SUBARACHNOID HAEMORRHAGE

a study on long-term consequences

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Subarachnoid Haemorrhage
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Een studie naar de langetermijngevolgen van een subarachnoïdale bloeding

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Chapter 1

General introduction

Wendy Boerboom

SUBARACHNOID HAEMORRHAGE

Subarachnoid haemorrhage (SAH) is a spontaneous bleeding in the subarachnoid space. This space is located just above the brain under the arachnoid membrane (Figure 1).[1]

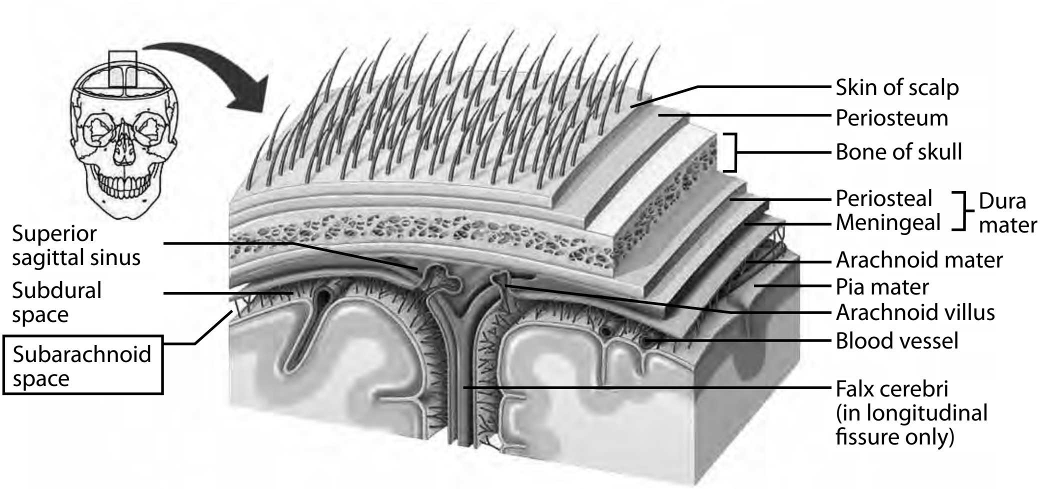

Figure 1. Location of the subarachnoid space.[2]

SAH accounts for 5% of all cases of stroke. Approximately 85% of the SAH cases is caused by a ruptured aneurysm in one of the cerebral vessels, this type of SAH is called aneurysmal subarachnoid haemorrhage (A-SAH). Ten percent of patients is diagnosed with a perimesencephalic subarachnoid haemorrhage (PM-SAH). This means that no aneurysm is found and the haemorrhage is restricted to the cisterns surrounding the brainstem and the suprasellar cistern.[3] PM-SAH's are often considered to have a benign clinical course.[4] The remaining 5% of patients have a non-aneurysmal, non-perimesencephalic SAH. They tend to have a clinical course similar to A-SAH.[4]

EPIDEMIOLOGY

The incidence of SAH in the Netherlands in 2012 was 7.6 for men and 11.2 for women per 100,000 persons per year. The 1580 patients with SAH, that were admitted to a hospital in 2012, had a mean age of 57 for men and 61 for women.[5,6] The mortality rate for patients with A-SAH is 35% in the first months after onset, and survivors have a decreased life expectancy and an increased risk for vascular diseases.[4,7-9] For patients with

PM-SAH the outlook is better. Mortality is less than 1% in this group, patients have a low risk for complications and their life expectancy is comparable to the general population.[4,9,10]

