before the previous one. The 0-back condition requires continuous attention (vigilance) and only minimal working memory; the 1-back condition represents moderate, and the 2-back condition high working memory load. A single task consisted of 13 blocks, and the task was performed twice. Conditions were counterbalanced within and across the two tasks, ie, each condition was equally often preceded and followed by each of the other conditions (39).

Stroop task: selective attention

To engage selective attention, the Counting Stroop task was used (25), which was presented visually. Responses were given by means of 2 response boxes, 1 held in each hand, with 2 buttons each to be pressed with the thumb. Simple visual instructions indicated the start of the rest, the neutral, and the interference conditions. The task

started and ended with the rest condition, during which no stimuli were presented and the participant was instructed to do nothing. A further 10 blocks were presented, alternating the neutral and the interference condition. During the neutral condition, single or multiple (up to 4 times) animal names were presented every 1.5 s for 1.4 s, and the participant was instructed to press the response button (representing the numbers 1 to 4) that matched the presented number of animal names. During the interference condition, single or multiple (up to 4 times) written-out numbers (one, two, three, four) were presented, and the participant was instructed to press the response button matching the presented number of words (ie, 'three three' = button no. 2). During this condition, oddballs were interspersed pseudo-randomly, during which the participant was required to press the response button matching the presented number itself (and not the number of words) when it was written in capital letters (ie, 'THREE THREE' = button no. 3). A single task consisted of 12 blocks, and the task was performed twice. Conditions were counterbalanced within and across the two tasks.

Statistical analysis

Participant characteristics

The minor head injury patients were divided into two groups, according to their RPSQ score, to best fit the data distribution: patients with a score below the median RPSQ score were classified as having minor postconcussive symptoms (PCS), while patients with a score of or above the median RPSQ score were classified as having severe PCS. Controls were classified as having no PCS. We tested differences in participant characteristics between the 3 groups (no, minor, severe PCS) for significance ($p < 0.05$) using one-way analysis of variance (ANOVA) and Student's t-test for continuous (age, MMSE, GCS score), Pearson's chi-square test for categorical (gender), and Kruskal Wallis for ordinal (educational level) variables.

Task performance

Task performance consisted of response times and the percentage correct responses (number of correct responses divided by the number of required responses), averaged per participant and per acquisition for each condition of the n-back task (0-back, 1-back, 2-back) and the Stroop task (interference, neutral). Potential session effects were assessed by testing differences in task performance for each condition between the two sessions using an independent samples t-test for significance ($p < 0.05$). For each task, differences in performance between the conditions were assessed for significance ($p < 0.05$) using a paired t-test. Differences between the 3 groups (no, minor, severe PCS) in task performance for each condition were assessed using one-way ANOVA for significance ($p < 0.05$).

Functional MRI

Analysis of fMRI data was performed with Statistical Parametric Mapping version 2 (SPM2, Wellcome department University College London, London, UK) implemented in Matlab version 6.5.1 (The Mathworks, Sherborn, MA, US). For individual analysis, all T2* weighted functional images were realigned to correct for the participant's motion during data acquisition and were co-registered with the high-resolution T1 weighted anatomical image (40). The functional and anatomical images were normalised to the standard brain space defined by the Montreal Neurological Institute (MNI) as provided within SPM2, using affine and nonlinear registration (41). The normalised functional images were smoothed with a 3D Gaussian filter of 6×6×6 mm^3 Full Width Half Maximum (FWHM)

to increase the signal-to-noise ratio, correct for interindividual anatomical variation, and to normalise the data. For each task and each acquisition, individual statistical parametric maps were calculated using the general linear model by modelling the conditions as a box car function convolved with the haemodynamic response function, corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cut-off. Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects due to motion. The following t-contrast images were generated: right-hand finger tapping versus rest (finger tapping task); 0-back versus rest, 1-back versus 0-back, 2-back versus 0-back, and 2-back versus 1-back (n-back task); interference versus neutral (Stroop task).

These individual t-contrast images were then used for second-level random effects group analyses. We used 1-sample t-tests to assess main effects, using a threshold of $p < 0.05$ with Family Wise Error (FWE) correction for multiple comparisons and a minimum cluster size (k) of 20 voxels. We then performed multiple regression analysis to assess differences in activation between the 3 groups, using postconcussive symptoms (categorised as no, minor or severe PCS) as a regressor of interest, and adjusting for potential confounders (based on our analysis of group differences for participant characteristics and task performance) added to the model as regressors of no interest. We assessed brain activation changes for significance at a threshold of $p < 0.05$ with FWE correction for multiple comparisons and a minimum cluster size of 20 voxels, as well as at a more lenient threshold of $p < 0.001$ not corrected for multiple comparisons, and a minimum cluster size of 20 voxels. Finally, we repeated the multivariable regression analyses, using the same thresholds, after exclusion of the patients with chronic postconcussive symptoms.

Anatomical labelling of significantly activated clusters was performed using the MNI Space Utility software extension to SPM2 according to the methods described by Brett on http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html (42, 43).

RESULTS

Study population

Between December 2005 and November 2006, 236 patients with recent minor head injury presented to our emergency department who were eligible for inclusion in the study. Of these, 51 could be contacted, 36 of whom were willing to participate. Of these, 6 did not fulfill the study's inclusion criteria, and 9 were excluded because of contraindications for MR imaging (n = 2), previous history of neurological or psychiatric disease (n = 4), and previous history of head injury (n = 3). The 21 remaining patients were imaged at an average of 30.6 days (range, 18–40 days) after minor head injury. None of these patients had a neurocranial traumatic finding on CT performed within 24 hours of the injury.

From the CHIP study database, which included patients with minor head injury between February 2002 and August 2004, 28 patients were identified still suffering from postconcussive symptoms since the head injury. Of these, 9 were willing to participate, 1 of whom was excluded because of contraindications for MR imaging, leaving 8 patients with postconcussive symptoms at an average of 3.1 years (range, 2.1–4.7 years) after minor head injury. All of these patients had one or multiple neurocranial traumatic findings on CT performed within 24 hours of the injury, consisting of skull (base) fractures (n = 5), intraparenchymal haemorrhagic contusion (n = 2), and traumatic subarachnoid haemorrhage (n = 3).

In addition to the total number of 29

minor head injury patients, 12 healthy volunteers were included in the study. In one control subject, the n-back task was not performed due to technical difficulties. In a different control subject, the Stroop task was not performed due to the subject's poor visual acuity without spectacle correction.

Participant characteristics

The median RPSQ score was 10 (mean, 14.6; range, 0–46). Patients with an RPSQ score below 10 were classified as minor PCS (n = 13), and patients with an RPSQ of 10 or higher were classified as severe PCS (n = 16). A significantly larger proportion of patients with chronic postconcussive symptoms than of patients with recent head injury was classified as severe PCS (p = 0.04; Table 1).

The majority of participants were male (n = 26; 63.4%), which was not different between the 3 groups (p = 0.31; Table 1). The mean age of the participants was 29.4 years (range, 18–50), which was significantly higher (p = 0.02; Table 1) in the severe PCS patients (mean, 34.7 years), than in the minor PCS patients (mean, 24.3 years) and controls (mean, 27.8 years). Age was therefore adjusted for as a potential confounder in the multivariable regression analysis. Neurological examination was normal in all participants. There was no difference between the 3 groups in educational level (p = 0.69; Table 1) or crude cognitive function as measured with the MMSE (p = 1.00; Table 1).

All but one patient had a history of loss of consciousness or (posttraumatic) amnesia after the injury. Most patients had a GCS score of 15 upon presentation (n = 19; 65.5%); 8 patients presented with a GCS score of 14 (27.6%), and 2 patients with a GCS score of 13 (6.9%). There was no

Table 1. Participant characteristics

	Minor PCS (RPSQ <10)	Severe PCS (RPSQ ≥10)	Controls	P value
Age, years (SD)	24.3 (6.2)	34.7 (11.2)	27.8 (10.0)	0.02*
Male gender, n (%)	10 (77)	8 (50)	8 (67)	0.31†
Recent head injury, n (%)	12 (57)	9 (43)	-	0.04†
Chronic complaints, n (%)	1 (13)	7 (87)	-	
Educational level, mean (SD)	3.2 (0.9)	3.3 (1.0)	3.3 (1.1)	0.69‡
MMSE, mean (SD)	27.5 (1.1)	27.6 (2.2)	27.5 (1.8)	1.00*
GCS, mean (SD)	14.6 (0.7)	14.6 (0.6)	-	0.83*

SD = standard deviation; PCS = postconcussive symptoms; RPSQ = Rivermead Postconcussion Symptoms Questionnaire; MMSE = Mini Mental Status Examination; GCS = Glasgow Coma Scale.
* One-way ANOVA/Student's t-test; † Pearson's chi square test; ‡ Kruskal Wallis.

Table 2a. Performance on the n-back task

	0-back (SD)	1-back (SD)	2-back (SD)
Average proportion correct (n = 37)	0.96 (0.17)	0.88 (0.26)	0.84 (0.24)
Controls (n = 10)	0.99 (0.03)	1.00 (0.00)	0.95 (0.10)
Minor PCS (n = 12)	1.00 (0.00)	0.97 (0.09)	0.90 (0.17)
Severe PCS (n = 15)	0.91 (0.27)	0.74 (0.36)	0.72 (0.30)
Average response time, s (n = 37)	0.76 (0.17)	0.85 (0.29)	0.97 (0.32)
Controls (n = 10)	0.70 (0.11)	0.79 (0.21)	0.84 (0.25)
Minor PCS (n = 12)	0.80 (0.09)	0.88 (0.16)	0.93 (0.18)
Severe PCS (n = 15)	0.77 (0.24)	0.86 (0.40)	1.09 (0.41)

SD = standard deviation; PCS = postconcussive symptoms.

difference in average GCS score between the group of patients with severe and minor PCS ($p = 0.83$; Table 1).

Task performance

Due to technical difficulties, task performance (both for the n-back and the Stroop task) was not recorded in 3 participants (1 control, 1 minor, and 1 severe PCS).

N-back task (vigilance and working memory)

There was no significant session effect on n-back task performance. As expected, performance became significantly worse with increasing levels of working memory load (Table 2a). The average proportion of correct responses was significantly decreased for the 1-back versus the 0-back condition ($p = 0.03$) as well as for the 2-back versus the 0-back ($p < 0.001$) or the 1-back ($p = 0.04$) condition. The average response time showed a significant increase for the 1-back versus the 0-back condition ($p = 0.01$), as well as for the 2-back versus the 0-back ($p < 0.001$) or the 1-back ($p = 0.05$) condition.

Severe PCS patients had a significantly lower percentage of correct responses than controls for the 1-back ($p = 0.03$) and the 2-back ($p = 0.03$) conditions. The percentage correct responses was therefore adjusted for as a potential confounder in the multivariable regression analysis. There was no difference in the average response times for any of the conditions between the 3 groups.

Table 2b. Performance on the Counting Stroop task

	Neutral (SD)	Interference (SD)
Average proportion correct (n = 37)	0.97 (0.03)	0.89 (0.10)
Controls (n = 10)	0.98 (0.02)	0.95 (0.32)
Minor PCS (n = 12)	0.97 (0.27)	0.92 (0.06)
Severe PCS (n = 15)	0.96 (0.27)	0.86 (0.14)
Average response time, s (n = 37)	0.81 (0.09)	0.93 (0.10)
Controls (n = 10)	0.78 (0.11)	0.89 (0.09)
Minor PCS (n = 12)	0.82 (0.11)	0.94 (0.12)
Severe PCS (n = 15)	0.83 (0.07)	0.95 (0.09)

SD = standard deviation; PCS = postconcussive symptoms.

Table 3a. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the main effect of the 0-back versus rest condition (one-sample t-test; $p_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Insula (33%)	R	318	58	-24	-6	6.94
Precentral gyrus (6%)	R					
Inferior frontal gyrus (53%)	R					
Insula (49%)	L	73	-34	22	12	6.28
Inferior frontal gyrus (36%)	L					
Middle temporal gyrus (53%)	R	337	42	16	6	7.49
Superior temporal gyrus (47%)	R					
Middle temporal gyrus (4%)	L	455	-66	-30	6	6.63
Superior temporal gyrus (96%)	L					
Superior temporal gyrus (82%)	L	22	-40	-36	14	5.35
Transverse temporal gyrus (18%)	L					

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

Table 3b. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the regression analysis of the 0-back versus rest condition with severity of postconcussive symptoms (multivariable regression analysis; $p_{uncorrected}$ <0.001, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Precentral gyrus (23%) Inferior frontal gyrus (35%) Middle frontal gyrus (42%)	L L L	108	-50	4	38	4.16
Medial superior frontal gyrus (97%)	L	32	-8	42	36	3.77
Precentral gyrus (100%)	R	71	46	-10	44	4.47
Inferior parietal lobule (32%) Postcentral gyrus (17%)	R R	107	28	-42	48	3.88
Inferior parietal lobule (54%) Postcentral gyrus (46%)	R R	147	50	-34	48	4.92
Inferior parietal lobule (24%) Superior parietal lobule (10%) Postcentral gyrus (14%)	R R R	21	38	-54	62	3.80
Inferior parietal lobule (100%)	L	31	-48	-42	46	4.31

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

Table 4. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the main effect of the 1-back versus 0-back condition (one-sample t-test; $p_{corrected}$ <0.05, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Precentral gyrus (10%) Inferior frontal gyrus (5%) Middle frontal gyrus (85%)	R R R	112	46	18	44	5.28
Middle frontal gyrus (100%)	R	28	32	2	56	5.00
Inferior frontal gyrus (80%) Middle frontal gyrus (20%)	L L	41	-38	6	34	5.03
Supramarginal gyrus (10%) Inferior parietal lobule (89%)	R R	290	36	-58	46	5.89
Supramarginal gyrus (12%) Inferior parietal lobule (58%)	L L	156	-36	-50	40	5.64

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

Stroop task (selective attention)

There was no significant session effect on Stroop task performance. The average proportion of correct responses was significantly lower for the interference than for the neutral condition (p <0.001), whereas the average response time was significantly longer for the interference than for the neutral condition (p <0.001). There was no difference in task performance between the 3 groups for either of the conditions (Table 2b).

Functional MRI

Areas of significant activation are detailed in Tables 3–7.

Right-hand finger tapping

During right-hand finger tapping versus rest, significant activation was seen bilaterally (left more than right) in the pre- and postcentral gyrus (primary sensorimotor cortex), bilaterally in the medial superior frontal gyrus

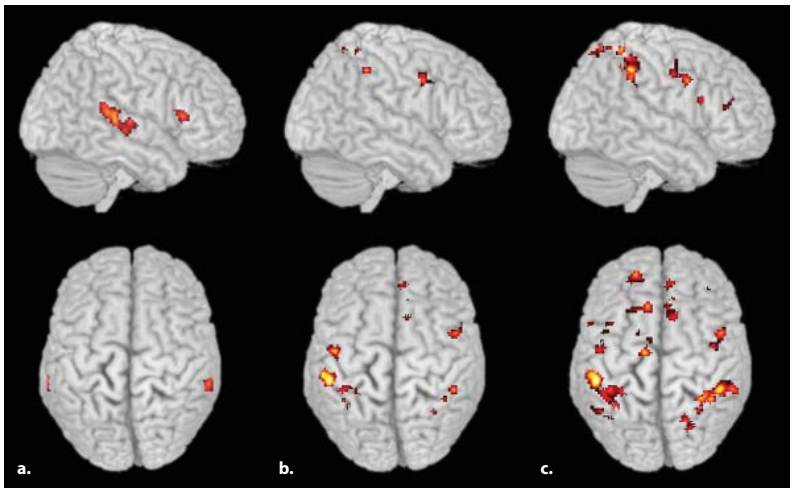

Figure 1. Three dimensional brain rendering with right lateral (upper row) and top views (lower row), showing significant activation for the 0-back versus rest comparison. (a) Activation in all participants (main effect analysis, $p_{corrected}$ <0.05; k ≥20; n = 40); (b) activation associated with severity of postconcussive symptoms (regression analysis, $p_{uncorrected}$ <0.001; k ≥20; n = 40); (c) activation associated with severity of postconcussive symptoms after exclusion of patients with chronic complaints (regression analysis, $p_{uncorrected}$ <0.001; k ≥20; n = 32).

Table 5a. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the main effect of the 2-back versus 0-back condition (one-sample t-test; $p_{corrected}$ <0.05, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Precentral gyrus (7%) Inferior frontal gyrus (9%) Middle frontal gyrus (72%)	R R R	2136	28	-2	62	10.41
Precentral gyrus (9%) Inferior frontal gyrus (15%) Middle frontal gyrus (60%)	L L L	1994	-46	12	32	9.69
Anterior cingulate gyrus (10%) Medial superior frontal gyrus (40%) Superior frontal gyrus (50%)	L + R L + R L + R	790	4	18	52	10.60
Insula (23%) Inferior frontal gyrus (56%)	R R	284	32	22	4	8.34
Insula (24%) Inferior frontal gyrus (48%)	L L	195	-34	24	0	7.91
Supramarginal gyrus (9%) Inferior parietal lobule (36%) Superior parietal lobule (15%) Precuneus (19%)	L + R L + R L + R L + R	4263	-36	-52	38	10.98
Lentiform nucleus (18%)	L	172	-18	8	14	6.41

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

Table 5b. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the regression analysis of the 2-back versus 0-back condition with severity of postconcussive symptoms (multivariable regression analysis; $p_{uncorrected}$ <0.001, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Parahippocampal gyrus* (49%)	R	285	24	-18	-14	5.38
Culmen (10%)	R					
Insula (30%)	R	20	40	-4	18	3.44
Insula (38%)	L	65	-38	-2	22	4.05
Insula (32%)	L	50	-30	18	4	3.99
Claustrum (30%)	L					
Parahippocampal gyrus (7%)	R	55	26	0	-14	3.95
Lentiform nucleus (7%)	R					
Parahippocampal gyrus (22%)	L	91	-20	-36	-2	3.86
Thalamus (37%)	L					
Posterior cingulate gyrus (55%)	L + R	228	-6	-50	2	5.05
Lingual gyrus (17%)	L					
Cuneus (14%)	L + R					
Precuneus (66%)	R	59	16	-66	20	4.22
Lentiform nucleus (80%)	L	35	-30	-14	0	4.25

* Significant activation at $p_{corrected}$ <0.05. L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

Table 6a. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the main effect of the 2-back versus 1-back condition (one-sample t-test; $p_{corrected}$ <0.05, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Middle frontal gyrus (59%)	R	135	24	-4	54	5.92
Middle frontal gyrus (59%)	L	174	-24	-2	62	6.21
Superior frontal gyrus (76%)	L	123	-6	14	56	6.37
Medial superior frontal gyrus (17%)	L					
Inferior parietal lobule (31%)	R	42	32	-50	38	5.53
Inferior parietal lobule (100%)	R	22	44	-46	44	5.40
Inferior parietal lobule (12%)	L	393	-22	-78	50	6.00
Precuneus (34%)	L					
Superior parietal lobule (26%)	L					
Precuneus (64%)	R	187	30	-74	40	6.28
Superior parietal lobule (14%)	R					
Precuneus (85%)	L + R	40	6	-70	50	5.53
Superior parietal lobule (8%)	R					

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

(supplementary motor area), the inferior parietal lobule and insula, as well as in the left lentiform nucleus, and left temporal gyrus. No association with severity of PCS was seen at either threshold for significance ($p_{corrected}$ <0.05 or $p_{uncorrected}$ <0.001).

N-back task: vigilance and working memory

0-back versus rest: vigilance

The 0-back condition compared with the rest condition (main effect; Table 3a, Figure 1a) yielded significant activation bilaterally

Table 6b. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the regression analysis of the 2-back versus 1-back condition with severity of postconcussive symptoms (multivariable regression analysis; $p_{uncorrected}$ <0.001, k ≥20)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Paracentral lobule (40%)	L	98	-6	-16	54	3.81
Medial superior frontal gyrus (60%)	L					
Precuneus (87%)	R	38	10	-68	20	3.82
Precuneus (45%)	L + R	54	-4	-52	64	3.73
Paracentral lobule (9%)	L					
Postcentral gyrus (30%)	L					
Postcentral gyrus (100%)	L	36	-64	-16	20	4.01
Superior parietal lobule (54%)	L	48	-22	-66	62	4.21
Parahippocampal gyrus (30%)	R	170	14	-32	-4	4.34
Lingual gyrus (6%)	R					
Cuneus (14%)	R					
Culmen (12%)	R					
Posterior cingulate gyrus (10%)	R	77	22	-58	0	3.98
Parahippocampal gyrus (23%)	R					
Lingual gyrus (48%)	R					
Parahippocampal gyrus (43%)	R	28	22	-22	-14	5.07
Posterior cingulate gyrus (21%)	L	210	-24	-60	-2	4.44
Parahippocampal gyrus (10%)	L					
Lingual gyrus (50%)	L					
Parahippocampal gyrus (56%)	L	25	-10	-38	-4	4.01
Culmen (20%)	L					
Transverse temporal gyrus (13%)	R	366	56	-34	16	4.53
Superior temporal gyrus (38%)	R					
Insula (29%)	R					
Postcentral gyrus (18%)	R					
Middle temporal gyrus (73%)	R	71	50	-26	-6	4.53
Superior temporal gyrus (21%)	R					
Middle temporal gyrus (53%)	R	59	60	-44	4	3.85
Superior temporal gyrus (47%)	R					
Middle temporal gyrus (84%)	R	43	50	-64	12	4.02
Superior temporal gyrus (12%)	R					
Transverse temporal gyrus (6%)	L	1355	-56	-30	-6	5.22
Middle temporal gyrus (20%)	L					
Superior temporal gyrus (48%)	L					
Insula (12%)	L					

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

in the inferior frontal gyrus and insula (ventrolateral prefrontal cortex), as well as in the middle and superior temporal gyrus (primary and secondary auditory cortex).

Increased activation was seen associated with increased severity of PCS (Table 3b; Figure 1b), at a lenient threshold only, in the left inferior and middle frontal gyrus and in the precentral gyrus bilaterally (dorsolateral prefrontal cortex), in the left medial superior frontal gyrus (supplementary motor area); and in the right superior parietal lobule and inferior parietal lobule bilaterally (posterior parietal area).

When patients with chronic complaints were excluded from the analysis, a comparable

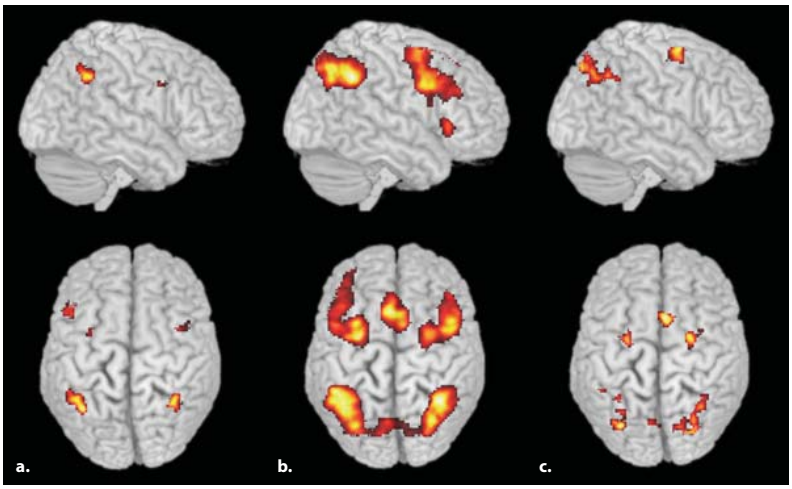

Figure 2. Three dimensional brain rendering showing right lateral (upper row) and top views (lower row), showing significant ($p_{corrected}$ <0.05; k ≥20) activation in all participants (main effect; n = 40) for (a) the 1-back versus 0-back, (b) the 2-back versus 0-back, and (c) the 2-back versus 1-back comparisons.

pattern of – more widespread – activation was seen (Figure 1c).

1-back versus 0-back: moderate working memory load

The 1-back compared with the 0-back condition (main effect; Table 4, Figure 2a) yielded significant activation in the right precentral gyrus and bilaterally in the inferior and middle frontal gyrus (dorsolateral prefrontal cortex), as well as in the supramarginal gyrus and inferior parietal lobule (posterior parietal area). No association with severity of PCS was seen at either threshold for significance.

2-back versus 0-back: high working memory load

The activation pattern for the 2-back compared with the 0-back condition (main effect; Table 5a, Figure 2b) was similar to the comparison of the 1-back with the 0-back condition, with activation in the dorsolateral prefrontal cortex, premotor area and posterior parietal area, but activation was much more widespread and less lateralised. Additional significant activation was seen bilaterally in the insula and inferior frontal gyrus (ventrolateral prefrontal cortex), as well as in the (medial) superior frontal gyrus (supplementary motor area).

A single cluster of increased activation associated with increased severity of PCS (Table 5b, Figure 3a) was observed in the right parahippocampal gyrus. At a more lenient threshold activation was seen bilaterally in the parahippocampal gyrus, the posterior cingulate gyrus, the right precuneus (posterior parietal area), and the insula (ventrolateral prefrontal cortex).

When patients with chronic complaints were excluded from the analysis, a comparable pattern of activation was seen (Figure 3b).

2-back versus 1-back: differential working memory load

The comparison of the 2-back with the 1-back condition (main effect; Table 6a, Figure 2c) yielded significant activation in the middle frontal gyrus bilaterally (premotor area), the left (medial) superior frontal gyrus (supplementary motor area), and in the inferior and superior parietal

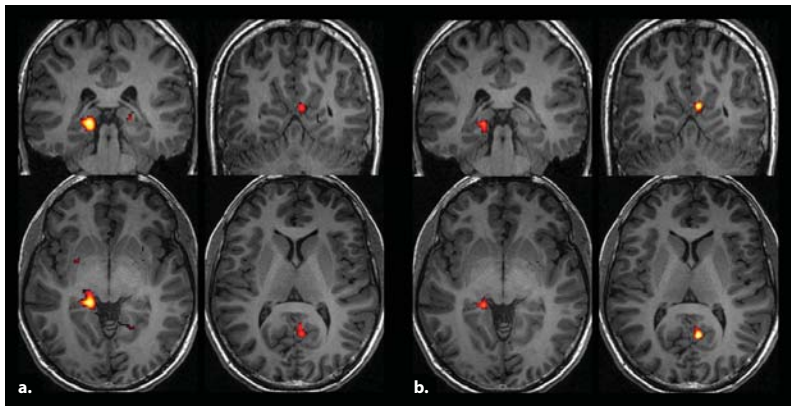

Figure 3. Coronal (upper row) and axial (lower row) T1 weighted sections of the brain showing significant ($p_{uncorrected}$ <0.001; k ≥20) activation associated with severity of postconcussive symptoms for the 2-back versus 0-back comparison in the parahippocampal (left column) and posterior cingulate (right column) gyrus (a) in all participants (regression analysis; n = 40), and (b) after exclusion of patients with chronic complaints (regression analysis; n = 32).

lobule and precuneus bilaterally (posterior parietal area).

Increased activation associated with increased severity of PCS was seen at a lenient threshold only (Table 6b) in the following regions: the left medial superior frontal gyrus (supplementary motor area), as well as bilaterally in the insula, in the left superior parietal lobule and precuneus (posterior parietal area), the posterior cingulate gyrus and parahippocampal gyrus, and the transverse, middle and superior temporal gyrus (primary and secondary auditory cortex).

When patients with chronic complaints were excluded from the analysis, a comparable pattern of – less widespread – activation was seen.

Stroop task: selective attention

The comparison of the interference with the neutral condition (main effect; Table 7) yielded significant activation in the left precentral gyrus and insula as well as bilaterally in the inferior and middle frontal gyrus (dorsolateral and ventrolateral prefrontal cortex), in the (medial) superior frontal gyrus (supplementary motor area), and in the right angular gyrus as well as bilaterally in the inferior and superior parietal lobule and precuneus (posterior parietal area). No association with severity of PCS was seen at either threshold for significance.

DISCUSSION

In this study we examined the neural correlates of postconcussive symptoms after minor head injury. Two important observations merit further discussion: 1, a positive correlation was found between the severity of postconcussive symptoms and increased activation in the posterior parietal areas, as well as additional activation in the posterior cingulate and parahippocampal gyrus during a working memory task; 2, neural correlates of postconcussion syndrome were task-specific. Together, these findings indicate a manifestation of underlying neurophysiological damage following minor head injury.

Working memory and selective attention, essential for normal functioning in everyday

Table 7. Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates and statistical T-values of areas of significant activation for the main effect of the Stroop interference versus neutral condition (one-sample t-test; $p_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			T-value
			x	y	z	
Inferior frontal gyrus (97%)	R	100	36	22	-2	6.54
Inferior frontal gyrus (35%) Middle frontal gyrus (47%)	R R	319	42	18	34	7.53
Precentral gyrus (10%) Inferior frontal gyrus (20%) Middle frontal gyrus (39%)	L L L	225	-40	0	30	6.94
Insula (7%) Inferior frontal gyrus (93%)	L L	27	-36	22	-8	5.97
Superior frontal gyrus (90%) Medial superior frontal gyrus (6%)	L + R L + R	67	-8	10	58	7.19
Inferior parietal lobule (40%) Superior parietal lobule (52%)	R R	147	30	-66	46	7.76
Angular gyrus (13%) Precuneus (66%)	R R	32	34	-74	34	5.47
Precuneus (45%) Superior parietal lobule (19%)	L + R L + R	116	2	-70	54	6.40
Inferior parietal lobule (57%) Superior parietal lobule (23%)	L L	30	-44	-52	56	5.90
Precuneus (76%) Superior parietal lobule (9%)	L L	34	-26	-78	50	6.47
Precuneus (38%)	L	66	-30	-68	32	7.46
Cuneus (32%) Precuneus (14%)	L L	63	-30	-80	32	6.71

L = left hemisphere; R = right hemisphere; MNI = Montreal Neurological Institute.

life, are the two cognitive domains commonly affected in patients after minor head injury (16–18). This is reflected in the time course of postconcussive symptoms, which, after an initial spontaneous decrease over the course of several weeks after the injury, typically aggravate when patients resume their normal activities, such as return to work or school (16). In order to probe these cognitive domains following minor head injury, we used the n-back and Stroop tasks to evaluate brain activation changes.

Our study confirms involvement of the areas previously reported during performance of the n-back task of verbal working memory, namely the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area (19–23, 44). In accordance with previous studies, activation increased with increasing working memory demands (22, 32, 45, 46), both in the prefrontal cortex and particularly in the posterior parietal cortex, due to the higher demands placed on attentional and short-term storage components of working memory.

Likewise, during performance of the Stroop task activation was found in the dorsolateral prefrontal cortex and the supplementary motor area, as reported in previous studies. (25, 26). In the anterior cingulate cortex, no activation was seen surviving our significance threshold, which was more stringent than thresholds used in previous studies (25, 26).

In this study, we found that the severity of postconcussive symptoms was associated with differences in activation related to verbal working memory processing. In contrast to

previous fMRI studies of minor head injury patients, patients were not simply compared with healthy controls, but the presence and severity of postconcussive symptoms was correlated with the neural correlates of verbal working memory. Thus, the activation is not just correlated with minor head injury in general, but with the severity of postconcussive symptoms explicitly. Specifically, at minimal working memory load, activation was not only observed in brain areas involved in vigilance (inferior frontal gyrus) (47), but also in areas involved in working memory processing (dorsolateral prefrontal cortex, supplementary motor area and posterior parietal area). Such activation may be explained by increased attentional and short-term memory demands respectively in patients with postconcussive symptoms, providing evidence of an elevated resting state of the 'working memory network' in patients exhibiting postconcussive symptoms. With an increase of working memory load, differential activation in the supplementary motor area and in the posterior parietal area was more pronounced in patients reporting a greater severity of postconcussive symptoms. Our findings support previous work by McAllister et al (31, 32), who also found increased activation in the working memory network with increasing working memory load in patients one month after minor head injury, when compared with healthy controls. In our study, additional activation was seen in the superior and middle temporal cortex bilaterally, which is involved in the articulatory loop of working memory and related to verbal rehearsal (34). Furthermore, at high, as well as differential, working memory load, activation associated with postconcussive symptoms was seen in areas outside the working memory network, most notably in the parahippocampal gyrus and the posterior cingulate gyrus. Both these areas are involved in memory processing: the parahippocampal gyrus in the consolidation of episodic information into memory, and the posterior cingulate gyrus in memory retrieval (48, 49). Typically, both regions are implicated in relation to long-term, rather than short-term or working memory processing. Involvement in working memory has been observed, however, both in healthy controls at very high working memory challenges, as well as in patients with other cognitive syndromes, such as minor cognitive impairment and probable Alzheimer disease (50), multiple sclerosis (49) and depression (51). While the relationship of these regions with verbal working memory remains to be established, our findings together with previous reports indicate that these regions may subserve strategies for dealing with very high working memory demands, possibly when the working memory network itself is exhausted (32).

Contrary to our original hypothesis, no significant association between neural correlates of selective attention and the severity of postconcussive symptoms was observed. Close inspection of the behavioural and fMRI results indicates that the Counting Stroop task was not exacting enough to dissociate such correlations. While the original Stroop colour word task is known to be very sensitive to subtle deficits of selective attention in minor head injury patients (16), this is not established for the Counting Stroop task used in this study (25). In contrast to the original Stroop colour word task, the Counting Stroop task is not self-paced; stimuli were presented every 1.5 s. Both task performance and response times were very high (>90%) and well below 1.5 s respectively, indicating a low stimulus load. Furthermore, the lack of activation in the anterior cingulate cortex in the main effect analysis indicates that the task was too easy to perform (25). As far as we are aware, there are no published reports on the use of the Counting Stroop task in minor head injury patients, with only one study

reporting reduced activation in the anterior cingulate cortex in severely head injury patients compared with healthy controls using this task (52). The interpretation of our lack of a significant association thus remains speculative, but we postulate that differences in activation will only become apparent when the task is sufficiently demanding, as we observed for working memory. Future studies with a further modification and more challenging version of the Counting Stroop task, eg, by using a self-paced and parametric design, are needed.

It is also conceivable that minor head injury incurs more global alterations in brain functioning. Our results provide evidence to the contrary, as no association of postconcussive symptoms with activation during a simple non-cognitive finger tapping task was observed. Thus, changes in brain activation after minor head injury seem to be task-specific rather than global, suggesting that specific neural pathways are selectively vulnerable to neurophysiological damage, which is not detectable with conventional structural imaging.

Despite more widespread and additional brain activation, task performance was slightly worse in minor head injury patients with severe postconcussive symptoms. Theoretically, poorer task performance, inducing some form of error monitoring, could also be underlying the differences in activation. Since no feedback was given on task performance, however, it seems unlikely that participants were aware of the missed responses. Also, since it is the anterior cingulate cortex which is implicated in error monitoring (53–55), and which exhibited no increased or additional activation, it seems unlikely that the activation patterns we found in association with severity of postconcussive symptoms are due to error monitoring.

As increases in fMRI signal are generally accepted to be correlated with increased brain activity (30, 32, 56, 57), our finding of increased activation in areas of the brain related to working memory most likely reflects increased brain activity in these regions in patients with postconcussive symptoms. Such increases in activation only become apparent with increased task difficulty, which is consistent with the aggravation of postconcussive symptoms in demanding situations, such as upon return to work or school. Additionally, our findings provide evidence that patients with postconcussive symptoms recruit brain areas outside of the normal working memory network, reflecting altered or multiple strategies used for working memory processing to counterbalance functional deficits in working memory processing. Thus, the recruitment of these additional brain areas reflects both the brain's plasticity in response to – microstructural – injury and a neuropathological correlate of the postconcussion syndrome.

Such observations have significant clinical importance. Identifying brain areas associated with postconcussive symptoms after minor head injury is not only important for an understanding of the underlying neuropathology of postconcussion syndrome, but it may also have implications for future diagnostic and therapeutic strategies. Early intervention, such as neurocognitive training, has shown to be effective in reducing cognitive symptoms and risk of chronicity (58, 59), but diagnosis and patient selection for intervention is problematic (60, 61). Early detection and subsequent intervention is important, since chronic postconcussion syndrome is difficult to treat, and treatment results are often not satisfactory (6). Due to the non-specific nature of the symptoms and their high base-rate in the general and other trauma populations early diagnosis is challenging. To account for spontaneous resolution of symptoms, persistence of symptoms for more than three months is commonly

used as a diagnostic criterion, even though earlier diagnosis would be desirable (12). Additionally, many confounding factors for the development of postconcussion syndrome have been identified, such as litigation, psychological distress or anxiety due to the traumatic event, premorbid levels of complaints, and female gender (6, 9, 60, 62). At an individual level, the use of cognitive fMRI may make early and reliable diagnosis possible and facilitate the identification of patients suitable for therapeutic intervention. Furthermore, such imaging techniques may be used to evaluate and guide treatment strategies, specifically targeting brain areas involved in recovery of brain injury (63, 64).

We acknowledge that our study had some limitations. Firstly, the statistical power of our study was limited by a relatively small sample size. As far as we are aware, however, our study represents the largest published cognitive fMRI study of minor head injury patients, as previously published study populations ranged from 5 to 18 patients (31–34, 52, 63). Furthermore, the varying inclusion criteria, definitions of minor head injury and intervals between injury and scanning reflect the general difficulty of studying this patient population. To increase our sample size, we also included patients with chronic postconcussive symptoms. Such inclusion introduced heterogeneity in our patient population, with the chronic patient cohort being older, and having traumatic CT findings as opposed to the recent minor head injury patients. Although these factors can certainly be considered confounders, results were found to be very similar when patients with chronic complaints were excluded from the analysis. Secondly, only limited testing of cognitive function was performed. Testing cognition in the present study served solely to assess potential heterogeneity, and thus confounding across subgroups, and not to evaluate neuropsychological deficits after minor head injury, studies of which are already numerous (16–18). We feel that using MMSE and educational level as crude measures of cognitive function were sufficient for the purpose of this study.

Conclusion

We confirmed that minor head injury was significantly associated with increased brain activation for verbal working memory processing. These brain activation changes were detectable as early as one month after minor head injury. Our observation that the severity of postconcussive symptoms was associated with increased as well as additional activation suggests a causal relationship and potentially represents a manifestation of a neuropathological correlate of the postconcussion syndrome.

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CHAPTER 9

Microstructural brain injury in postconcussion syndrome

work in progress

Background After minor head injury (MHI), postconcussive symptoms (PCS) commonly occur, even in the absence of traumatic abnormalities on conventional computed tomography (CT) or magnetic resonance imaging (MRI). The purpose of this study was to correlate MRI measures of microstructural brain injury, in terms of changes in diffusivity and anisotropy as well as the incidence of microhaemorrhages, with the severity of postconcussive symptoms in MHI patients.

Methods Twenty MHI patients and 12 healthy controls were scanned at 3 T, using T1 weighted, Fluid Attenuation Inversion Recovery (FLAIR), diffusion tensor imaging (DTI), and high resolution gradient recalled echo (HRGRE) T2* weighted sequences. The mean participant age was 26.4 years (range, 18–50); 18 participants were male. One patient was excluded from the analysis because of traumatic brain abnormalities. DTI data were preprocessed using Tract Based Spatial Statistics. Resulting mean diffusivity (MD) and fractional anisotropy (FA) images were correlated with the severity of PCS as evaluated with the Rivermead Postconcussion Symptoms Questionnaire (RPSQ) in a voxelwise regression group analysis. The number and location of microhaemorrhages were assessed on the HRGRE T2* weighted images.

Results Significant increase as well as decrease of MD was found in association with the RPSQ score in multiple white matter tracts as well as in the temporal and frontal subcortical white matter. A significant reduction of FA was found in association with the RPSQ score in multiple white matter tracts, including the splenium of the corpus callosum, as well as in the temporal, occipital and parietal subcortical white matter. An association of the RPSQ score with the number or location of microhaemorrhages could not be assessed, as microhaemorrhages were observed in one patient only.