LONG-TERM IMPACT

One-third of the patients who survived A-SAH remain dependent.[11] Months to years post-onset, problems in cognitive and psychological functioning and subjective complaints, such as increased irritability may persist even when the degree of impairment in functional outcome is relatively mild.[7] Approximately 25% of SAH patients with favourable neurological outcome (Glasgow Outcome Scale of 1) exhibit substantial emotional maladjustment.[12,13] Most problems are found in the cognitive domains of memory, executive functioning and language. Concerning functional outcome, problems are found in Activities of Daily Living (ADL), return to work and quality of life.[7,8,14] Important problems associated with cognitive and functional outcomes after A-SAH are fatigue and mood disturbances.[7,15] Although PM-SAH is described as a benign form of SAH, there is growing evidence that these patients may also experience cognitive problems, depression and difficulties in returning to work.[4,16-18]

Gaining insight in the long-term impact of SAH is important. Patients are in the most productive stage of their life, in which work and family are important responsibilities.[7] At this stage of life the complications of SAH mentioned above, can have a major and long-lasting impact on the life of the patients and their families.[19] Insight in the long-term functional impairments and psychosocial consequences of SAH has potential consequences for post-acute rehabilitation programs and long-term psycho-education and counselling.

OUTLINE OF THIS THESIS

The main objective of this thesis is to evaluate the long-term consequences 4 years after subarachnoid haemorrhage, and to define which patients are in need of long-term professional support. **Chapter 2** describes the differences in cognitive and emotional outcomes between patients with PM-SAH and A-SAH in the first year after SAH. It elaborates on the question if patients with PM-SAH indeed have a more favourable outcome one year post-onset than patients with A-SAH. **Chapter 3** elaborates on the long-term consequences for patients with PM-SAH and investigates the relationships between fatigue, cognitive functioning, and mood. Furthermore, it is determined whether cognitive functioning differs between patients with and without fatigue. In **Chapter 4** a prospective study is described which assesses multiple outcomes for patients with A-SAH over a follow-up period of 4 years. The outcomes are evaluated based on all domains of the International Classification of Functioning, Disability and Health (ICF) model and related to normative values. This chapter creates an overview of long-term consequences of A-SAH to help rehabilitation services in adapting their programs to long-term needs. **Chapter 5** focuses on long-term community integration after SAH. It aims to identify [1] if cognitive functioning, depression and coping strategy are associated with community integration and [2] the level in which patients face unmet needs, questions that have not yet been addressed by health care providers. **Chapter 6** is about the impact SAH may have on caregivers. This chapter investigates the relationship of coping style with depression, burden, and life dissatisfaction in caregivers. **Chapter 7** is a general discussion based on the previous chapters. It describes the main findings of this thesis, discusses methodological considerations and proposes clinical implications and directions for future research.