Conclusion The severity of postconcussive symptoms after MHI was significantly correlated with a reduction of white matter integrity as manifested by changes in diffusivity and reduced anisotropic diffusion, providing the first reported evidence of microstructural injury as a neuropathological substrate of the postconcussion syndrome.

HEAD INJURY is one of the most common injuries in the Western world, with minor head injury accounting for 70%–90% of the head injury cases (1). Despite being classified as minor, as clinically determined by a normal or near-normal level of consciousness (Glasgow Coma Scale [GCS] score of 13–15) and a brief period of loss of consciousness (<15 min) or posttraumatic amnesia (<60 min), a large proportion (15%–80%) of patients suffer from a wide variety of symptoms for months after the injury (2–5). This so-called postconcussion syndrome includes symptoms such as headache, fatigue, and cognitive complaints such as memory and attention deficits. Despite the subjective severity of these symptoms, conventional imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) are generally normal. Upon neuropsychological examination cognitive deficits, if any, are subtle and most often in the executive domain (6–8). Symptoms persisting for more than 3 to 6 months are difficult to treat and can lead to vocational disability (9, 10), representing a substantial burden to society and healthcare services. The apparent discrepancy between the subjective severity of complaints and the relative lack of objective neuropsychological and imaging findings has led to controversy about this syndrome, and the exact aetiology as well as the neuropathological substrate remain unclear. Age, gender, previous disease, substance abuse, litigation, and emotional factors have all been suggested to be associated with occurrence and persistence of symptoms, but correlations are inconsistent (2, 11).

A widely accepted hypothesis for an organic origin of the postconcussion syndrome postulates that the symptoms are due to microstructural white matter damage due to shearing injury, which is not detectable with conventional neuroimaging (12–16). This hypothesis is indirectly supported by findings from single photon emission computed tomography (SPECT), showing hypoperfusion in the frontal and parietal lobes of minor head injury patients in general (9), and magnetisation transfer imaging (MTI), showing a reduction of the magnetic transfer ratio (MTR) in minor head injury patients with postconcussive symptoms (9, 17). Further support is provided by a positive correlation between postconcussive symptoms and serum concentrations of protein S100-b, which is found in high concentrations in glial cells and Schwann cells and is highly specific for lesions of the central nervous system (18, 19).

As yet, there is no direct evidence for microstructural injury in relation with the severity of postconcussive symptoms. The shearing injury presumed to underlie the microstructural injury typically occurs during rapid acceleration and/or deceleration trauma mechanisms at interfaces of tissues with differences in density and rigidity, such as at the corticomedullary junction (subcortical white matter), as well as in the corpus callosum and the rostral brainstem adjacent to cerebellar peduncles (pontine-mesencephalic junction) (12, 20, 21).

Two advanced neuroimaging techniques, diffusion tensor imaging (DTI) and three dimensional (3D) high-resolution gradient recalled echo (HRGRE) T2* weighted imaging (22, 23), bear promise to detect axonal injury in vivo with higher sensitivity (24–28) and to provide direct evidence of microstructural brain damage after minor head injury. Diffusion weighted imaging (DWI) provides image contrast based on differences in diffusion of water molecules (24–26). Thus, DWI, offers an in vivo assessment of cell integrity and pathology of the white matter by means of the mean diffusivity as a measure of the magnitude of diffusion. With DTI, in which diffusion weighted gradients are applied in multiple directions, the anisotropy of diffusion can

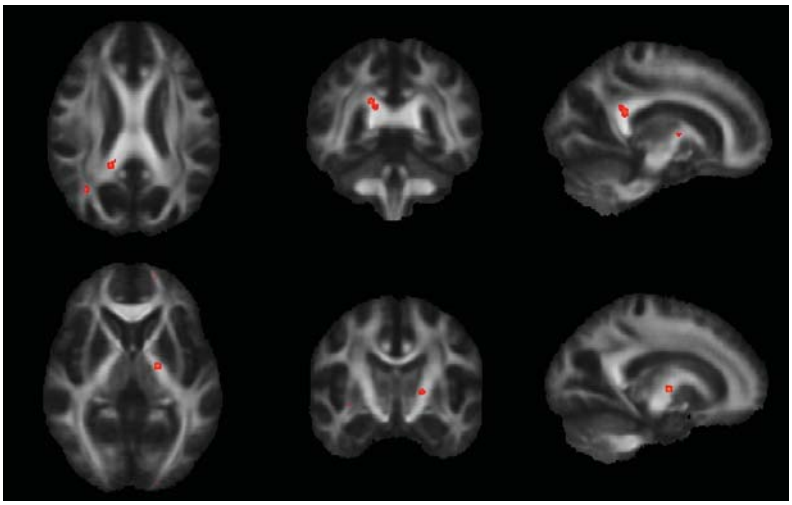

Figure 1. Mean fractional anisotropy (FA) images in axial, coronal and sagittal view, showing areas of significantly reduced FA in the splenium of the corpus callosum (upper row) and the in the corticospinal tract (lower row), in association with the severity of postconcussive symptoms.

be assessed in addition to mean diffusivity. A higher anisotropy of diffusion reflects a motion of water molecules favoured in a specific direction, such as parallel to highly structured white matter fibres. A reduction of anisotropy is generally thought to reflect a reduction of the integrity of white matter fibres, such as in diffuse axonal injury (21, 24, 27–30). A small proportion (10%–30%) of diffuse axonal injury lesions is haemorrhagic (21). Improved detection, as compared with conventional gradient-echo sequences, of these microhaemorrhagic shearing lesions is attained with HRGRE T2* weighted sequences (31–33).

The purpose of this study was to correlate measures of microstructural brain injury, in terms of changes in diffusivity and anisotropy as well as the incidence of microhaemorrhages, with the severity of postconcussive symptoms in minor head injury patients, in the absence of conventional MRI traumatic abnormalities.

METHODS

Study population

Patients were prospectively and consecutively included 1 month after presentation to our emergency department with blunt head trauma if they met the following inclusion criteria: aged 18 to 50 years, a GCS score of 13 to 15 and a normal neurological examination upon presentation, as well as a normal CT of the head performed within 24 hours of injury. As a control group, healthy volunteers matched for age, gender and educational level, were recruited from the included patients' peers and family where possible, and additionally from hospital co-workers.

Head injury patients and controls were excluded if they had a history of neurological or psychiatric disease, had previous head injury, used prescription medication other than oral contraceptives, or had contraindications for MR imaging.

The study protocol was approved by the institutional review board and written informed consent was obtained from all participants.

Participant characteristics

General demographical data were collected from all participants. Educational level was classified as follows: 1, primary education only; 2, lower-level secondary education; 3, middle-level secondary education; 4, higher-level secondary or post-secondary education. All participants underwent general neurological examination and testing of crude cognitive function by means of the Mini Mental Status Examination (MMSE) (34).

In the head injury patients, the number and severity of postconcussive symptoms was assessed by means of the Rivermead Postconcussion Symptoms Questionnaire (RPSQ) (35). The RPSQ is a 5 point-scale of 16 symptoms that are common after head injury, and has a high test-retest and interrater agreement for the assessment of the presence and severity of postconcussive symptoms (35, 36). Patients rate severity of each symptom in comparison with pre-injury levels on a scale from 0 (no symptoms) to 4 (severe symptoms), thus adjusting for the high base-rate of (some of these) symptoms in the general population. Additional symptoms may be recorded and rated similarly. The higher the sum score, the more (severely) symptoms are present after the injury.

MRI acquisition protocol

Imaging was performed on a 3 T MR system (HD platform, GE Healthcare, Milwaukee, WI, US). An 8-channel head coil was used for reception of the signal. For anatomical reference a high-resolution 3D Fast Spoiled Gradient Echo (FSPGR) T1 weighted image with an inversion recovery (IR) pre-pulse was acquired, with the following pulse sequence parameters: repetition time (TR)/echo time (TE)/ inversion time (TI) 10.7/2.2/300 ms; flip angle 18°; acquisition matrix 416×256; field of view (FOV) 250×175 mm^2; 192 slices with a slice thickness of 1.6 mm and 0.8 mm overlap; acquisition time 4:57 min.

As a highly sensitive sequence for the detection of white matter brain injury (37), a Fluid Attenuated Inversion Recovery (FLAIR) acquisition was obtained with the following pulse sequence parameters: TR/TE/TI 8000/120/2000 ms; acquisition matrix 256×128; FOV 210×210 mm^2; 64 contiguous slices with a slice thickness of 2.5 mm; acquisition time 3:13 min.

For diffusion tensor imaging (DTI) we used a 2D single shot spin-echo diffusion weighted EPI acquisition with TR/TE 14200/68.9 ms; acquisition matrix 64×128; FOV 220×220 mm^2; 70 contiguous slices with a slice thickness of 2.0 mm; Array Spatial Sensitivity Encoding Technique (ASSET) acceleration factor 2; acquisition time 6:38 min. One image with a b value of 0 s/mm^2 was acquired, and the maximum b value used was 1000 s/mm^2 acquired in 25 non-collinear directions.

For high resolution T2* weighted imaging, we used a 3D low-bandwidth, high-resolution gradient recalled echo (HRGRE) acquisition with the following pulse sequence parameters: TR/TE 43/29.5 ms; flip angle 14°; bandwidth 88 Hz/pixel; acquisition matrix 512×320; FOV 260×156mm^2; 128 contiguous slices with slice thickness of 1.0 mm; ASSET acceleration factor 2; acquisition time 9:14 min.

Data analysis

Participant characteristics

We tested differences in participant characteristics between patients and controls for significance ($p < 0.05$) with the Student's t-test for continuous (age, MMSE), Pearson's chi-square test for categorical (gender),

Table 1. Participant characteristics

	Patients	Controls	P value
Age, years (SD)	26 (7.4)	28 (10)	0.47
Male gender, n (%)	10 (53)	8 (67)	0.49
Educational level, mean (SD)	3.2 (1.0)	3.3 (1.1)	0.42
MMSE, mean (SD)	27 (1.8)	28 (1.8)	0.91
GCS score, mean (SD)	15 (0.5)	-	-
RPSQ score, mean (SD)	15 (16)	-	-

Abbreviations: SD = standard deviation. MMSE = Mini Mental Status Examination. GCS = Glasgow Coma Scale. RPSQ = Rivermead Postconcussion Symptoms Questionnaire.

and Kruskal Wallis for ordinal (educational level) variables using the Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, Ill, US).

Conventional structural imaging

The T1 weighted and FLAIR images were transferred to a work station and reviewed by two radiologists (A.L. and M.S.) in consensus for abnormalities consistent with traumatic brain injury. Participants with traumatic brain injury abnormalities on either of these two sequences were excluded from the analysis.

DTI analysis

The DTI data were transferred to a work station and spatially pre-processed using Tract Based Spatial Statistics (TBSS) (38), part of the FMRIB Software Library (FSL, Analysis Group, FMRIB, Oxford, UK) (39).

First, DTI data were corrected for head motion and eddy current artefacts. Fractional anisotropy (FA) and mean diffusivity (MD) were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET based on the B0-image (40). All participants' FA data were then aligned into $1\times1\times1$ mm^3 Montreal Neurological Institute (MNI) common space using the nonlinear registration IRTK (41, 42). The mean FA image was created and thinned to create a mean FA skeleton representing the centres of all tracts common to the group, using an FA-threshold of 0.20. Each participant's aligned FA and MD were then projected onto this skeleton.

Voxelwise statistical analysis was performed with Statistical Parametric Mapping version 2 (SPM2, Wellcome department University College London, London, UK) implemented in Matlab version 6.5.1 (The Mathworks, Sherborn, MA, US). In a univariable linear regression analysis, we

Table 2. Areas of significant positive correlation of MD and RPSQ score

Anatomical location	Side	MNI coordinates			Cluster size (No. voxels)	T-value
		x	y	z		
Uncinate/SLF subcortical fibres (temporal lobe)	R	38	6	-33	11	5.41
Uncinate/SLF subcortical fibres (temporal lobe)	R	46	0	-28	5	4.24
IFO fasciculus/ILF (occipital lobe)	L	-33	-79	-2	5	5.08
IFO fasciculus/ILF (temporal lobe)	L	-35	-24	1	6	4.52

Abbreviations: MD = mean diffusivity. RPSQ = Rivermead Postconcussion Symptoms Questionnaire. MNI = Montreal Neurological Institute. SLF = superior longitudinal fasciculus. IFO = inferior fronto-occipital fasciculus. ILF = inferior longitudinal fasciculus.

correlated the individual FA and MD images with the participants' RPSQ scores. Results were thresholded at p <0.001 (not corrected for multiple comparisons) and a minimum cluster size of 5 voxels.

The thresholded statistical t-contrast maps were projected on the T1 weighted anatomical images, after the thresholded contrast maps were thickened to fill them out into the local tracts from the mean FA image. Anatomical labelling was performed manually using the DTI atlases provided by Hermoye et al (43) and Wakana et al (44).

Microhaemorrhage assessment

The 3D HRGRE T2* weighted images were transferred to a work station and minimum intensity projections (minIP) were created with a slab thickness of 10 mm. The number and location of microhaemorrhages were

Table 3. Areas of significant negative correlation of MD and RPSQ score

Anatomical location	Side	MNI coordinates			Cluster size (No. voxels)	T-value
		x	y	z		
Cerebellum	L	-5	-55	-15	6	3.78
Callosal subcortical fibres (frontal lobe)	R	20	59	5	5	4.09
SLF subcortical fibres (frontal lobe)	L	-31	-2	42	5	4.16

Abbreviations: MD = mean diffusivity. RPSQ = Rivermead Postconcussion Symptoms Questionnaire. MNI = Montreal Neurological Institute. SLF = superior longitudinal fasciculus.

Table 4. Areas of significant negative correlation between FA and RPSQ

Anatomical location	Side	MNI coordinates			Cluster size (No. voxels)	T-value
		x	y	z		
Uncinate/IFO fasciculus (frontal lobe)	R	29	10	-8	6	4.28
IFO fasciculus subcortical fibres (occipital lobe)	L	-32	-81	-4	7	4.53
Internal capsule (posterior limb)	L	-19	-8	5	6	4.11
Uncinate/SLF subcortical fibres (temporal lobe)	L	-32	0	-31	7	4.43
Uncinate/SLF subcortical fibres (temporal lobe)	R	53	-13	-18	5	4.87
Uncinate/SLF subcortical fibres (temporal lobe)	R	36	-2	-17	7	4.63
SLF subcortical fibres (temporal lobe)	L	-58	-28	9	6	3.97
Corpus callusum (splenium)	R	13	-40	23	7	4.12
Corpus callosum (splenium)	R	16	-43	26	5	4.01
Callosal fibres (parietal lobe)	R	34	-60	27	7	4.39
Callosal fibres (parietal lobe)	L	-22	-97	35	12	4.05

Abbreviations: FA = fractional anisotropy. RPSQ = Rivermead Postconcussion Symptoms Questionnaire. MNI = Montreal Neurological Institute. SLF = superior longitudinal fasciculus. IFO = inferior fronto-occipital fasciculus. ILF = inferior longitudinal fasciculus.

recorded by two radiologists (A.L. and M.S.) in consensus, who were unaware of the subjects' RPSQ scores at the time of the evaluation.

RESULTS

Study population

Between December 2005 and November 2006, 236 patients with recent minor head injury presented to our emergency department who were eligible for inclusion in the study. Of these, 51 could be contacted, 36 of whom were willing to participate. Of these, 6 did not fulfil the study's inclusion criteria, and 9 were excluded because of contraindications for MR imaging (n = 2), previous history of neurological or psychiatric disease (n = 4), and previous history of head injury (n = 3). One patient did not complete the entire scanning session due to claustrophobia. The 20 remaining patients were imaged at an average of 30.6 days (range, 18–40 days) after the injury. In 19 patients, no traumatic abnormalities were observed on the T1 weighted and FLAIR images. One patient was found to have bilateral subdural haematomas, and was excluded from the analysis. Additionally, 12 healthy volunteers were imaged.

Participant characteristics

The majority of participants were male (n = 18; 58%) and the mean age was 26.4 years (range, 18–50 years). Neurological examination was normal in all participants. There was no difference between patients and controls in age (p = 0.47), gender (p = 0.49), educational level (p = 0.42) or crude cognitive function as measured with the MMSE (p = 0.91) (Table 1). The mean patient RPSQ score was 15 (median, 5; range, 0–46).

All but one patient had a history of loss of consciousness or (posttraumatic) amnesia after the injury. Most patients had a GCS score of 15 upon presentation (n = 13; 68.4%); 6 patients presented with a GCS score of 14 (31.6%).

DTI analysis

A significant increase of MD associated with the severity of postconcussive symptoms was seen in the left inferior fronto-occipital (IFO) fasciculus and inferior longitudinal fasciculus (ILF), as well as in the area of the uncinate and superior longitudinal fasciculus (SLF) fibres underlying the cortex in the right temporal lobe (Table 2).

A significant decrease of MD in association with the severity of postconcussive symptoms was observed in the left cerebellar hemisphere, the callosal subcortical fibres in the right frontal lobe, and SLF subcortical fibres in the left frontal lobe (Table 3).

A significant reduction of FA in association with the severity of postconcussive symptoms was seen in the right uncinate and IFO fasciculus, the left posterior limb of the internal capsule (PLIC), the splenium of the corpus callosum on the right side, as well as in the uncinate and SLF subcortical fibres bilaterally in the temporal lobe, the IFO fasciculus subcortical fibres in the left occipital lobe, and the callosal fibres bilaterally in the parietal lobe (Table 4; Figure 1).

There was no significant increase of FA in association with the severity of postconcussive symptoms.

Microhaemorrhage assessment

Microhaemorrhages were observed in one patient only, localised in the right frontal lobe (Figure 2). Although this patient had a high degree of postconcussive symptoms (RPSQ score = 21), there were not enough lesions to make any inferences on their association with postconcussive symptoms.

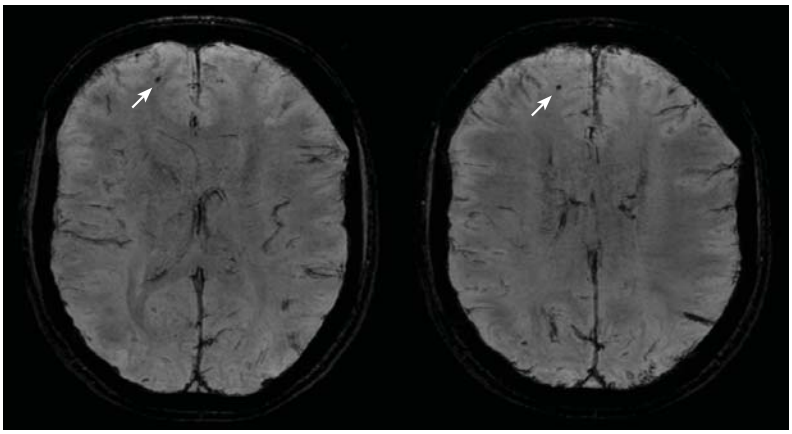

Figure 2. Three dimensional, high-resolution gradient recalled echo T2* weighted images from the same patient, showing two microhaemorrhages (arrows) in the right frontal lobe.

DISCUSSION

In this study of minor head injury patients we found a significant relationship between white matter changes and the severity of postconcussive symptoms of minor head injury, in the absence of macrostructural traumatic abnormalities. To the best of our knowledge, this is the first report of direct evidence of microstructural white matter injury in relation to the severity of postconcussion syndrome.

Postconcussive symptoms are common after minor head injury, but their organic origin has been debated, due to the poor correlation between objective imaging abnormalities and the degree of symptoms. Consistently, both autopsy and in vivo longitudinal studies report evidence of much more widespread and generalised damage to the brain than visualised with conventional imaging, which has led to the generally accepted idea that conventional neuroimaging studies with CT and MRI underestimate the true extent of brain damage after head injury (12). The hypothesis, that postconcussive symptoms are the result of microstructural brain injury is therefore now well recognised.

The microstructural injury consists of shearing or diffuse axonal injury, which has evolved from its original definition of prolonged traumatic coma not associated with mass lesions or ischemic damage, to a spectrum of degrees of axonal damage. It is thought to be due to rotational acceleration and/or deceleration forces occurring at the time of the injury, with a prediliction for the corpus callosum, rostral brainstem and subcortical white matter, and has been observed in post mortem brains with even very brief periods of recorded loss of consciousness (12). Three stages, of increasing severity, of diffuse axonal injury are recognised. The first consists of a biochemical alteration, in which the minimally stretched axons do not tear and changes may be transient. In the second stage the cytoskeleton itself is damaged, accompanied by local swelling and enlargement of the injured axon. In the third stage, axotomy occurs, either primarily or secondarily, in which the axon is severed and antero- and retrograde degeneration follows, leading to disproportionate reduction in white matter, evidenced by the

well recognised global white matter atrophy in the later stages after head injury.

FLAIR and GRE T2* weighted sequences are the two sequences that are most sensitive to the secondary white matter changes and haemorrhage that occur with diffuse axonal injury, respectively (27, 37). The histological changes in diffuse axonal injury, such as changes in axolemmal permeability and misalignments of the cytoskeletal network, however, are not detectable with conventional structural imaging techniques. DTI offers the unique possibility to detect these histological effects directly in vivo through changes in mean diffusivity and a reduction of diffusion anisotropy. A good correlation between diffuse axonal injury lesions and reduction of white matter anisotropy was found using a mouse model (45). In heterogeneous patient populations with all degrees of head injury severity, reductions of anisotropy were found in the typical locations of diffuse axonal injury, such as the corpus callosum (27, 29), and the mesencephalon (28), as well as in the internal capsule (28, 29, 46), the cerebral peduncle (28), the corticospinal tract (47), the medial temporal lobe (28), the IFO fasciculus and SLF (28, 47), the anterior and posterior cingulate (46), and the anterior and posterior periventricular white matter (46). In agreement with these previous studies, we found areas of reduced anisotropy in the splenium of the corpus callosum, the internal capsule, and the uncinate and IFO fasciculus, as well as in the temporal, occipital and parietal subcortical white matter fibres. Our findings indicate reduction of white matter integrity, in association with the severity of postconcussive symptoms, which, given the location of the areas of significant anisotropy reduction, may be attributed to diffuse axonal injury.

Reports on changes in diffusivity have been less consistent. As observed in the present study, both increases and decreases of diffusivity have been reported (21, 29, 46, 48). In the acute stage of minor head injury, Arfanakis et al (29) did not find any changes in diffusivity in relation to head injury, whereas others have reported changes in diffusivity to be a more sensitive measure than reduction of anisotropy for white matter injury (46). In a study correlating diffuse axonal injury lesions with DWI findings, Huisman et al (21) found that 65% of shearing injuries showed decreased diffusivity, thought to be due to trauma-induced changes in tissue metabolism as well as trauma-induced ischemia, in turn leading to cytotoxic oedema (48). Trauma-induced axotomy with the formation of retraction balls and concomitant cytoskeletal collapse along severed axons may be another explanation for reduction of diffusivity. Increase in diffusivity is hypothesised to represent vasogenic oedema, possibly in relation with less severe injury, or to be due to increased molecular mobility as a result of neuronal or glial loss in the later stages of injury (27).

As far as we are aware, there are no previous studies reporting changes in white matter diffusivity and anisotropy correlated with the severity of postconcussive symptoms after minor head injury, although there are some reports of such correlations with clinical measures after head injury. Poor performance on learning and memory indices were found to be correlated with increased diffusivity in the posterior cingulate, the hippocampal formation and the temporal, frontal and occipital cortex in a study by Salmond et al (49). In patients who had recovered from coma, Nakayama et al (50) found reduction of anisotropy in the splenium of the corpus callosum correlated with the MMSE. Kraus et al (47) found a modest negative correlation between FA and executive function, attention and memory.

Our findings of changes in diffusivity, as well as decreased anisotropic diffusion in areas shown to be affected by diffuse axonal injury support the hypothesis that

postconcussive symptoms are the result of microstructural shearing injury, even in the absence of macrostructural evidence of brain injury. The correlation of microstructural white matter injury with neuropsychological measures of cognition in more severely injured patients (47, 49, 50) supports the idea, that microstructural white matter injury leads to cognitive deficits. After minor head injury, neurocognitive deficits, if present, are generally subtle, most commonly affecting working memory and selective attention, which are essential for normal functioning in everyday life (6–8). This is reflected in the time course of postconcussive symptoms, which, after an initial spontaneous decrease over the course of several weeks after the injury, typically aggravate when patients resume their normal, and more demanding, activities, such as return to work or school (6). In a previous study of minor head injury patients using functional MRI to assess the neural correlate of working memory (Smits M, et al. Unpublished data), we found that patients with more severe postconcussive symptoms showed increased brain activity in, as well as the recruitment of brain areas outside the normal working memory network. We postulated that these findings reflect altered or multiple strategies used for working memory processing to counterbalance functional deficits in working memory processing in response to – microstructural – injury.

A limitation of our study seems to be its modest statistical power. This may be due to the relatively small sample size, but also to our study population of exclusively minor head injury patients with (near-)optimal GCS scores. Furthermore, we used FLAIR imaging to exclude patients with any injury-related white matter abnormalities. In previous studies, generally mixed and more severe head injury populations were included. In some studies patients with traumatic abnormalities were not excluded, while in others less sensitive imaging sequences such as the anatomical T1 weighted image were used to exclude patients with traumatic abnormalities.

Conclusion

The severity of postconcussive symptoms after minor head injury was found to be significantly correlated with a reduction of white matter integrity as manifested by changes in diffusivity and reduced anisotropic diffusion, providing the first direct indication of microstructural injury as a neuropathological substrate of the postconcussion syndrome.

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CHAPTER 10

Summary and discussion

THIS THESIS covers both the early complications and late consequences of minor head injury, incorporating findings from two studies: the CT in Head Injury Patients (CHIP) study and our MRI study of minor head injury patients. In the CHIP study, in which data were collected on 3181 consecutive adult patients with minor head injury in four university hospitals in the Netherlands, we evaluated the use of CT in the acute stages after the injury.

In an extension of the CHIP study, patients with a neurocranial traumatic complication were followed up to assess their long-term functional outcome and the presence and severity of postconcussive symptoms.

In the MRI study, we used advanced neuroimaging techniques to study the neuropathological substrate of the postconcussion syndrome. We prospectively included adult minor head injury patients with no abnormalities on CT performed 24 h after the injury. Additionally, patients from the CHIP follow-up study who were known to still suffer postconcussive complaints many years after the injury were included in this study.

INDICATIONS FOR CT IN MINOR HEAD INJURY

CT scanning is the imaging modality of choice for the rapid and reliable diagnosis of neurocranial complications after minor head injury (1–4). Neurocranial complications, however, are infrequent, which raises the question whether routine scanning of all minor head injury is justified in the light of overuse of resources and unnecessary radiation exposure. In the CHIP study, neurocranial traumatic findings were present in fewer than 10% of patients, and in only 7.6% were findings deemed clinically relevant. The most important reason for scanning after minor head injury is the timely identification of patients who require urgent neurosurgical intervention, such as removal of sub- or epidural haematoma, which is a rare but potentially life-threatening complication after minor head injury. Neurosurgical intervention for a neurocranial complication was performed in 17 patients (0.5%) from the CHIP study.

Attempts to reduce CT scanning in minor head injury are preferably based on empirically derived decision algorithms, which are used to select patients at risk for scanning, and may be implemented in the form of hospital policies and clinical guidelines. Clinical guidelines have been published by the Scottish Intercollegiate Guidelines Network (SIGN) (5), the UK National Institute for Clinical Excellence (NICE) (6), the World Federation of Neurosurgical Societies (WFNS) (7), the European Federation of Neurological Societies (EFNS) (8), as well as by the Scandinavian countries (9) and the Netherlands (10). Two excellent decision rules for indications of CT in patients with minor head injury were also published in recent years, namely the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC) (11, 12). Before their implementation in clinical practice, however, external validation was necessary.

Validation of published decision rules and clinical guidelines

In the CHIP study, we validated and compared the published decision rules, as well as the various national and international clinical guidelines for indications of CT in minor head injury. Primary outcome was any neurocranial traumatic finding on CT. Secondary outcomes were neurosurgical intervention and clinically important CT findings. We estimated sensitivity and specificity for each outcome measure of the NOC and CCHR and each of the guidelines. We also estimated the number of patients needed to scan to detect one outcome (ie,

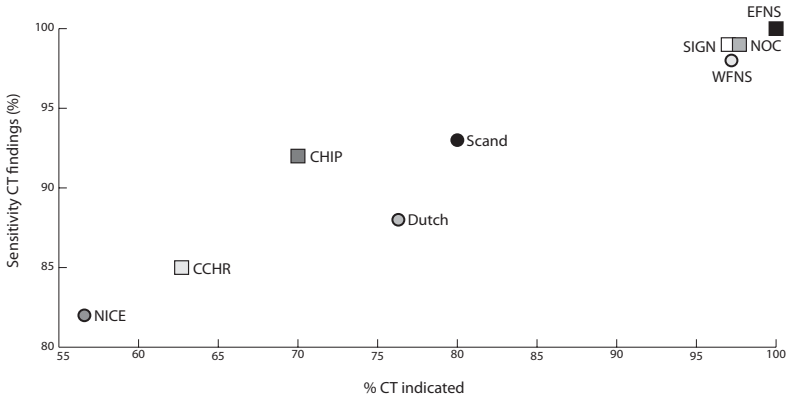

Figure 1. Sensitivity (%) for neurocranial traumatic CT findings for the validated decision rules and clinical guidelines versus the percentage of patients in whom CT would be indicated according to the decision rule or guideline. Squares indicate that the decision rule/guideline had a sensitivity of 100% for the identification of patients requiring neurosurgical intervention. NICE = National Institute for Clinical Excellence; CCHR = Canadian CT Head Rule; Dutch = Dutch national guidelines; CHIP = CT in Head Injury Patients; Scand = Scandinavian guidelines; NOC = New Orleans Criteria; WFNS = World Federation of Neurosurgical Societies; EFNS = European Federation of Neurological Societies; SIGN = Scottish Intercollegiate Guidelines Network.

the number of patients needed to undergo CT to find one patient with a neurocranial traumatic CT finding, a clinically relevant traumatic CT finding, or a CT finding that required neurosurgical intervention) for each of the guidelines.

All published guidelines and decision rules showed a similar trade-off between sensitivity and specificity for the identification of patients with a traumatic finding on CT, and by extension between sensitivity and the proportion of patients needing to be scanned (Figure 1). Both the NOC and the CCHR, as well as the guidelines set forth by the EFNS and SIGN, had a sensitivity of 100% for the identification of patients requiring neurosurgical intervention. The lowest number needed to scan for either outcome measure was reached with the UK NICE criteria. Of the published guidelines, the Dutch national guidelines had the lowest sensitivity for neurosurgical interventions, with which almost 25% of patients requiring neurosurgical intervention would be missed. Three of these four missed patients presented with a normal level of consciousness, and did not have a history of loss of consciousness or posttraumatic amnesia (PTA). Applying the Dutch national guidelines strictly, as we did in our study, these patients are classified as having minimal head injury, irrespective of the presence of other risk factors, such as headache, vomiting, or seizure, and are sent home without any imaging or observation.

Loss of consciousness in minor head injury

A history of loss of consciousness or PTA is commonly considered a prerequisite for minor head injury and as such often used for triaging patients in the emergency department. As evidenced by findings from the CHIP study, neurocranial complications also occur when loss of consciousness or PTA are absent, particularly in the presence of other risk factors, and sometimes even require neurosurgical intervention. To assess whether loss of consciousness and PTA need to be considered as independent risk factors

rather than a prerequisite for the definition of minor head injury, we evaluated whether known risk factors for complications after minor head injury in the absence of loss of consciousness and PTA have the same predictive value as when loss of consciousness or PTA are present.

We selected the 2462 patients from the CHIP study who presented with a normal level of consciousness (GCS score = 15) and a risk factor. A history of loss of consciousness or PTA was present in 1708 (69%) and absent in 754 (31%). Neurocranial traumatic findings on CT were more common when a history of loss of consciousness or PTA was present (9%) than absent (5%). Neurosurgical intervention was required in 0.4%, irrespective of the presence of loss of consciousness or PTA.

We estimated common odds ratios (ORs) for each of the risk factors and tested them for homogeneity. ORs were comparable across the two subgroups, indicating that loss of consciousness and PTA need to be considered as independent risk factors for neurocranial complications after minor head injury, with ORs of 1.9 and 1.7, respectively.

The CHIP prediction rule

Patients without a history of loss of consciousness or PTA were included neither in the NOC, nor in the CCHR, limiting generalisability of both these decision rules. We therefore developed a more widely applicable prediction rule for the selective use of CT in all minor head injury patients, regardless of the presence or absence of a history of loss of consciousness or PTA. Using logistic regression analysis with variables from the existing decision rules and guidelines, we developed the so-called CHIP prediction rule, which we validated internally with bootstrapping procedures.

We present a detailed and a simplified version of the CHIP prediction rule, both versions having a sensitivity of 100% for neurosurgical interventions by definition, with associated specificities of 23% to 30%. The simplified CHIP prediction rule consisted of 10 major and 8 minor risk factors (Table 1). Potential CT reduction by implementing the prediction rule was 23% to 30% (Figure 1).

Discussion

The main findings from the CHIP study are: 1, in all of the validated guidelines and decision rules a similar trade-off was seen between sensitivity and specificity for neurocranial traumatic lesions, and a corresponding trade-off between sensitivity and the proportion of patients in whom a CT is indicated; 2, the Dutch national guidelines

Table 1. Simplified CHIP prediction rule

A CT is indicated in the presence of 1 major criterion
Pedestrian or cyclist versus vehicle
Ejected from vehicle
Vomiting
Posttraumatic amnesia ≥4 h
Clinical signs of skull fracture†
GCS score <15
GCS deterioration ≥2 points 1 h after presentation
Use of anticoagulant therapy
Posttraumatic seizure
Age ≥60 y
A CT is indicated in the presence of at least 2 minor criteria
Fall from any elevation
Persistent anterograde amnesia‡
Posttraumatic amnesia of 2 to <4 h
Contusion of the skull
Neurological deficit
Loss of consciousness
GCS deterioration of 1 point 1 h after presentation
Age 40–60 y

GCS = Glasgow Coma Scale.
† Any injury that suggests a skull fracture, such as palpable discontinuity of the skull, leakage of cerebrospinal fluid, 'raccoon eye' bruising, and bleeding from the ear.
‡ Persistent anterograde amnesia is any deficit of short-term memory.

have unacceptably low sensitivity for identifying patients requiring neurosurgical intervention; and 3, loss of consciousness and PTA need to be considered as independent risk factors for neurocranial traumatic complications after minor head injury.

The similar trade-off between sensitivity and specificity for the identification of patients with a neurocranial traumatic finding on CT indicates that none of the guidelines or decision rules were obviously superior. Only the two decision rules and the EFNS guidelines reached a – desired if not mandatory – 100% sensitivity for neurosurgical intervention. The NOC's and CCHR's sensitivities, and particularly specificities for the identification of patients with any neurocranial traumatic finding on CT were much lower than originally reported, which especially for the NOC resulted in a much lower potential to reduce scans. This may be a reflection of differences in patient populations visiting emergency departments in our participating centres in the Netherlands as compared with those in North America, where the original studies originated from. This is inherent to external validation studies, and demonstrates why external validation studies are necessary before implementation.

The Dutch national guidelines are currently being revised, as their ambiguity regarding patients without a history of loss of consciousness or PTA leads to an unacceptably low sensitivity for the identification of patients requiring neurosurgical intervention. Minor head injury patients *without* a history of loss of consciousness or PTA need to be carefully evaluated and may also need imaging or clinical observation. In the CHIP rule, loss of consciousness and PTA are included as independent risk factors, which renders it more widely applicable than the NOC or CCHR. The CHIP rule has a high potential to reduce the number of CTs while identifying all patients requiring neurosurgical intervention and most patients with an intracranial traumatic finding on CT.

Given the similar balance of each of the guidelines and decision rules between sensitivity and specificity, the question is, what we need to aim for. It is desirable for a guideline to identify all patients with CT findings requiring neurosurgical intervention. The importance of identifying other traumatic lesions on CT, however, depends on the effect of management decisions on the patient's clinical outcome. A CT scan is the only reliable way to rule out serious intracranial complications, while observation performs badly as a diagnostic tool and may lead to a less than optimal outcome since intervention subsequent to deterioration is delayed (13, 14). CT findings do generally affect clinical management, eg, the decision between discharge or clinical observation, but since patients only occasionally deteriorate during observation, it is difficult, if not impossible, to assess whether observation, and therefore the CT scan, really does affect the patient's clinical outcome. This would imply that a 100% sensitivity for traumatic findings on CT may not be necessary.

The choice of which guideline to use will depend largely on the objective of implementing a guideline. If the objective is not to miss any patients with a traumatic finding on CT, basically all patients with minor head injury will need to undergo CT, such as recommended in the NOC decision rule or the EFNS guidelines. If, however, the objective is to reduce the number of CTs performed for minor head injury, eg, to reduce workload or due to limited availability, and one is willing to accept the risk of missing the occasional patient presenting with minor symptoms, the CHIP prediction rule has a high potential to reduce the number of CTs while still having a reasonable sensitivity to identify patients with traumatic brain injury and identifying all patients requiring neurosurgical intervention.

COST-EFFECTIVENESS OF THE SELECTIVE USE OF CT

The question is, however, whether selection of patients for CT scanning is truly desirable. Selection of patients for CT introduces the inherent risk of leaving minor head injury patients with traumatic complications, and particularly those requiring neurosurgical intervention, undiagnosed with potentially devastating consequences in terms of loss of (quality) of life. To address this question, we performed a cost-effectiveness analysis of selective CT scanning strategies, taking the uncertainty of the prediction algorithms' sensitivities into account, in comparison with the routine use of CT in all minor head injury patients.

Cost-effectiveness analysis

We evaluated 5 strategies: scanning all minor head injury patients; selective CT according to the NOC, the CCHR or the CHIP rule; and no scanning (reference strategy). Model parameters were primarily based on the CHIP study. We used a decision tree for the short-term, and a Markov model for the long-term costs and effectiveness. Outcome measures were first-year and lifetime costs, quality adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER). The model's robustness was tested against varying the model parameters across their 95% confidence intervals (CIs) in n-way and probabilistic sensitivity analysis. Also, value of information (VOI) analysis was performed.

We found that selective CT scanning according to the CCHR or CHIP rule could lead to substantial cost-savings in the US of US$ 120 million or US$ 71 million, respectively, without loss of effectiveness. The prediction rules' sensitivities to identify patients requiring neurosurgery influenced the model outcome: at sensitivities below 97% scanning all patients was cost-effective (ICER < US$ 75 000/QALY). N-way and probabilistic sensitivity analyses demonstrated that scanning according to the CHIP rule was most likely to be cost-effective. VOI analysis demonstrated an expected value of perfect information of US$ 7 billion, which was mainly due to uncertainty in long-term functional outcome.

Discussion

We found that using the CCHR to select patients for CT after minor head injury was the most cost-effective scanning strategy and can potentially lead to annual cost-savings in the US of US$ 120 million. This finding, however, was only valid under the assumption that this prediction rule is highly sensitive for the identification of patients requiring neurosurgical intervention of a neurocranial traumatic lesion after head injury. At lower sensitivities cost-savings were less, and at sensitivities below 91%–99% scanning all patients was cost-effective compared with selective CT. Furthermore, we found that the uncertainty concerning long-term functional outcome after minor head injury currently precludes a definitive decision on whether selective CT is more cost-effective than scanning all minor head injury patients, and that further research is warranted.