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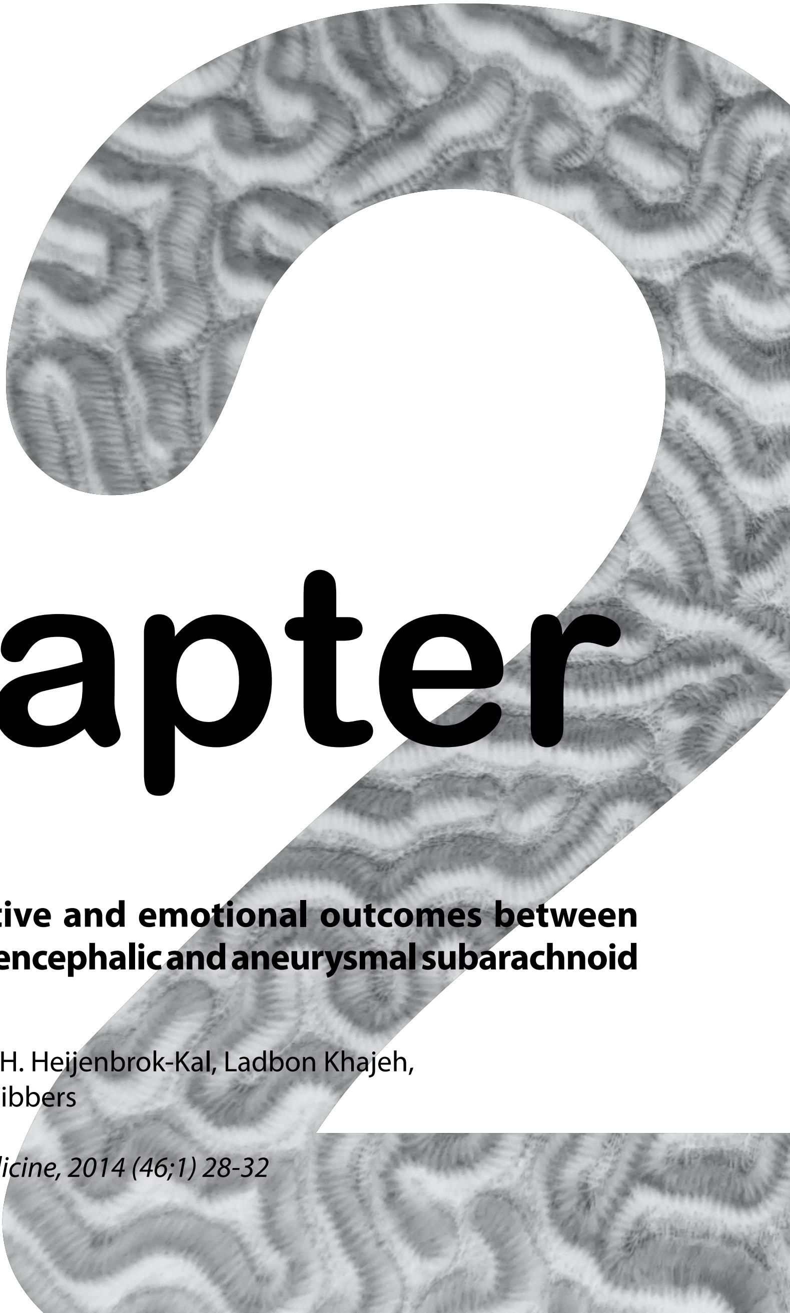

Chapter 2

Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage

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Fop van Kooten, Gerard M. Ribbers

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ABSTRACT

Objectives: To compare cognitive and emotional outcomes between patients with aneurysmal- and perimesencephalic subarachnoid haemorrhage and norm scores.
Design: First measurement in prospective cohort study.
Patients: Sixty-seven patients with subarachnoid haemorrhage, divided into perimesencephalic (*n*=8) and aneurysmal (*n*=59) subarachnoid haemorrhage groups.
Methods: Patients completed several questionnaires within the first year after haemorrhage. Depression was measured with the Center for Epidemiologic Studies Depression scale, fatigue with the Fatigue Severity Scale, and objective cognitive functioning with the Trail Making Test. Glasgow Coma Scale scores were collected at hospital admission.
Results: Perimesencephalic patients had lower depression (*p*=0.006) and lower fatigue scores (*p*=0.029) and were faster on the Trail Making Test A (*p*=0.002) than aneurysmal patients. No differences between the groups were found on Trail Making Test B (*p*=0.112) and presence of fatigue (*p*=0.105). Compared with norm scores, aneurysmal patients scored significantly worse on all outcomes, whereas perimesencephalic patients scored worse on Trail Making Test B (*p*<0.008), fatigue (*p*=0.073) and presence of fatigue (*p*=0.058).
Conclusions: Perimesencephalic patients may experience problems in complex cognitive functioning and fatigue. In this respect, they have similar sequelae as aneurysmal patients which may interfere with daily activities and social participation. These findings are of clinical relevance, as perimesencephalic patients often are discharged from hospital without long-term follow-up.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is a subtype of stroke that occurs at a relatively young age. The mean age of onset of SAH is 55 years, compared with 70 years in men and 75 years in women for stroke in general.[1,2] The overall case fatality rate is 50% in population-based studies. Only 5% of all strokes are SAH, with an incidence in the Netherlands of 5.8 per 100,000 persons per year for men and 9.9 for women.[3,4] In approximately 15% of all SAHs, no structural cause for the haemorrhage can be identified on radiographic imaging, termed angiogram-negative SAH, previously described as SAH of unknown origin or non-aneurysmal SAH.[5-8] This group can be subdivided into perimesencephalic and non-perimesencephalic angiogram-negative SAH.[9-13] This study focuses on 2 subtypes of SAH based on the cause of the haemorrhage: aneurysmal subarachnoid haemorrhage (A-SAH) and perimesencephalic subarachnoid haemorrhage (PM-SAH).[3] PM-SAH is defined as a haemorrhage restricted to the cisterns surrounding the brainstem and the suprasellar cistern combined with a negative angiogram.[3,7,14] The cause of PM-SAH is unknown and no surgical treatment is required.[3]