With the CCHR, the best distinction between patients with a neurosurgical versus those with a non-neurosurgical lesion was made. As identification of non-neurosurgical lesions increases the use of resources without a gain in effectiveness, while identification of patients with a neurosurgical lesion averts costs and loss of (quality of) life, it was not surprising that the CCHR was found to be the most cost-effective strategy in the base-case analysis, confirming previous findings by Stein et al (15).

The use of prediction algorithms such as the CCHR, however, introduces the risk of misclassifying patients, and consequently leaving patients with a neurosurgical

traumatic lesion undiagnosed. The question is how many of these patients we can afford to miss using a selective CT strategy. Previous cost-effectiveness studies have left this question unanswered (15, 16). In our sensitivity analyses we found that selective CT scanning only had a probability of 51%–64% to be cost-effective compared with scanning all minor head injury patients. Furthermore, at sensitivities for identifying patients requiring neurosurgical intervention below 91%–99% scanning all patients was the most cost-effective strategy. So, even though a neurosurgical traumatic lesion after minor head injury is very rare, scanning all minor head injury patients seems to be more cost-effective than missing even a small proportion of these patients, as delayed diagnosis of patients requiring neurosurgical intervention presumably leads to poorer outcome, incurring higher costs due to disability and loss of quality of life.

Due to the rare occurrence of lesions requiring neurosurgical intervention after minor head injury, the reported 95% CIs for the prediction rules' sensitivities to identify such lesions are wide, with lower limits well below 90% (17, 18). Given this rare occurrence of lesions requiring neurosurgery, the 3 prediction rules for selective CT scanning were originally designed considering any intracranial traumatic lesion on CT as a proxy for a lesion requiring neurosurgical intervention. With the CCHR's lower limit of the 95% CI for sensitivity of intracranial traumatic lesions being well below 90%, there is a real possibility that the CCHR is less cost-effective than scanning all minor head injury patients, even though the CCHR has the largest potential for cost-savings. With the CHIP prediction rule, on the other hand, annual cost-savings are also considerable (US$ 71 million), and, given a 95% CI lower limit for overall sensitivity of intracranial traumatic lesions of 91%, it is more likely to be cost-effective compared with scanning all minor head injury patients, which was confirmed in our probabilistic sensitivity analysis. Furthermore, the CHIP rule is more widely applicable since it also applies to patients without a history of PTA or loss of consciousness.

LONG-TERM OUTCOME

Although most patients with minor head injury, as the term suggests, fully recover, there is evidence to suggest that patients with a neurocranial traumatic complication have worse functional outcome than patients without traumatic findings on CT (19, 20). The long-term outcome in these patients with so-called complicated minor head injury, however, is as yet largely unknown.

We therefore performed a follow-up study on all 312 patients from the CHIP study with a neurocranial traumatic CT finding. Data from this follow-up study were used in the previously described cost-effectiveness analysis. We assessed functional outcome according to the Glasgow Outcome Scale (GOS) as a primary outcome measure. Other outcome measures were the modified Rankin Scale (mRS), the Barthel Index (BI), and number and severity of postconcussive symptoms. Of the patients we were able to reach (76%) at an average of 15 months after injury, a small majority had fully recovered (63%). A substantial proportion of patients was moderately disabled (30%), and a small percentage was severely disabled (3%), or had died (4%). Outcome according to the mRS and BI was also favourable in most patients, but 82% of patients still had postconcussive symptoms.

Furthermore, we used univariable analyses to evaluate the association between CT findings and outcome, as well as multivariable regression analysis to assess whether certain CT findings were predictive of poor functional outcome. The only predictor of poor functional outcome on CT performed

within 24 hours of injury was evidence of parenchymal damage (OR = 1.9).

Discussion

Patients with neurocranial traumatic complications after minor head injury generally make a good functional recovery, but postconcussive symptoms may persist for many years after the injury. We found that evidence of parenchymal damage on CT was independently predictive of poor functional outcome. Interestingly, none of the neurocranial traumatic findings was significantly associated with a *better* outcome, suggesting that good outcome even for so-called clinically non-significant lesions may not be certain.

The most important limitation of our study was the fact that a substantial number of patients were lost to follow-up, in part accounting for the uncertainty on long-term functional outcome after complicated minor head injury we encountered in the cost-effectiveness analysis. This is inherent to the patient population we studied and the fact that we assessed outcome several years (2–4 years) after the injury had occurred.

We found a very high rate of postconcussive symptoms in patients with complicated minor head injury. Postconcussive symptoms are very common after head injury, especially in the first weeks to months after the injury (21–28). Since many of the reported symptoms, such as headache and fatigue, have a high base-rate in the general population, patients with postconcussive symptoms are often considered malingerers, especially when no objective (imaging) abnormalities can be found, or, as in our study, no relationship between specific imaging findings and postconcussive symptoms can be determined. Despite the high reported rates, symptoms generally disappear in the majority of patients after 3 to 6 months, only persisting in a minority of patients (24, 29). Rates of postconcussive symptoms in patients with neurocranial traumatic complications after minor head injury have not been previously reported. The high rate of symptoms we found suggests that minor head injury patients with neurocranial complications are at high risk of persistence of symptoms for years after the injury.

POSTCONCUSSION SYNDROME

Even in the absence of CT or even MR imaging findings, postconcussive symptoms after minor head injury such as fatigue, headache and memory and attention deficits frequently occur. The neuropathological substrate of this so-called postconcussion syndrome is still largely unknown, although it has been hypothesised that microstructural damage of the brain, not detectable with conventional imaging techniques, may be responsible (30–34).

Two advanced MRI techniques hold promise to gain evidence for support of this hypothesis. With functional MRI (fMRI), brain activation can be visualised, potentially providing evidence for a functional deficit, as a result of microstructural brain damage. Three-dimensional (3D) high-resolution gradient recalled echo (HRGRE) T2* weighted imaging and Diffusion Tensor Imaging (DTI) provide sensitive measures for the detection of microhaemorrhages and of changes in white matter integrity respectively, both being techniques to directly visualise microstructural brain damage in vivo.

Twenty-nine minor head injury patients and 12 healthy controls (mean age, 29 years; male gender, 63%) were scanned at 3.0 T using fMRI, DTI and 3D HRGRE T2* weighted imaging. The severity of postconcussive symptoms (PCS) was measured with the Rivermead Postconcussion Symptoms Questionnaire (RPSQ) and expressed as the RPSQ score (median, 10; range, 0–46).

Neural correlates of PCS

Using Blood Oxygenation Level Dependent (BOLD) fMRI, we correlated the severity of postconcussive symptoms with brain activation of the two cognitive domains most commonly affected in postconcussion syndrome, namely working memory and attention, which were engaged with the n-back task and the Counting Stroop task, respectively.

No association was found between the severity of PCS and brain activation related to selective attention. At minimal working memory load, increased activation was seen in patients with greater severity of PCS in brain areas involved in vigilance, as well as in the working memory network. With an increase of working memory load, differential activation was more pronounced in patients reporting a greater severity of PCS. Furthermore, at high, as well as differential, working memory load, activation associated with PCS was seen in areas outside the working memory network, namely the parahippocampal gyrus and the posterior cingulate gyrus.

Microstructural injury in PCS

For the assessment of microstructural injury in association with PCS, we excluded patients with traumatic brain abnormalities as assessed with T1 weighted and Fluid Attenuation Inversion Recovery (FLAIR) imaging. Imaging data from 19 minor head injury patients and 12 healthy volunteers (mean age, 26.4 years; male gender, 58%) were analysed, using Tract Based Spatial Statistics (TBSS) for pre-processing of the DTI data. Resulting mean diffusivity (MD) and fractional anisotropy (FA) images were correlated with the severity of PCS as evaluated with the RPSQ in a voxel-wise group regression analysis. The number and location of microhaemorrhages were assessed on the HRGRE T2* weighted images.

Significant increase as well as decrease of MD was found in association with the RPSQ score in multiple white matter tracts as well as in the temporal and frontal subcortical white matter. A significant reduction of FA was found in association with the RPSQ score in multiple white matter tracts, including the splenium of the corpus callosum, as well as in the temporal, occipital and parietal subcortical white matter. An association of the RPSQ score with the number or location of microhaemorrhages could not be assessed, as microhaemorrhages were observed in one patient only.

Discussion

In this MRI study of minor head injury patients, we correlated brain activation as well as white matter integrity changes with the severity of PCS. Our findings provide evidence for microstructural brain injury and the brain's plasticity compensating for the resulting functional deficit in verbal working memory processing.

The severity of postconcussive symptoms was found to be associated with changes in verbal working memory activation. In contrast to previous fMRI studies of minor head injury patients, we did not simply compare patients with healthy controls, but correlated the presence and severity of postconcussive symptoms with the neural correlates of working memory. We found an elevated resting state of the 'working memory network' in patients with greater severity of PCS, and more pronounced increases in working memory network activation with higher working memory demands. Additionally, activation was seen in areas outside the working memory network, most notably in the parahippocampal gyrus and the posterior cingulate gyrus, indicating that these regions may subserve strategies for dealing with very high working memory demands, possibly when the working memory network itself is exhausted (35).

The recruitment of these additional brain areas reflects both the brain's plasticity in response to – microstructural – injury and a neuropathological correlate of PCS.

Further, and more direct support for the hypothesis that the postconcussion syndrome may be due to microstructural brain injury was provided by our DTI study, in which a reduction of fractional anisotropy was found in several white matter tracts and in the subcortical white matter of the temporal, parietal and occipital lobes. Our findings provide the first direct in vivo evidence for white matter changes, in the absence of macrostructural abnormalities, in relation with postconcussive symptoms.

Identifying brain areas injured in relation to and functionally associated with postconcussive symptoms after minor head injury is not only important for an understanding of the underlying neuropathology of the postconcussion syndrome, but it may also have implications for future diagnostic and therapeutic strategies. Early intervention, such as neurocognitive training, has shown to be effective in reducing cognitive symptoms and risk of chronicity (28, 36), but diagnosis and patient selection for intervention is problematic (27, 37). At an individual level, the use of cognitive fMRI and DTI may make early and reliable diagnosis possible and facilitate the identification of patients suitable for therapeutic intervention. Furthermore, functional imaging techniques may be used to evaluate and guide treatment strategies specifically targeting brain areas involved in recovery of brain injury (38, 39).

CONCLUSION

In this thesis, we have approached the subject of minor head injury from multiple perspectives. The combined health and clinical sciences perspective, as used for the assessment of the use of CT in the management of minor head injury patients, ideally leads to improved, evidence-based health care, providing clinicians with cost-effective, easy to implement management strategies. From the perspective of the fundamental sciences, we assessed the poorly understood, but well-recognised long-term consequences of minor head injury and provide evidence for an organic aetiology of the postconcussion syndrome.

The management of minor head injury patients is a matter of debate, balancing the use of resources and the risk of misdiagnosing patients with a life-threatening neurocranial complication. Although this risk is low, owing to the high incidence of minor head injury, overall mortality due to minor head injury is in fact higher than that due to more severe head injuries (40). In the CHIP study, mortality was indeed low, but, while the majority of patients with complications after minor head injury recovered well, these patients seem to be at increased risk of postconcussive symptoms for many years after the injury.

Postconcussion syndrome is a controversial diagnosis, due to many confounding factors, the high base-rate of symptoms in the general population and the commonly observed absence of objective imaging or neuropsychological abnormalities. In our MRI study, we provide support for the hypothesis that the postconcussion syndrome is the result of microstructural damage, as evidenced by decreased fractional anisotropy in multiple white matter tracts, causing a functional deficit in working memory processing, as indicated by compensatory brain activation. We will explore this hypothesis further in a longitudinal study of these patients, to assess whether brain activation patterns and white matter fractional anisotropy values normalise with the resolution of postconcussive symptoms. Better understanding of the postconcussion syndrome not only provides

objective support for this diagnosis, but may in the future also be used for guiding neurocognitive training or support. Whether the use of such advanced MRI techniques will remain mostly in the domain of research or will become available for clinical use, will depend greatly on their potential application in the individual patient.

CT, on the other hand, is routinely used in the management of the acute stages after minor head injury. As CT scanners are now widely available, providing rapid and reliable diagnosis, and due to the high pressure of medico-legal issues, many clinicians would probably welcome a lenient CT scanning strategy. Selective CT scanning based on prediction rules is cost-saving and is potentially cost-effective. Out of the 3 prediction rules, the highest annual cost-savings are expected with the CCHR, which, however, potentially has a sensitivity for identifying patients requiring neurosurgical intervention below the threshold at which scanning all minor head injury patients is cost-effective. The CHIP prediction rule is more sensitive than the CCHR, was more likely to be cost-effective in sensitivity analyses, is more widely applicable, and also has the potential of substantial cost-savings. More research is warranted to increase certainty on long-term patient outcome after minor head injury. Until such time, scanning all minor head injury patients, instead of implementing a prediction rule, is also justified.

It has become clear, from our follow-up study of complicated minor head injury patients, the decision-modelling exercise, the results from the value of information analysis, the MRI findings, and the many associated discussions among those involved in this study that knowledge and understanding concerning long-term functional outcome is still sorely lacking. Future research needs to be focused on assessing long-term functional outcome after minor head injury and to evaluate these outcomes in a large, prospective cohort study, preferably taking implementation of several management strategies into account. An approach from multiple perspectives, in line with this thesis, would be ideal, studying not only the patients' objective functional outcome according to the Glasgow Outcome Scale, but also their subjective quality of life, the neurocognitive consequences, and the neuropathological substrate of postconcussive symptoms using advanced neuroimaging techniques.

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CHAPTER 11

Samenvatting en conclusies

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IN DIT proefschrift over de vroege complicaties en gevolgen op lange termijn van licht traumatisch schedel-/hersenletsel (LTSH) worden de bevindingen van twee studies beschreven: de *CT in Head Injury Patients* (CHIP) studie en onze MRI studie van patiënten met LTSH.

INDICATIES VOOR CT BIJ LICHT TRAUMATISCH SCHEDEL-/HERSENLETSEL

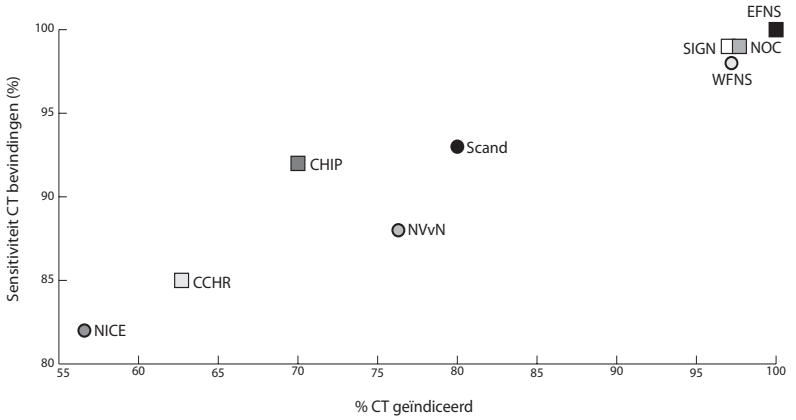
Het licht traumatisch schedel-/hersenletsel vormt een belangrijke belasting voor de Nederlandse gezondheidszorg. Jaarlijks presenteren zich in Nederland naar schatting 60 000 LTSH-patiënten op de Spoedeisende Hulp. LTSH wordt over het algemeen gedefinieerd als stomp hoofdtrauma met een normaal tot minimaal verlaagd bewustzijn bij presentatie (*Eye Motor Verbal* [EMV] score = 13–15), kortdurend bewustzijnsverlies (<15 min) of posttraumatische amnesie (PTA, <60 min). De incidentie van intracraniale complicaties van LTSH is laag (<10%); deze zijn echter potentieel levensbedreigend en vormen in zeldzame gevallen (<1%) een indicatie tot spoedeisend neurochirurgisch ingrijpen (1–4). Een CT scan van de schedel is de beeldvormende techniek van keuze om intracraniale complicaties snel en betrouwbaar te diagnosticeren (5–7); reden dat in Nederland een ruime indicatiestelling voor een CT scan bij het LTSH wordt aanbevolen (8).

De huidige Nederlandse richtlijnen zijn voornamelijk gebaseerd op de predictieregel van Haydel et al (3). Deze zogenaamde *New Orleans Criteria* (NOC) betreffen een zevental risicofactoren op grond waarvan patiënten met een risico van intracraniale complicaties geïdentificeerd zouden kunnen worden met zeer hoge (100%) sensitiviteit en matige specificiteit (25%). In een gelijkaardige studie van Stiell et al (4) werd een verschillend aantal risicofactoren geïdentificeerd, de *Canadian CT Head Rule* (CCHR), eveneens met een sensitiviteit van 100% voor het identificeren van patiënten met klinisch relevante intracraniale complicaties en een veel hogere specificiteit (50%) dan de NOC. Op deze CCHR zijn diverse andere richtlijnen voor de indicaties voor een CT scan bij LTSH gebaseerd, zoals de criteria van het Britse *National Institute for Clinical Excellence* (NICE) (9). Hoewel reeds geïmplementeerd in klinische richtlijnen, waren beide predictieregels slechts intern gevalideerd met als gevolg dat de gerapporteerde sensitiviteit en specificiteit in externe patiëntenpopulaties waarschijnlijk anders zullen uitvallen. Externe validatie was daarom dringend gewenst.

Validatie van gepubliceerde predictieregels

In onze prospectieve, multicentrische CHIP studie hebben we data verzameld van 3181 opeenvolgende volwassen patiënten met LTSH met als doel de NOC en de CCHR te valideren in de Nederlandse populatie. Alle geïncludeerde patiënten hadden een CT scan van de schedel ondergaan, op grond waarvan de primaire uitkomstmaat, de aanwezigheid van een neurocraniale traumatische afwijking, bepaald werd. Secundaire uitkomstmaten waren klinisch relevante traumatische afwijkingen op de CT scan, gedefinieerd als iedere neurocraniale traumatische bevinding met uitzondering van een geïsoleerde lineaire schedelfractuur, en neurochirurgische interventie voor een traumatische afwijking op de CT scan.

Driehonderd en twaalf (9,8%) patiënten hadden een neurocraniale traumatische afwijking op de CT scan. Bij zeventien patiënten was neurochirurgisch ingrijpen verricht (0,5%). Zowel de NOC als de CCHR had een sensitiviteit van 100% (95% CI, 82%–100%) voor het identificeren van patiënten die neurochirurgische interventie hadden ondergaan (10). De proportie van



Figuur 1. Sensitiviteit (%) voor neurocraniale CT bevindingen van de gevalideerde predictieregels en klinische richtlijnen versus het percentage patiënten bij wie een CT geïndiceerd zou zijn volgens de predictieregel of richtlijn. Weergave met een vierkantje betekent dat deze predictieregel/richtlijn een sensitiviteit van 100% had voor het identificeren van patiënten die neurochirurgische interventie hadden ondergaan. NICE = National Institute for Clinical Excellence; CCHR = Canadian CT Head Rule; NVvN = Nederlandse richtlijnen van de Nederlandse Vereniging voor Neurologie; CHIP = CT in Head Injury Patients; Scand = Scandinavische richtlijnen; NOC = New Orleans Criteria; WFNS = World Federation of Neurosurgical Societies; EFNS = European Federation of Neurological Societies; SIGN = Scottish Intercollegiate Guidelines Network.

patiënten met LTSH bij wie een CT scan geïndiceerd zou zijn volgens de NOC was zeer hoog (97%) en volgens de CCHR een stuk lager (63%), terwijl de sensitiviteit voor het identificeren van patiënten met een neurocraniale of klinisch relevante traumatische bevinding op de CT scan voor de NOC veel hoger was (98%–99%) dan voor de CCHR (83%–87%) (Figuur 1).

Validatie van gepubliceerde klinische richtlijnen

Naast de Nederlandse richtlijnen zijn er diverse andere klinische richtlijnen gepubliceerd voor de indicaties voor een CT scan bij LTSH, zoals de richtlijnen van de *European Federation of Neurological Societies* (EFNS) (11), de *World Federation of Neurosurgical Societies* (WFNS) (12), het Britse NICE (9), het *Scottish Intercollegiate Guidelines Network* (SIGN) (13) en de Scandinavische richtlijnen (14). Zoals gezegd zijn sommige hiervan – ten dele – gebaseerd op de NOC of de CCHR, terwijl andere tot stand zijn gekomen mede op basis van empirische klinische expertise. Hoewel er zeker overlap bestaat tussen de verschillende richtlijnen, zijn er ook belangrijke verschillen, wat zich uit in een liberaal CT scanbeleid van sommige richtlijnen, terwijl volgens andere een CT scan slechts beperkt geïndiceerd is. Implementatie van de laatste zou kunnen leiden tot een reductie in het aantal CT scans verricht bij LTSH met als voordeel het voorkómen van overdiagnostiek en beperking van stralingsdosis. De vraag is echter of een beperkte indicatiestelling wel gerechtvaardigd is wanneer niet zeker is of het risico bestaat dat patiënten met een ernstige (neurochirurgische) complicatie onterecht niet gescand worden.

In onze validatiestudie laten alle richtlijnen eenzelfde balans zien tussen sensitiviteit voor neurocraniale traumatische bevindingen op de CT scan en de proportie patiënten

bij wie een CT scan volgens de richtlijn geïndiceerd zou zijn (Figuur 1) (15). Alleen de richtlijnen van de EFNS behaalden een sensitiviteit van 100% voor het identificeren van patiënten met een neurocraniale traumatische bevinding op de CT scan. Echter, om deze sensitiviteit te behalen zou een CT scan geïndiceerd zijn bij alle in onze studie geïncludeerde patiënten. De meest restrictieve richtlijn wat de indicaties voor een CT scan betreft, waren de NICE-criteria, volgens welke slechts 57% van de patiënten gescand zou hoeven worden. Deze richtlijn had echter ook de laagste sensitiviteit voor het identificeren van patiënten met een neurocraniale traumatische afwijking op de CT scan (82%).

De Nederlandse richtlijnen hadden de laagste sensitiviteit voor het identificeren van patiënten die neurochirurgische interventie hadden ondergaan (76%). Deze bevinding is toe te schrijven aan het feit dat er in de huidige Nederlandse richtlijnen geen duidelijkheid is over de categorie van patiënten zonder bewustzijnsverlies of PTA, maar die wel een andere risicofactor hadden. Strikt genomen vallen deze patiënten volgens de Nederlandse richtlijnen in de categorie 'trauma capitis' en zouden zonder verdere beeldvorming naar huis ontslagen kunnen worden. Drie van de zeventien patiënten die een neurochirurgische interventie hadden ondergaan, vielen in deze categorie.

Bewustzijnsverlies of PTA: een 'conditio sine qua non' voor LTSH?

De aanwezigheid van bewustzijnsverlies of PTA wordt vaak als voorwaarde gesteld voor de diagnose LTSH, zeker bij een patiënt met maximaal bewustzijn. Het risico van neurocraniale complicaties bij patiënten zonder bewustzijnsverlies of PTA wordt geschat op een kwart van dat bij patiënten met bewustzijnsverlies of PTA (16, 17). De aan- of afwezigheid van bewustzijnsverlies of PTA wordt daarom vaak gebruikt bij de triage van traumapatiënten op de Spoedeisende Hulp. Patiënten met bewustzijnsverlies of PTA worden doorverwezen naar de neuroloog, terwijl patiënten zonder bewustzijnsverlies of PTA door de poortarts gezien worden en dus over het algemeen zonder aanvullende diagnostiek naar huis ontslagen zullen worden. Hoewel dit voor het merendeel van de patiënten waarschijnlijk gerechtvaardigd is, is er een aparte groep van patiënten zonder bewustzijnsverlies of PTA bij wie het risico van neurocraniale complicaties zeker reëel is, namelijk wanneer dezen wel een (of meerdere) risicofactor(en) hebben.

Van de patiënten in onze studiepopulatie met een maximaal bewustzijn (EMV = 15; n = 2462) had 69% bewustzijnsverlies of PTA (18). Neurocraniale traumatische afwijkingen op de CT scan waren aanwezig bij 7,5% van de patiënten, vaker bij aandan bij afwezigheid van bewustzijnsverlies of PTA (8,7% respectievelijk 4,9%). Neurochirurgische interventie was echter net zo vaak verricht bij patiënten met als bij patiënten zonder bewustzijnsverlies of PTA (0,4%).

De *odds ratios* van de bekende risicofactoren voor neurocraniale complicaties na LTSH verschilden niet tussen de patiënten met en de patiënten zonder bewustzijnsverlies of PTA. Dit impliceert dat bewustzijnsverlies en PTA als onafhankelijke risicofactoren beschouwd kunnen en dienen te worden. Bewustzijnsverlies en PTA hadden *odds ratios* voor een neurocraniale complicatie van respectievelijk 1,9 en 1,7.

De CHIP-predictieregel

Zowel in de NOC als de CCHR zijn patiënten zonder bewustzijnsverlies of PTA niet meegenomen. Beide predictieregels zijn daarom slechts van toepassing op een beperkte patiëntenpopulatie. Voor implementatie in de klinische praktijk zal dus aanpassing noodzakelijk zijn, die bij voorkeur plaatsvindt op wetenschappelijke

basis.

Hiertoe ontwikkelden we de CHIP-predictieregel, die gebaseerd is op de risicofactoren zoals deze al in de NOC en CCHR geïdentificeerd waren, maar die ook van toepassing is op patiënten zonder bewustzijnsverlies of PTA (19). Er zijn twee versies van de CHIP-predictieregel: het gedetailleerde model, waarmee een risicoscore berekend kan worden (http://www.marionsmits.net/chip-prediction-rule/), en een versimpelde versie, bestaande uit tien *major* en acht *minor* criteria (Tabel 1).

Tabel 1. De vereenvoudigde versie van de CHIP-predictieregel (19)

Een CT scan is geïndiceerd bij aanwezigheid van 1 major criterium
Voetganger of fietser versus voertuig
Uit voertuig geslingerd
Braken
Posttraumatische amnesie van ≥4 uur
Klinische tekenen van schedelfractuur
EMV score van <15
≥2 punten achteruitgang van EMV score 1 uur na presentatie
Gebruik van anticoagulantia
Posttraumatisch insult
Leeftijd ≥60 jaar
of bij aanwezigheid van minimaal 2 minor criteria
Val van iedere hoogte
Persisterende anterograde amnesie
Posttraumatische amnesie 2–4 uur
Uitwendig letsel van de schedel (zonder tekenen van fractuur)
Neurologische uitval
Bewustzijnsverlies
1 punt achteruitgang van EMV score 1 uur na presentatie
Leeftijd 40–60 jaar

Bij de aanwezigheid van minimaal één *major* criterium of twee *minor* criteria is een CT scan geïndiceerd. De CHIP-predictieregel heeft net als de NOC en CCHR een sensitiviteit van 100% (95% CI, 82%–100%) voor het identificeren van patiënten die neurochirurgische interventie ondergingen. Volgens de CHIP-predictieregel zou naar schatting bij 70%–77% van de patiënten een CT scan geïndiceerd zijn (Figuur 1). Overigens is de CHIP-predictieregel tot op heden alleen intern gevalideerd.

Conclusie

Na LTSH is er een kleine doch klinisch zeer relevante kans op neurocraniale complicaties (10%), die zelden neurochirurgische interventie behoeven (0,5%). Juist voor deze laatste patiënten is snelle en betrouwbare diagnose middels een CT scan geïndiceerd. Predictieregels kunnen gebruikt worden als hulpmiddel bij de selectie van LTSH-patiënten voor een CT scan op basis van de aan- of afwezigheid van risicofactoren, die hun implementatie in de kliniek vinden in de vorm van klinische richtlijnen. De huidige Nederlandse richtlijnen hebben een onacceptabel lage sensitiviteit voor de identificatie van patiënten die neurochirurgische interventie behoeven, en revisie is inmiddels in gang. Wat de identificatie van patiënten betreft met een neurocraniale traumatische bevinding op de CT scan, vertonen alle gepubliceerde predictieregels en klinische richtlijnen een vergelijkbare balans tussen sensitiviteit en specificiteit. De implicatie hiervan is dat voor het bereiken van een hoge sensitiviteit er een groot aantal patiënten gescand zal moeten worden, terwijl een terughoudend scanbeleid betekent dat niet alle patiënten met een neurocraniale traumatische complicatie geïdentificeerd zullen worden en zonder beeldvormende diagnostiek naar huis ontslagen worden.

De vraag welke richtlijn de voorkeur heeft, is dus zowel afhankelijk van de bereidheid LTSH-patiënten te scannen als van de gewenste sensitiviteit voor het identificeren van neurocraniale traumatische complicaties na LTSH, die

niet per definitie 100% hoeft te zijn. Deze beslissing zal afhangen van de gezondheidseffecten, maar voornamelijk van kosten-effectiviteit (doelmatigheid) en haalbaarheid in de praktijk.

KOSTEN-EFFECTIVITEIT VAN SELECTIE VAN LTSH PATIËNTEN VOOR CT

De selectie van patiënten voor een CT scan brengt het inherente risico met zich mee dat patiënten met een neurocraniale complicatie, en met name diegenen met een indicatie tot neurochirurgisch ingrijpen, niet geïdentificeerd worden. In een kosten-effectiviteitsanalyse vergeleken we selectieve scanstrategieën waarin deze onzekerheid van selectie mee in overweging werd genomen, met het scannen van alle patiënten met LTSH.

Kosten-effectiviteitsanalyse

Vijf strategieën werden geëvalueerd: het scannen van alle LTSH patiënten; het selectief scannen van LTSH patiënten volgens de NOC, de CCHR of de CHIP-predictieregel; en niet scannen (referentie strategie). Parameters voor het model waren voornamelijk afkomstig uit de CHIP studie. We gebruikten een beslisboom voor het modelleren van korte termijns- en een Markov model voor lange termijnskosten en -effecten. Uitkomstmaten waren kosten voor het eerste jaar en voor de gehele levensduur, kwaliteits aangepaste levensjaren (QALY's), en de incrementele kosten-effectiviteitsratio (ICER). De robuustheid van het model werd getest met (probabilistische) sensitiviteitsanalyses, waarbij de parameters in het model binnen hun 95% betrouwbaarheidsintervallen (95% CI) gevarieerd werden. Daarnaast werd een *value of information* (VOI) analyse verricht.

We vonden dat selectief scannen volgens de CCHR of de CHIP-predictieregel tot forse kostenbesparingen zou kunnen leiden, die in Nederland jaarlijks €5 miljoen respectievelijk €3 miljoen zouden bedragen. De sensitiviteit van de predictieregels voor het identificeren van patiënten met een neurochirurgische indicatie had een belangrijke invloed op de uitkomst van het model: bij een sensitiviteit van minder dan 97% was het scannen van alle LTSH patiënten kosten-effectief (ICER < *willingness-to-pay threshold* van €50 000). Uit (probabilistische) sensitiviteitsanalyses bleek dat de CHIP-predictieregel de grootste kans had om kosten-effectief te zijn. Uit de VOI analyse bleek dat de waarde van perfecte informatie in Nederland €308 miljoen zou bedragen, die voornamelijk toe te schrijven was aan de onzekerheid over de functionele uitkomst op de lange termijn.

Conclusie

Selectief scannen op basis van de CCHR was de meest kosten-effectieve strategie en kan leiden tot een jaarlijkse kostenbesparing in Nederland van €5 miljoen. Deze bevinding is echter alleen valide onder de aanname dat deze predictieregel zeer sensitief is voor de identificatie van patiënten die neurochirurgische interventie behoeven. Bij een lagere sensitiviteit voor de identificatie van deze patiënten zijn de kostenbesparingen lager, en bij een sensitiviteit van minder dan 91%–99% is het zelfs kosten-effectief om alle patiënten te scannen in plaats van patiënten te selecteren voor een CT scan. Daarnaast bleek uit de VOI analyse dat ten gevolge van de onzekerheid ten aanzien van de functionele uitkomst van LTSH patiënten op lange termijn, nog geen zekere uitspraak gedaan kan worden over de vraag of selectief scannen kosten-effectiever is dan het scannen van alle LTSH patiënten, en dat meer onderzoek geïndiceerd is.

Met de CCHR kan het best een onderscheid gemaakt worden tussen

patiënten met een laesie die neurochirurgische interventie behoeft, en diegenen met een niet-neurochirurgische laesie (10, 20, 21). Aangezien de identificatie van een niet-neurochirurgische laesie gepaard gaat met hogere kosten zonder winst in effectiviteit, terwijl de tijdige identificatie van patiënten met een neurochirurgische laesie hoge kosten en verlies van (kwaliteit van) leven voorkomt (22–26), is het niet verwonderlijk dat met de CCHR de grootste kostenbesparing te verwachten valt (27).

Het selecteren van patiënten voor een CT scan brengt echter het risico met zich mee dat patiënten niet correct gediagnosticeerd en geïdentificeerd worden. Uit onze sensitiviteitsanalyses bleek dat een strategie van selectief scannen slechts een kans van 51%–64% had om kosten-effectief te zijn in vergelijking met het scannen van alle patiënten. Daarnaast bleek dat bij het verlagen van de sensitiviteit voor het identificeren van patiënten met een neurochirurgische indicatie tot onder de 91%–99% het scannen van alle patiënten kosten-effectief werd. Met andere woorden, hoewel complicaties na LTSH die neurochirurgisch behandeld moeten worden zeer zeldzaam zijn, is het scannen van alle LTSH patiënten kosten-effectiever dan het missen van zelfs een klein percentage van deze neurochirurgische patiënten. Dit is het gevolg van de slechtere uitkomst na verlate diagnose, met hogere kosten en verlies van (kwaliteit van) leven. Gezien de lage sensitiviteit van de CCHR voor het identificeren van patiënten met een intracraniale traumatische laesie, waarbij de ondergrens van het 95% CI ruim onder de 90% ligt, is er een reële kans dat de CCHR minder kosten-effectief is dan het scannen van alle patiënten (10, 20, 21). Met de CHIP-predictieregel daarentegen is deze sensitiviteit voldoende hoog en valt tevens een aanzienlijke kostenbesparing te verwachten. De kans dat de CHIP-predictieregel kosten-effectief is, is dus groter, zoals werd bevestigd in de probabilistische sensitiviteitsanalyse. Daarnaast is de CHIP-predictieregel, zoals reeds gezegd, van toepassing op een bredere patiëntenpopulatie.

FUNCTIONELE UITKOMST NA GECOMPLICEERD LTSH

Zoals de terminologie suggereert, herstellen de meeste patiënten met LTSH volledig. Er zijn echter aanwijzingen dat patiënten met een neurocraniale complicatie na LTSH een slechtere functionele uitkomst hebben dan patiënten zonder afwijkingen op de CT scan (28, 29). De functionele uitkomst van deze patiënten met zogenaamd gecompliceerd LTSH was echter nog niet onderzocht.

We voerden derhalve een vervolgstudie uit van alle 312 patiënten uit de CHIP studie die een neurocraniale traumatische bevinding op de CT scan hadden. De gegevens die we met deze studie verkregen, werden gebruikt in de hierboven beschreven kosten-effectiviteitsanalyse. We bepaalden de functionele uitkomst volgens de *Glasgow Outcome Scale* als primaire uitkomstmaat. Andere uitkomstmaten waren de *modified Rankin Scale* (mRS), de *Barthel Index* (BI), en het aantal en de ernst van de postcommotionele klachten. Van de patiënten die gemiddeld vijftien maanden na het trauma bereikt konden worden (76%), was een kleine meerderheid volledig hersteld (63%). Een derde was matig gehandicapt (30%) en een klein percentage was ernstig gehandicapt (4%) of overleden (3%). De meerderheid van de patiënten had ook een gunstige uitkomst volgens de mRS en BI, maar wel bleek nog 82% van de patiënten last te hebben van postcommotionele klachten.

Verder evalueerden we de associatie tussen CT bevindingen en uitkomst met behulp van univariabele en multivariabele regressie-analyses.

Parenchymschade op de CT scan was de enige onafhankelijke predictor voor een ongunstige uitkomst (*odds ratio* = 1,9). Opvallend was dat geen van de CT bevindingen geassocieerd was met een gunstige uitkomst, hetgeen aangeeft dat een gunstige uitkomst zelfs bij de zogenaamd klinisch niet-relevante afwijkingen niet zeker is.

Conclusie

De meerderheid van de patiënten met gecompliceerd LTSH herstelt volledig, maar postcommotionele klachten kunnen nog lange tijd tot na het trauma voortduren.
Een belangrijke beperking van deze vervolgstudie was dat een substantieel deel van de patiëntenpopulatie niet bereikt kon worden ter beoordeling van de functionele uitkomst, hetgeen deels aan de onzekerheid hieromtrent in de kosten-effectiviteitsanalyse ten grondslag ligt. Dit is inherent aan de bestudeerde patiëntenpopulatie en het feit dat patiënten pas geruime tijd (2–4 jaar) na het trauma voor deelname in deze studie benaderd werden.

POSTCOMMOTIONEEL SYNDROOM

Zelfs wanneer er geen afwijkingen zichtbaar zijn op de CT of zelfs MRI scan, komen postcommotionele klachten zoals vermoeidheid, hoofdpijn en geheugen- en concentratiestoornissen na LTSH veelvuldig voor (30–37). Het neuropathologisch substraat van dit zogenaamde postcommotionele syndroom is tot op heden niet bekend, hoewel gepostuleerd wordt dat microstructurele hersenschade, niet zichtbaar met conventionele beeldvorming, aan het syndroom ten grondslag ligt (38–42).

Twee geavanceerde beeldvormende MRI technieken bieden perspectief voor het verkrijgen van inzicht in het neuropathologisch substraat van het postcommotionele syndroom en het onderbouwen van de gepostuleerde hypothese. Met functionele MRI (fMRI) kan hersenactiviteit in beeld gebracht worden. Eventuele veranderingen in hersenactiviteit zouden de hypothese kunnen ondersteunen dat hersenplasticiteit compenseert voor de functionele beperking als gevolg van de microstructurele hersenschade. Drie dimensionele (3D), hoog-resolutie gradiënt-echo (HRGRE) T2* gewogen sequenties en *Diffusion Tensor Imaging* (DTI) zijn zeer gevoelige technieken voor het aantonen van microbloedingen respectievelijk veranderingen in de integriteit van de witte stof (uitgedrukt in de mate van fractionele anisotropie [FA]), en waarmee microstructurele schade dus rechtstreeks gevisualiseerd zou kunnen worden.

Negenentwintig LTSH patiënten en twaalf gezonde vrijwilligers (gemiddelde leeftijd, 29 jaar; man, 63%) werden gescand op 3.0T met fMRI, DTI en 3D HRGRE T2* gewogen sequenties. De ernst van postcommotionele klachten werd gemeten met behulp van de *Rivermead Postconcussion Symptoms Questionnaire* (RPSQ) en uitgedrukt in de RPSQ score (mediaan, 10; range, 0–46).

Hersenactiviteit bij het postcommotionele syndroom

Hersenactiviteit gerelateerd aan werkgeheugen en selectieve aandacht, gemeten met *Blood Oxygenation Level Dependent* (BOLD) fMRI werd gecorreleerd met de ernst van postcommotionele klachten. De gebruikte taken waren de *n-back* taak voor het verbale werkgeheugen en de *Counting Stroop* taak voor selectieve aandacht.

Er was geen significante associatie tussen de ernst van postcommotionele klachten en activatie gerelateerd aan selectieve aandacht. Bij patiënten met ernstige postcommotionele klachten werd reeds bij minimale belasting van het werkgeheugen activatie van het werkgeheugen netwerk gezien. Bij toenemende belasting van het werkgeheugen nam de hersenactiviteit in het

werkgeheugen netwerk sterker toe wanneer de postcommotionele klachten ernstiger waren. Tevens werd er bij hoge, alsmede differentiële werkgeheugenbelasting activatie gezien in hersengebieden gelegen buiten het werkgeheugen netwerk, namelijk in de gyrus parahippocampalis en de gyrus cinguli posterior.