A-SAH covers 85% of all SAH and is characterized by the rupture of an intracranial aneurysm and the subsequent accumulation of blood in the subarachnoid space.[3,15] Neuroradiological intervention or neurosurgical clipping are the 2 options for treatment of the ruptured aneurysm.[3,15] PM-SAH accounts for 10% of all SAH cases and the remaining 5% has various other causes.[3,7] In 1985 van Gijn et al. first described PM-SAH as a benign form of SAH.[16]

Several studies have suggested that patients with A-SAH have a significantly less favourable prognosis than PM-SAH patients, based on the need for surgical or endovascular treatment, a risk of re-bleeding, shorter life expectancy and reduced quality of life.[1,5,15,17-22] Of the patients who survive, approximately one-third remain dependent (Rankin grade 3-5).[23] Even those who are independent may have cognitive impairments after recovery from A-SAH, in particular in the domains memory, executive functioning and language. Furthermore, half of the A-SAH patients experience mood disturbances and one-third experience fatigue.[15,21,22,24] Therefore, the majority of patients with A-SAH are referred to inpatient or outpatient rehabilitation services or nursing homes for follow-up treatment.[25,26]

Patients with PM-SAH have a shorter length of stay in hospital, and are considered to experience good recovery not requiring follow-up treatment or meeting the criteria for rehabilitation services.[27] Most studies showing these results are focused on survival and clinical outcomes.[10,12,13,28,29] However, the premise of good functional outcome and cognitive functioning of PM-SAH is unclear. Only 2 studies were found confined to cognition and psychosocial outcome in the subgroup of PM-SAH patients.[18,30] In these studies several problems are reported, such as cognitive deficits, depression, reduced activity levels, headaches, irritability and psychosocial problems, such as returning to a (current) job.[18,30,31] However, in a long-term follow-up study in angiogram-negative SAH patients, problems in selective attention during the first year of follow-up were found, which normalized within 3 years.[9] Two studies comparing the diverse group of SAH patients of unknown origin with selected A-SAH patients, reported impairments in diffuse cognitive functions, such as attention in the first group versus focal cognitive functions, such as short- and long-term memory, in the latter group.[6,8] Outcome studies comparing isolated PM-SAH and A-SAH are not available, to our knowledge.

The aim of this study was to investigate the differences in cognitive and emotional outcomes of the subgroup PM-SAH and A-SAH patients in the first year after SAH. Based on the literature, we expect that patients with PM-SAH will have better outcomes than those with A-SAH, but we also expect to find cognitive problems and mood disturbances in patients with PM-SAH that might require medical attention or follow-up treatment in rehabilitation services.

METHODS

Participants and procedures

All patients diagnosed with SAH, who were hospitalized between 2006 and 2009 at the neurology or neurosurgery department of the Erasmus University Medical Center Rotterdam, were screened for participation in this study. Inclusion criteria were: at least 18 years of age and survival of SAH at least until hospital discharge. Exclusion criteria were: serious comorbidity resulting in a short life expectancy less than 1 year and insufficient mastering of the Dutch language. Patients who agreed to participate were asked to sign an informed consent form. The study was approved by the Medical Ethics Committee of Erasmus MC.