Microstructurele hersenschade bij het postcommotionele syndroom

Voor de beoordeling van de relatie van microstructurele hersenschade met het postcommotionele syndroom werden patiënten met traumatische afwijkingen van de hersenen, zichtbaar op de T1 gewogen en *Fluid Attenuated Inversion Recovery* (FLAIR) beelden, geëxcludeerd. Data van negentien LTSH patiënten en twaalf gezonde vrijwilligers (gemiddelde leeftijd, 26 jaar; man, 58%) werden geanalyseerd en toonden een significante afname alsmede toename van de gemiddelde diffusiviteit in diverse witte stofbanen temporaal en frontaal in de subcorticale witte stof, in relatie met de ernst van postcommotionele klachten. Daarnaast werd, gecorreleerd met de ernst van postcommotionele klachten, een significante afname van fractionele anisotropie gezien in diverse witte stofbanen, inclusief het splenium van het corpus callosum, alsmede de temporale, occipitale en pariëtale witte stof. Microbloedingen werden slechts bij één patiënt waargenomen, waardoor geen uitspraak kon worden gedaan over enige associatie met de mate van postcommotionele klachten.

Conclusie

Onze bevindingen ondersteunen de hypothese dat het postcommotionele syndroom wordt veroorzaakt door microstructurele hersenschade met een functionele beperking van het verbale werkgeheugen tot gevolg, die door hersenplasticiteit wordt gecompenseerd.

CONCLUSIE

Over het beleid bij LTSH patiënten zijn de meningen verdeeld. Er dient een balans te worden gevonden tussen het gebruik van de diagnostische middelen en het risico van het misdiagnosticeren van patiënten met een zeldzame, maar levensbedreigende complicatie. Ondanks dit lage risico is door de hoge incidentie van het LTSH de mortaliteit ten gevolge van LTSH hoger dan die van ernstiger traumatisch schedel-/hersenletsel (43). In de CHIP studie was de mortaliteit inderdaad laag, maar hadden patiënten met een gecompliceerd LTSH, ondanks merendeels volledig herstel, een hoog risico op het persisteren van postcommotionele klachten tot vele jaren na het trauma.

Het postcommotionele syndroom is een controversiële diagnose ten gevolge van de vele bijkomende factoren, de hoge prevalentie van de klachten in de algemene bevolking, en de veelvuldige afwezigheid van objectiveerbare afwijkingen bij beeldvormend of neuropsychologisch onderzoek. Onze MRI studie ondersteunt de hypothese dat het postcommotionele syndroom het gevolg is van microstructurele hersenschade, blijkens verlaging van fractionele anisotropie in de witte stof, die een functionele beperking van het werkgeheugen tot gevolg heeft, zich uitend in met fMRI meetbare compensatoire hersenactiviteit. In een longitudinale studie zal deze hypothese verder worden geëxploreerd door te evalueren of hersenactiviteit en/of FA waarden normaliseren wanneer de symptomen afnemen. Een beter begrip van het postcommotionele syndroom biedt niet alleen een objectieve ondersteuning van dit ziektebeeld, maar kan in de toekomst ook zijn toepassing vinden in het geven van richting aan therapeutische en diagnostische strategieën (44, 45). Het is

echter de vraag of deze geavanceerde MRI technieken hun toepassing in de klinische praktijk zullen vinden. Dit zal onder meer afhankelijk zijn van bevindingen en toepassing op het niveau van de individuele patiënt.

De CT scan, daarentegen, heeft een belangrijke plaats in het beleid van LTSH patiënten in het acute stadium. CT scanners zijn wijdverbreid beschikbaar en bieden snelle en betrouwbare diagnose in een tijd waarin medicolegale overwegingen steeds meer gewicht krijgen. Veel clinici zullen een ruime indicatiestelling voor een CT scan daarom voorstaan. Het selecteren van patiënten voor een CT scan is kostenbesparend en potentieel kosten-effectief. Van de drie geëvalueerde predictieregels valt de grootste kostenbesparing te verwachten met de CCHR, die echter mogelijk een te lage sensitiviteit heeft voor het identificeren van neurochirurgische patiënten om kosten-effectiever te zijn dan het scannen van alle patiënten. De CHIP-predictieregel daarentegen heeft een hogere sensitiviteit, is breder toepasbaar, en kan ook leiden tot aanzienlijke kostenbesparing. Er is echter meer onderzoek nodig voordat een zekere uitspraak gedaan kan worden over de vraag of het selecteren van patiënten voor een CT scan daadwerkelijk kosten-effectiever is dan het scannen van alle patiënten. Tot die tijd is het ook verantwoord alle LTSH patiënten te scannen.

Toekomstig onderzoek zou zich moeten richten op de functionele uitkomst van patiënten na LTSH in een grote, prospectieve cohortstudie. Naar analogie van dit proefschrift zou dit onderzoek idealiter vanuit diverse perspectieven plaatsvinden. Meer zekerheid dient te worden verkregen over de functionele uitkomst op lange termijn na LTSH op objectieve gronden van bijvoorbeeld de *Glasgow Outcome Scale*, maar daarnaast ook voor wat betreft de subjectieve kwaliteit van leven, de neurocognitieve gevolgen, en het neuropathologisch substraat van de postcommotionele klachten met behulp van geavanceerde beeldvormende technieken.

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CHAPTER 12

Acknowledgements
Publications
Curriculum Vitæ

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ARTICLES

Smits M, Dippel DWJ, De Haan GG, Nederkoorn PJ, Kool DR, Vos PE, Dekker HM, Twijnstra A, Hofman PAM, Tanghe HLJ, Hunink MGM. External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. *JAMA, 2005;294:1519-1525.*

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Conference proceedings

(Co-)author of around 50 abstracts presented at various international conferences, listed in full at http://www.marionsmits.net/curriculum-vitae/

MARION SMITS was born on 30 April 1972 in Lugarawa, Tanzania. In 1990, she graduated from Jeanne d'Arc College, Maastricht and started her medical degree at Maastricht University. Marion went to McMaster University, Hamilton, Canada, in 1993 to follow electives in Child Psychiatry and Cardiology. After completing her preclinical years, she studied History and Philosophy of science at the faculty of Arts and Sciences at Maastricht University, between 1994 and 1995, which led to her first publication - 'Tristan and Isold: a Jungian interpretation'.

Marion resumed her medical studies in 1995 and spent the final months of her degree working on her first research project in the departments of Radiology and Neurology, studying 3D CT of the skull in plagiocephalic children. She published the study and was awarded first prize for presenting it at the 10th European Conference for Students and Young Doctors in Berlin, Germany.

Marion graduated with distinction in February 1998 and then moved to the United Kingdom where she worked in Walsall as a junior house officer in Surgery and in General Medicine, and in Basingstoke as a senior house officer in Geriatrics. She returned to the Netherlands in 1999, to work as a junior doctor in Neurology at the St. Lucas/Andreas hospital in Amsterdam.

Marion started her specialisation in Radiology in April 2000 at Erasmus MC in Rotterdam, and from 2002 combined this with the CT in Head Injury Patients (CHIP) study, which formed the major part of her PhD research. This study was inspired by her observation of increased CT scanning after the 2001 introduction of the Dutch guidelines for minor head injury management.

From 2002 to 2004, Marion was president of the Junior Doctor's Association at Erasmus MC. As president, she organised the Junior Doctor's Research Days 2002 and 2003 at Erasmus University.

In 2003, Marion was awarded a nine-month Marie Curie research fellowship at the Catholic University Leuven, Belgium, where she worked on functional MRI research of the gustatory cortex at 3 T, as well as of the auditory cortex in tinnitus patients.

Upon her return to Rotterdam in 2004, Marion became responsible for all clinical fMRI and DTI at Erasmus MC, in particular the presurgical assessment of brain tumour patients. She was also involved in the fMRI and DTI research in collaboration with the departments of Neuroscience, Neurology, Psychology, Rehabilitation Medicine and Psychiatry.

At the 12th Dutch Radiology Conference in 2007, the Neuroradiology section of the Radiological Society of the Netherlands awarded Marion the Lourens Penning Prize for her work on the use of CT in minor head injury.

Marion qualified as a Radiologist in April 2008, and continues to work in the department of Radiology at Erasmus MC, expecting to finish her subspecialisation in Neuroradiology in April 2009.

Marion lives in Rotterdam with her partner.

www.marionsmits.net

APPENDIX

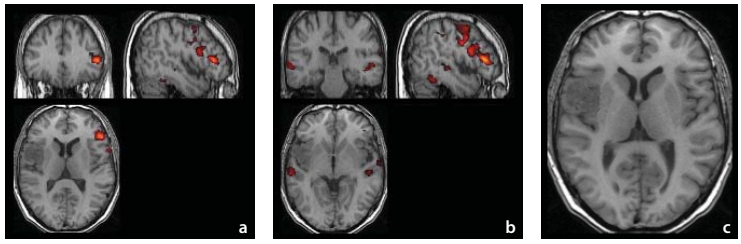
Further research

Functional MR imaging of language processing: An overview of easy-to-implement paradigms for patient care and clinical research

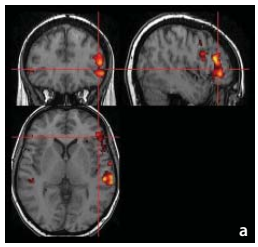
Marion Smits[1], Evy Visch-Brink[2], Caroline K Schraa-Tam[1], Peter J Koudstaal[2], Aad van der Lugt[1] • Radiographics, 2006;26:S145-158.

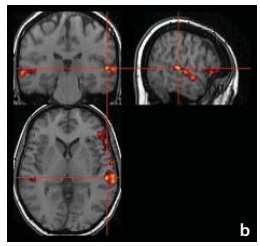
1. Radiology, Erasmus MC
2. Neurology, Erasmus MC

Functional magnetic resonance (MR) imaging is one of the most commonly used functional neuroimaging techniques for studying the cerebral representation of language processing and is increasingly being used for both patient care and clinical research. In patient care, functional MR imaging is primarily used in the preoperative evaluation of (a) the relationship of a lesion to critical language areas and (b) hemispheric dominance. In clinical research, this modality is used to study language disorders due to neurologic disease and is generally aimed at language function recovery. A variety of language paradigms (verbal fluency, passive listening, comprehension) have been developed for the study of language processing and its separate components. All of the tasks are easy to implement, analyze, and perform. Silent gap acquisition is preferable for the imaging of specific language processing components because auditory stimuli are not degraded by imager noise. On the other hand, continuous acquisition allows more data to be acquired in less time, thereby increasing statistical power and decreasing the effects of motion artifacts. Although functional MR imaging cannot yet replace intraoperative electrocortical stimulation in patients undergoing neurosurgery, it may be useful for guiding surgical planning and mapping, thereby reducing the extent and duration of craniotomy.

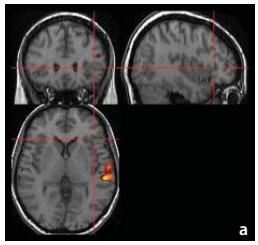


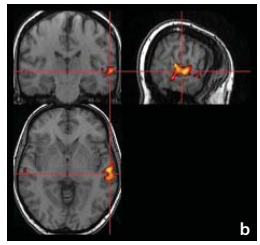
Areas of activation for the **verbal fluency–verb generation paradigm**. The subject was a left-handed 42-year-old man with a right hemispheric temporal lobe lesion who presented with headache and speech disorders. T1 weighted MR images show a lesion in the right temporal lobe (c), an area of superimposed activation in the left inferior frontal gyrus (classic Broca area) (a), and areas of equal activation bilaterally in the medial temporal gyri (classic Wernicke area) (b). Conclusions: left hemispheric dominance for language; no relationship between the areas of activation and the lesion.



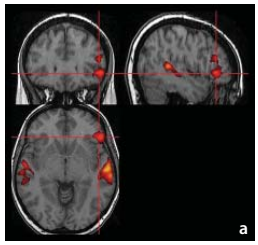


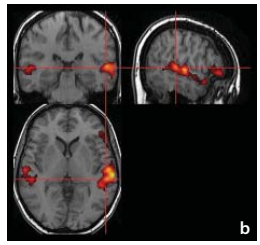
Areas of activation for the **phonologic paradigm** as determined with a fixed-effects group analysis of six right-handed volunteers (T >5, cluster >10 voxels). High-resolution T1 weighted MR images show superimposed activation in the frontal (a) and posterior parietotemporal (b) language areas, predominantly in the left hemisphere.



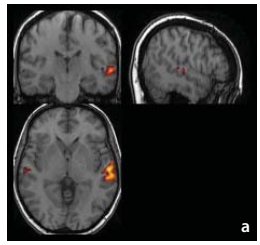


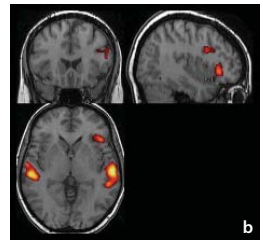
Areas of activation for the **semantic paradigm** as determined with a fixed-effects group analysis of six right-handed volunteers (T >5, cluster >10 voxels). High-resolution T1 weighted MR images show superimposed activation in the posterior parietotemporal language area in the left hemisphere (b). No activation is seen in the frontal language area (a).





Areas of activation for the **combined phonologic-semantic paradigm** as determined with a fixed-effects group analysis of six right-handed volunteers (T >5, cluster >10 voxels). High-resolution T1 weighted MR images show superimposed activation in the frontal (a) and posterior parietotemporal (b) language areas, predominantly in the left hemisphere.





Areas of activation for the semantic paradigm as determined with a fixed-effects group analysis of six right-handed volunteers (T >5, cluster >10 voxels). (a) **Silent gap acquisition**. On high-resolution T1 weighted MR images, superimposed activation is seen only in the posterior language areas, predominantly in the left hemisphere. (b) **Continuous acquisition**. High-resolution T1 weighted MR images show much more widespread (superimposed) activation, with additional activation in the frontal language areas. Although activation is still predominantly left hemispheric, a substantial amount is also seen in the right hemisphere. Presumably, since the words are more difficult to hear with continuous acquisition, the subject will need to concentrate more on the words themselves, not just on the meaning of the words (ie, additional phonologic processing areas of the brain are recruited).

Incorporating functional MR imaging into diffusion tensor tractography in the preoperative assessment of the corticospinal tract in patients with brain tumors

Marion Smits[1§], Meike W Vernooij[1,2§], Piotr A Wielopolski[1], Arnaud JPE Vincent[3], Gavin C Houston[4], Aad van der Lugt[1] • Am J Neuroradiol, 2007;28:1354-1361.

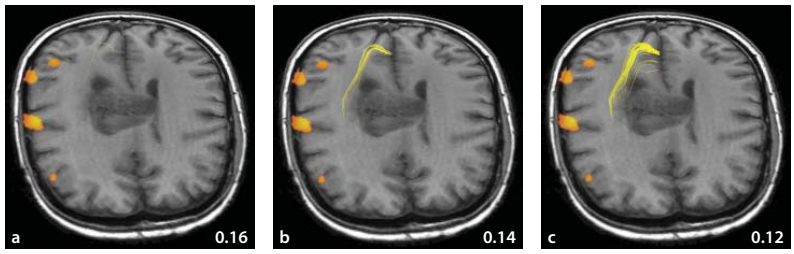
§ Joint principal author
1. Radiology, Erasmus MC
2. Epidemiology & Biostatistics, Erasmus MC
3. Neurosurgery, Erasmus MC
4. ASL Europe, GE Healthcare

Background and purpose Our goal was to improve the preoperative assessment of the corticospinal tract (CST) in patients with brain tumors. We investigated whether the integration of functional MR imaging (fMRI) data and diffusion tensor (DT) tractography can be used to evaluate the spatial relationship between the hand and foot fibers of the CST and tumor borders.

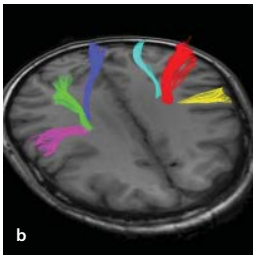
Materials and methods We imaged 10 subjects: 1 healthy volunteer and 9 patients. Imaging consisted of a 3D T1 weighted sequence, a gradient-echo echo-planar imaging (EPI) sequence for fMRI, and a diffusion-weighted EPI sequence for DT tractography. DT tractography was initiated from a seed region of interest in the white matter area subjacent to the maximal fMRI activity in the precentral cortex. The target region of interest was placed in the cerebral peduncle.

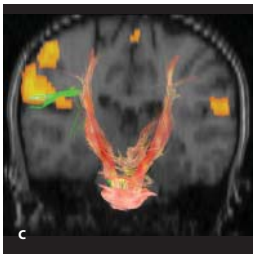
Results In the healthy volunteer, we successfully tracked hand, foot, and lip fibers bilaterally by using fMRI-based DT tractography. In all patients, we could track the hand fibers of the CST bilaterally. In 4 patients who also performed foot tapping, we could clearly distinguish hand and foot fibers. We were able to depict the displacement of hand and foot fibers by tumor and the course of fibers through areas of altered signal intensity.

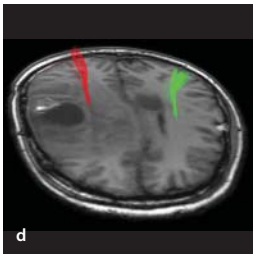
Conclusion Incorporating fMRI into DT tractography in the preoperative assessment of patients with brain tumors may provide additional information on the course of important white matter tracts and their relationship to the tumor. Only this approach allows a distinction between the CST components, while visualization of the CST is improved when fiber tracking is hampered by tumor (infiltration) or perifocal edema.

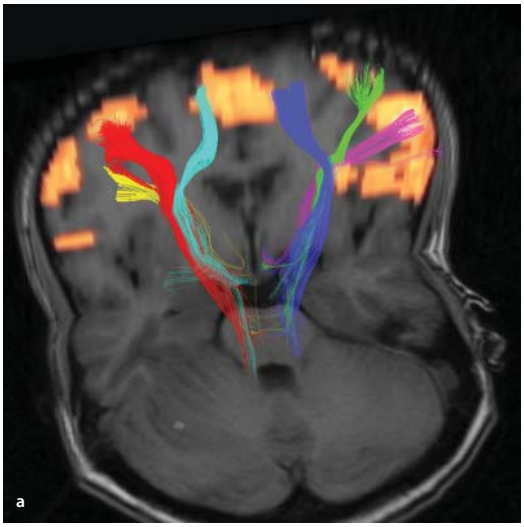


Axial T1 weighted MR images with foot fibers projected in color. Fibers pass through an area of altered signal intensity on T1 weighted images. **Varying the FA thresholds for fiber tracking** in this patient had a considerable influence on the fibers depicted (a-c, FA thresholds used are shown in each image).