Data collection

The presence of SAH was determined by computed tomography (CT) or lumbar puncture. The cause of SAH was determined using CT angiography or digital subtraction angiography. PM-SAH was defined by accumulation of blood around the mesencephalon on CT and a normal 4-vessel angiogram.[3,14]

During hospitalization baseline socio-demographic data and clinical characteristics, such as type, location and severity of SAH, and type of rehabilitation (none, outpatient, or inpatient rehabilitation) were collected by the staff of the neurology or neurosurgery department. Within the first year after SAH a research psychologist visited the patients at home to collect different measurements, which included validated questionnaires for depression and fatigue, and an objective test for cognitive functioning. Data were collected by 3 trained research psychologists.

Normative data from healthy subjects were obtained from the literature for each of the questionnaires and for the cognitive functioning test.[32-34]

Measurement instruments

The Barthel Index (BI) is used to evaluate the patient's state of independence. The total score ranges from 0 to 20, where 0 is completely dependent and 20 is completely independent.[35]

Glasgow Coma Scale scores (GCS) were collected as a measure of the severity of the SAH. The GCS is a scale to measure 3 different aspects of impaired consciousness and coma: motor response, verbal response and eye opening. The total score ranges from 3 to 15, of which the higher scores represent a higher level of consciousness.[36] In this study the first GCS score during hospital admission was used. These scores were assessed by physicians of the hospital department.

The Center for Epidemiological Studies Depression scale (CES-D) was used to measure emotional outcome. CES-D is a 20-item scale used to measure depressive symptoms over the previous week in a general population. This scale is validated in stroke patients.[37] Scores range from 0 to 60 and the higher the score, the more depressive symptoms are present. Scores of 16 or higher are an indication of presence of depression.[32,37,38]

The Fatigue Severity Scale (FSS) was used to measure the severity of fatigue. The questionnaire has 9 statements on fatigue in daily life. The patient can score these statements on a 7-point Likert scale ranging from 1 to 7, where 1 is "strongly disagree" and 7 is "strongly agree". Based on literature, patients with fatigue are distinguished from healthy controls if the mean score of the 9 items is 4 or higher.[33]

The Trail Making Test (TMT), parts A and B, were used as a measure of cognitive functioning. The TMT is widely used and has been researched extensively. The TMT score is a neuropsychological measure that is sensitive to a wide range of neurocognitive deficits.[39] The TMT is a pen and paper task to measure cognitive flexibility. In part A, which measures motor speed and processing speed, patients are asked to connect 25 numbered dots in ascending order as quickly as possible. In part B, which measures processing speed and divided attention, the 25 dots contain numbers and letters and the patient must connect the dots alternating between a number and a letter. The measured time (with a maximum of 180 sec.), including extra time for correcting potential errors, is recorded to calculate a time score.[40]

Statistical analysis

Statistical analyses were performed using SPSS version 19 (SPSS Inc, Chicago, USA). Descriptive statistics were used to describe the general population characteristics. Means and standard deviations (SDs) were calculated for interval variables and numbers and percentages for categorical variables. Mann-Whitney *U* tests were used to analyse the differences between patients with PM-SAH and those with A-SAH for the variables: GCS, CES-D and FSS and independent-samples *t*-test for the TMT-A and TMT-B scores. Fisher's exact tests were used to test the differences between the SAH types of the categorical variables: gender, education (≥high school), hypertension, smoking, presence of depression (CES-D>16) and presence of fatigue (FSS>4). Type of rehabilitation (inpatient/outpatient/none) was tested with the χ^2 test.

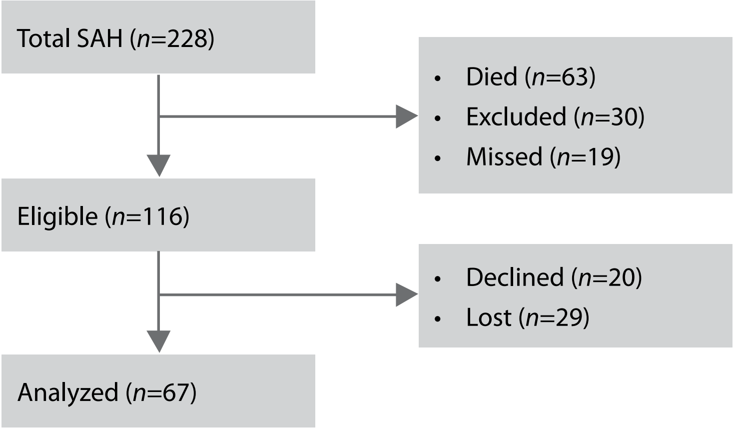

Figure 1. Flow of patient inclusion.

To test for potential selection bias, differences between the groups of missed patients and included patients (see Figure 1) were evaluated. For all analyses a significance level of $p<0.05$ was used.

Comparisons of the PM-SAH and A-SAH group with norm values of healthy subjects were performed with independent-samples *t*-tests and Fisher's exact tests, using a statistical internet tool (GraphPad Software Inc, La Jolla, CA, USA).

RESULTS

Study population

From a total of 228 patients with SAH, who were hospitalized in the neurology or neurosurgery department of the Erasmus MC between April 2006 and August 2009, 67 were eligible for inclusion in the study. The flow of patients is shown in Figure 1. Eight of the included patients had a PM-SAH (11.9%) and 59 patients had an A-SAH (88.1%). None of the patients in this sample was diagnosed with non-perimesencephalic angiogram-negative SAH. The mean age of the study population was 53.1 years (SD 11.6) and 37.3% were male. The mean length of hospital stay was 15.3 days (SD 9.9). Patient characteristics are presented in Table I.

Table I. *Patient characteristics.*

	Analyzed group (*n*=67)	**Missed group (*n*=29)**	***p*-value**
Age, years, mean (SD)	53.1 (11.6)	56.4 (12.0)	0.207[a]
Length of hospital stay, days, mean (SD)	15.3 (9.9)	16.3 (9.0)	0.645[a]
GCS, mean (SD)	13.2 (3.4)	12.2 (4.0)	0.218[b]
Time after SAH, months, mean (SD)	5.6 (8.6)	NA	NA
Type of bleeding, perimesencephalic, *n* (%)	8 (11.9)	3 (10.3)	1.000[c]
Gender, men, *n* (%)	25 (37.3)	11 (37.9)	1.000[c]
Education, ≥high school, *n* (%)	32 (47.8)	NA	NA
Hypertension, *n* (%)	29 (43.9)	NA	NA
Smoking, *n* (%)	27 (40.9)	NA	NA

[a] *t*-test; [b] Mann-Whitney *U* test; [c] Fisher's exact test.
SAH: subarachnoid haemorrhage; GCS: Glasgow Coma Scale score; SD: standard deviation; NA: not available.

No significant differences were found between the groups of missed patients and included patients for any of the variables available: type of bleeding, gender, age, length of stay and Glasgow Coma Scale scores (Table I). Data were complete for 92.5% of the TMT-A, 89.6% of the TMT-B, 83.6% of the FSS and 77.6% of the CES-D. The main reason for the missing data was the length of the test battery: time restrictions or fatigue were reasons for not finishing the test battery. Sum scores could sometimes not be calculated because of missing item scores.

Comparison between PM-SAH and A-SAH patients

Table II. *Comparison of patient characteristics between PM-SAH and A-SAH patients.*