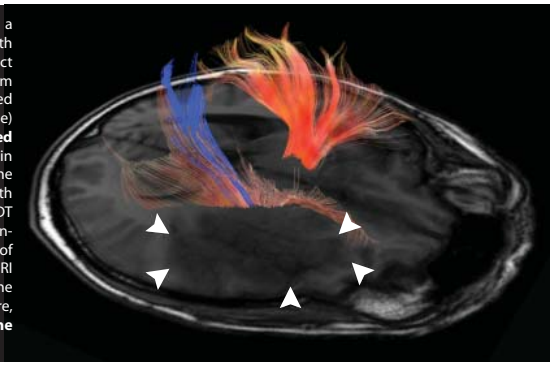






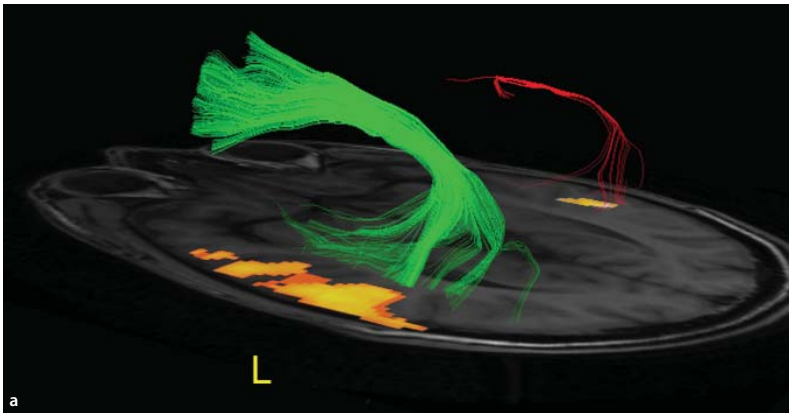
Orthogonal axial/coronal (a) and axial (b) projection of T1 weighted MR images with fiber tracts depicted in color in the healthy volunteer (violet and yellow, lip fibers; green and red, hand fibers; pale blue and dark blue, foot fibers). The **hand and foot fibers of the corticospinal and the lip fibers of the corticobulbar tract** can be clearly distinguished and visualized (a and b). The different fMRI activation areas used to choose the seed regions of interest are shown in color (a). The course of the **fibers through the corona radiata** follows the known somatotopic distribution (b). C, The results are shown from **conventional DT tractography** (in orange) as well as from **fMRI-based fiber tracking** with region-of-interest placement in the PMA of the lip of the right hemisphere (in green), projected on a coronal T1 weighted image of the healthy volunteer. fMRI activation (shown in yellow-orange) is visible in the PMA of the lip and supplementary motor area in both images. Clearly, the **lip fibers** are only visualized by using the fMRI-based fiber tracking approach and not with the conventional fiber tracking approach. D, axial T1 weighted MR image with fiber tracts projected in color (red and green for the right and left hemispheres, respectively). In this patient, hand **fibers ran through an area of altered signal intensity**.

Axial T1 weighted MR image of a patient with a brain tumor with fibers of the corticospinal tract projected in color. Results from conventional fiber tracking based on anatomic landmarks (in orange) show **dispersion and diminished visualization** of the CST fibers in the hemisphere affected by the lesion (arrowheads), compared with the unaffected hemisphere. DT tractography based on seed region-of-interest selection in the PMA of the hand as established with fMRI shows, in blue, the CST fibers of the hand in the affected hemisphere, allowing a **clear demarcation of the fibers of interest within the CST**.



Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: A combined fMRI and DTI study

Meike W Vernooij[1,2§], Marion Smits[1§], Piotr A Wielopolski[1], Gavin C Houston[3], Aad van der Lugt[1]
NeuroImage, 2007;28:1354-1361.



Previously reported leftward asymmetry in language-related gray and white matter areas of the brain has been proposed as a structural correlate of left-sided functional hemispheric language lateralization. However, structural asymmetry in non-left-sided functional language lateralization has as yet not been studied. Furthermore, the neuroanatomical basis of the reported volumetric white matter asymmetry is not fully understood. In 20 healthy volunteers, including 13 left-handers, we performed functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). We studied the relative fiber density (RFD) of the arcuate fasciculus (AF), using DT-tractography, in relation to functional hemispheric language lateralization. Hemispheric language lateralization was right-sided in five left-handed individuals. We demonstrated an overall significant leftward asymmetry in RFD of the AF, irrespective of handedness or functional language lateralization. Furthermore, in right-handers, the degree of structural asymmetry was found to be correlated with the degree of functional lateralization. We conclude that structural asymmetry in the AF does not seem to reflect functional hemispheric language lateralization, as has been proposed previously. Our findings suggest that the previously reported white matter asymmetry may be explained by a structural asymmetry in the arcuate fasciculus. These findings have important implications for the understanding of the functional and structural lateralization of brain regions as well as for the clinical evaluation of language function.

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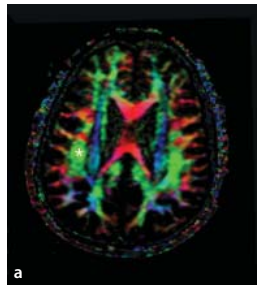
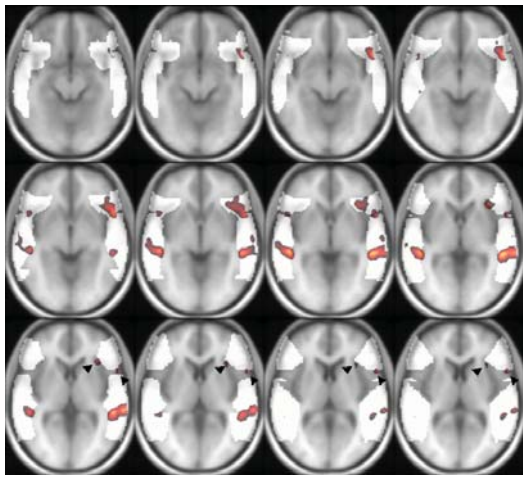
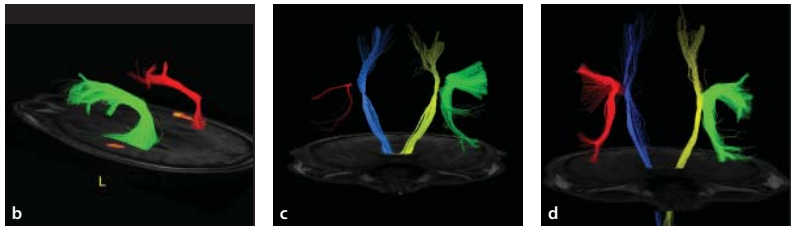
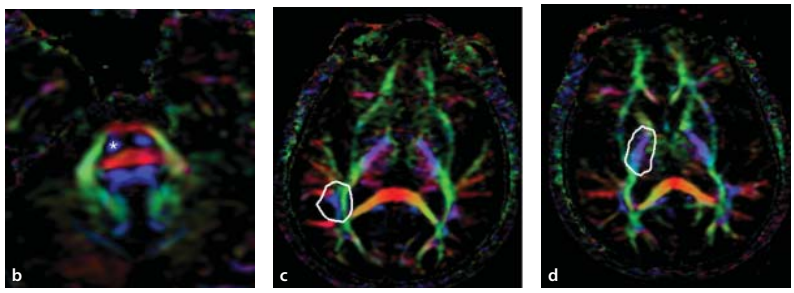




Functional activation map. Axial T1 weighted images of the brain with the anatomically defined ROI overlaid and shown in white. T-contrast activation map of all subjects combined (pooled data) shows **localization of the frontal and parietotemporal language areas** within the ROI. Two small activation clusters are located outside the ROI (black arrowheads). These activation clusters are located in the dorsolateral prefrontal cortex and are functionally related to non-language processes (working memory) that are commonly activated during a verb generation task.



Language-related **fMRI activation and DT-tractography** results for the **arcuate fasciculus and corticospinal tract** in a **right-handed** and a **left-handed** subject. T1 weighted images, axial views of a functionally left-lateralized, right-handed (a - facing page, c) and a functionally right-lateralized, left-handed (b, d) subject. fMRI activation in the left superior and middle temporal gyrus (red-orange overlay) is shown on the left side in the right-handed subject (a) and on the right side in the left-handed subject (b). The DT-tractography results for the arcuate fasciculus are shown in red (right) and green (left). Tractography results for the corticospinal tract are shown in blue (right) and yellow (left).



Positioning of seed and target ROIs for diffusion tensor tractography of the **arcuate fasciculus** (AF) and **corticospinal tract** (CST). Axial images (a–d) of directionally encoded tensor maps. Colors represent main direction of white matter tracts (red: left–right, blue: cranio-caudal, green: antero-posterior). White asterisks indicate the position of seed ROIs (in a for AF, in b for CST); white freeforms indicate the target ROIs (c: AF, d: CST).

Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus

Marion Smits[1,2], Silvia Kovacs[2], Dirk de Ridder[3], Ronald R Peeters[2], Paul van Hecke[2], Stefan Sunaert[2]
Neuroradiology, 2007;49:669-679.

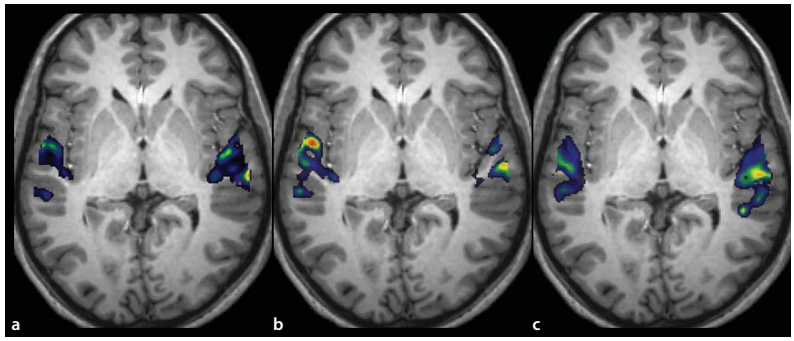
Introduction Tinnitus is hypothesized to be an auditory phantom phenomenon resulting from spontaneous neuronal activity somewhere along the auditory pathway. We performed fMRI of the entire auditory pathway, including the inferior colliculus (IC), the medial geniculate body (MGB) and the auditory cortex (AC), in 42 patients with tinnitus and 10 healthy volunteers to assess lateralization of fMRI activation.

Methods Subjects were scanned on a 3 T MRI scanner. A T2* weighted EPI silent gap sequence was used during the stimulation paradigm, which consisted of a blocked design of 12 epochs in which music was presented binaurally through headphones, which was switched on and off for periods of 50 s. Using SPM2 software, single subject and group statistical parametric maps were calculated. Lateralization of activation was assessed qualitatively and quantitatively.

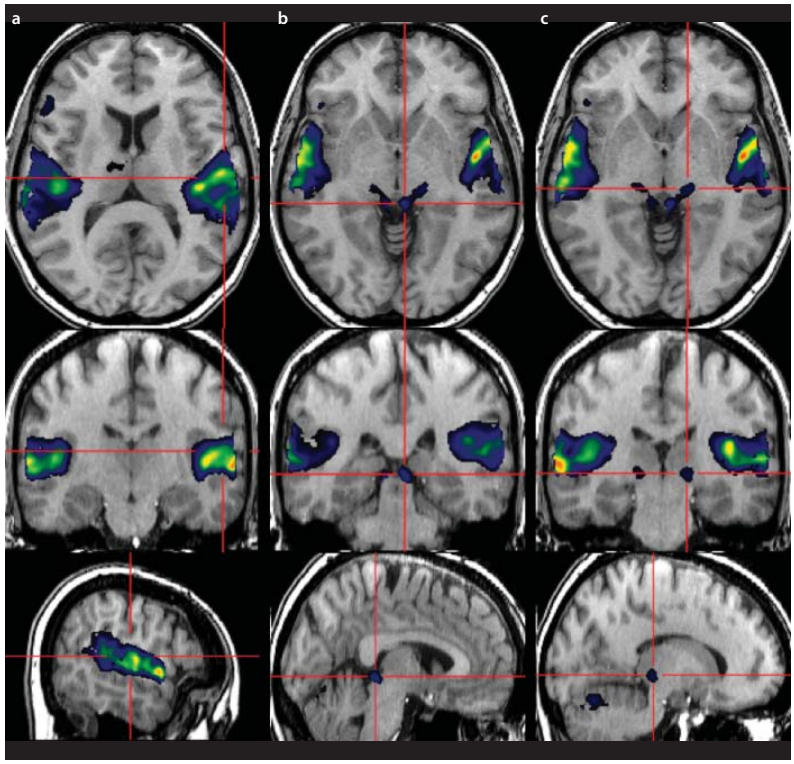
Results Tinnitus was lateralized in 35 patients (83%, 13 right-sided and 22 left-sided). Significant signal change ($P_{corrected}$ <0.05) was found bilaterally in the primary and secondary AC, the IC and the MGB. Signal change was symmetrical in patients with bilateral tinnitus. In patients with lateralized tinnitus, fMRI activation was lateralized towards the side of perceived tinnitus in the primary AC and IC in patients with right-sided tinnitus, and in the MGB in patients with left-sided tinnitus. In healthy volunteers, activation in the primary AC was left-lateralized.

Conclusion Our paradigm adequately visualized the auditory pathways in tinnitus patients. In lateralized tinnitus fMRI activation was also lateralized, supporting the hypothesis that tinnitus is an auditory phantom phenomenon.

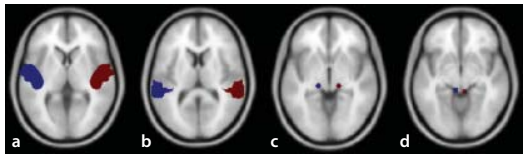
1. Radiology, Erasmus MC
2. Radiology, University Hospitals of the Catholic University Leuven
3. Neurosurgery, University of Antwerp



Areas of significant activation (one-way ANOVA; $P_{uncorrected}$ <0.001) in the primary and secondary auditory cortex in (a) patients with **left-sided tinnitus**, (b) patients with **right-sided tinnitus**, (c) patients with **bilateral tinnitus**.



Areas of significant activation (one-sample t-test; $P_{uncorrected}$ <0.001) in all subjects combined (n = 52) in the (a) **primary and secondary auditory cortex**, (b) **inferior colliculus**, and (c) **medial geniculate body**.



Regions of interest (ROIs) that were used for the quantitative analysis of activation in (a) the **primary auditory cortex**, (b) the **secondary auditory cortex**, (c) the **medial geniculate body**, and (d) the **inferior colliculus**. An activation ratio was calculated for each ROI by dividing the number of significantly activated voxels in the ROI on one side by the total number of significantly activated voxels in both ROIs of both sides. The activation ratio for the left primary auditory cortex, for instance, would be the number of activated voxels in the left primary auditory cortex (leftA1) divided by the total number of activated voxels in the left and in the right primary auditory cortex (leftA1+rightA1): leftA1/(leftA1+rightA1).

A 3 T event-related functional magnetic resonance imaging (fMRI) study of primary and secondary gustatory cortex localization using natural tastants

Marion Smits[1,2], Ronald R Peeters[2], Paul van Hecke[2], Stefan Sunaert[2]
Neuroradiology, 2007;49:61-71.

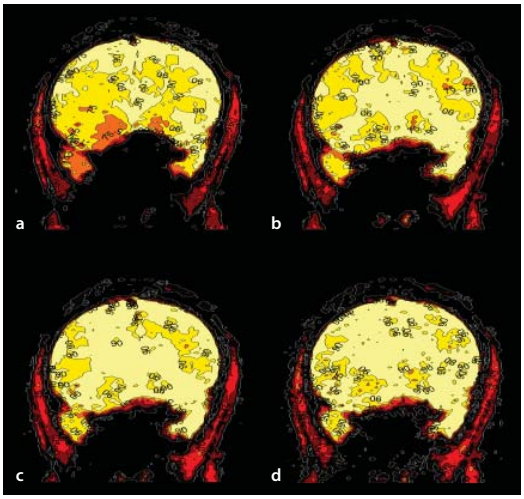
1. Radiology, Erasmus MC
2. Radiology, University Hospitals of the Catholic University Leuven

Introduction It is known that taste is centrally represented in the insula, frontal and parietal operculum, as well as in the orbitofrontal cortex (secondary gustatory cortex). In functional MRI (fMRI) experiments activation in the insula has been confirmed, but activation in the orbitofrontal cortex is only infrequently found, especially at higher field strengths (3 T). Due to large susceptibility artefacts, the orbitofrontal cortex is a difficult region to examine with fMRI. Our aim was to localize taste in the human cortex at 3 T, specifically in the orbitofrontal cortex as well as in the primary gustatory cortex.

Methods Event-related fMRI was performed at 3 T in seven healthy volunteers. Taste stimuli consisted of lemon juice and chocolate. To visualize activation in the orbitofrontal cortex a dedicated 3D SENSE EPI fMRI sequence was used, in addition to a 2D SENSE EPI fMRI sequence for imaging the entire brain. Data were analyzed using a perception-based model.

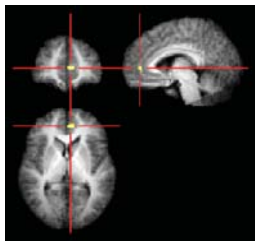
Results The dedicated 3D SENSE EPI sequence successfully reduced susceptibility artefacts in the orbitofrontal area. Significant taste-related activation was found in the orbitofrontal and insular cortices.

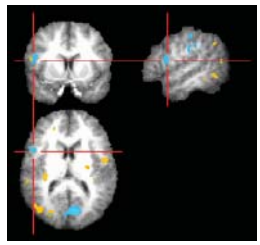
Conclusion fMRI of the orbitofrontal cortex is feasible at 3 T, using a dedicated sequence. Our results corroborate findings from previous studies.



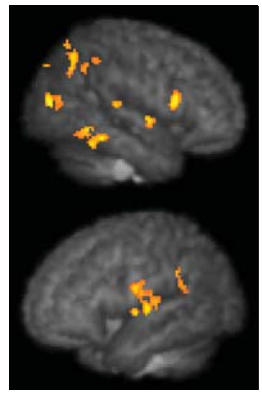
Color-coded maps of percentage relative signal intensity in a coronal section through the orbitofrontal cortex with the application of different SENSE reduction factors to a T2* weighted EPI sequence. Colors range from black (no signal) to yellow (maximum signal). When no SENSE (a: reduction factor 1) is applied, a large area of total signal dropout is seen, as well as a surrounding area of severely decreased signal intensity (red–orange). **With the application of SENSE** (b: reduction factor 2) the **area of total signal dropout decreases, and the surrounding signal intensity is improved** compared to when no SENSE is applied. With increasing SENSE reduction factors (c: reduction factor 4; d: reduction factor 6), the area of signal dropout decreases further, and the surrounding signal intensity improves.

Projection of the **taste** activation cluster found with the orbitofrontal sequence onto the mean T1 weighted image in the coronal, sagittal and transverse planes. Cross-bars indicate the activation cluster in the left **anterior cingulate/medial frontal gyrus**.

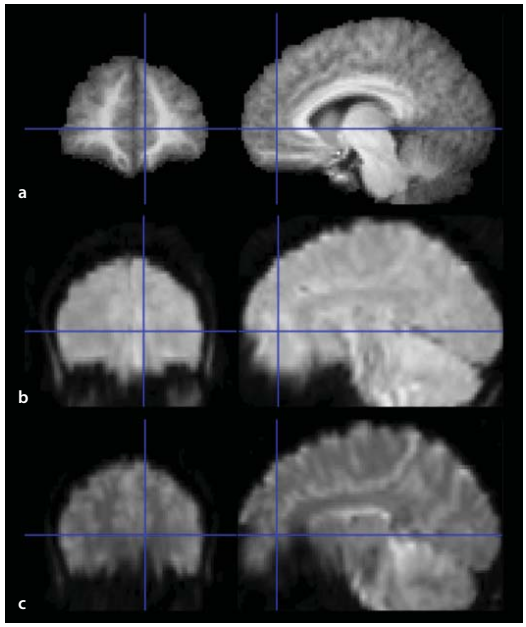




Projection of activation foci of **chocolate** versus control (blue) and **lemon juice** versus control (yellow) found with the entire brain sequence onto the mean T1 weighted image in the coronal, sagittal and transverse plane. Cross-bars indicate an activation cluster representing the cortical representation of chocolate in the **right frontal operculum**. Additional activation is seen in the occipital gyrus for both lemon juice and chocolate.



Projection of activation foci of **taste** versus control found with the entire brain sequence onto 3D reconstructions (top: right hemisphere; bottom: left hemisphere) of the mean high-resolution T1 weighted image. Activation foci are seen in the **insular cortex** bilaterally and in the **right frontal operculum**. Additional activation is seen in the right cuneus, right middle temporal gyrus and the parietal cortex.



Images obtained with (a) the **high-resolution T1 weighted** sequence, (b) the **orbitofrontal EPI** sequence and (c) the **entire brain EPI** sequence in the same coronal and sagittal plane through the orbitofrontal cortex. The cross-bars indicate the activation cluster that was found for taste versus control using the orbitofrontal sequence. With the entire brain sequence, a large area of signal dropout as well as image distortion is seen, as compared with the T1 weighted anatomical image. These effects are drastically decreased with the **dedicated orbitofrontal sequence, showing most of the orbitofrontal cortex and less image distortion**. Note that the orbitofrontal sequence in this figure is shown with total brain coverage, while for the experiment only the frontal brain area was covered.