	PM-SAH (*n*=8)	**PM-SAH (*n*=8)**	**PM-SAH vs A-SAH *p*-value**
Age (years), mean (SD)	48.9 (10.4)	53.6 (11.7)	0.278[a]
Time after SAH, months, mean (SD)	3.2 (2.5)	6.0 (9.1)	0.390[a]
Length of hospital stay, days, mean (SD)	7.1 (6.6)	16.4 (9.8)	0.012[a]
GCS, mean (SD)	14.8 (0.5)	13.0 (3.5)	0.121[b]
BI, mean (SD)	19.9 (0.4)	18.6 (2.9)	0.051[b]
Gender, men, *n* (%)	6 (75.0)	19 (32.2)	0.045[c]
Type of Rehabilitation, *n* (%)			0.230[d]
Inpatient	0 (0.0)	16 (27.1)	
Outpatient	1 (12.5)	7 (11.9)	
None	7 (87.5)	36 (61.0)	
Education, ≥high school, *n* (%)	5 (62.5)	27 (45.8)	0.464[c]
Hypertension[d], *n* (%)	3 (37.5)	26 (44.8)	1.000[c]
Smoking[d], *n* (%)	2 (25.0)	25 (43.1)	0.455[c]

[a] *t*-test; [b] Mann-Whitney *U* test; [c] Fisher's exact test; [d] χ^2test.
SAH: subarachnoid haemorrhage; GCS: Glasgow Coma Scale score; BI: Barthel Index score.

Compared with the A-SAH group, the PM-SAH group contained significantly more men and had a shorter length of stay (Table II). BI score, age and other patient characteristics did not differ significantly between the 2 groups. Rehabilitation type was also not significant. One PM-SAH patient received outpatient rehabilitation for cognitive complaints only. From the A-SAH patients 27.1% received inpatient rehabilitation including multidisciplinary functional and cognitive therapy. Table III presents the results of the questionnaires and cognitive testing. The PM-SAH patients had lower depression scores and fatigue scores compared with A-SAH patients. None of the PM-SAH patients had a significant depression (CES-D≥16) versus 20 (44.4%) in the A-SAH group. However, the proportion of PM-SAH patients with fatigue (FSS score≥4) was not significantly different from the A-SAH patients. For the tasks of cognitive functioning significant differences were found at the TMT-A. Patients with PM-SAH were faster on this task than those with A-SAH. No significant differences were found between the 2 groups on the more complex TMT-B task.

Comparison PM-SAH versus norm values

Comparing the results with the scores of a normal healthy population we found that patients with A-SAH scored significantly worse on all outcome measures. PM-SAH patients scored significantly worse than the norm population on the more complex TMT-B task (Table III). In addition, the mean fatigue scores of the patients with PM-SAH and the proportion of these patients with a FSS score ≥4 were borderline significant compared with the healthy subjects. No significant differences were found for the depression scores and the TMT-A task.

Table III. *Comparisons of outcomes between PM-SAH, A-SAH patients, and norm values.*

	PM-SAH	*n*	A-SAH	*n*	Norm values	*n*	PM-SAH vs A-SAH *p*-value	PM-SAH vs norm *p*-value	A-SAH vs norm *p*-value
CES-D, mean (SD)	5.0 (4.9)	7	13.9 (8.7)	45	8.2 (7.2)	255	0.006[b]	0.244[a]	0.000[a]
CES-D ≥6, *n* (%)	0 (0.0)	7	20 (44.4)	45	32 (12.7)	255	0.035[c]	0.601[c]	0.000[c]
FSS, mean (SD)	3.1 (1.6)	8	4.5 (1.4)	48	2.3 (0.7)	20	0.029[b]	0.073[a]	0.000[a]
FSS ≥4, *n* (%)	3 (37.5)	8	34 (70.8)	48	1 (5.0)	20	0.105[c]	0.058[c]	0.000[c]
TMT-A, mean (SD)	33.0 (8.3)	7	47.9 (20.1)	56	31.8 (9.9)	41	0.002[a]	0.764[a]	0.000[a]
TMT-B, mean (SD)	87.0 (42.4)	7	118.8 (49.1)	56	63.8 (14)	41	0.112[a]	0.008[a]	0.000[a]

[a] *t*-test; [b] Mann-Whitney *U* test; [c] Fisher's exact test.
CES-D: Center for Epidemiologic Studies Depression Scale score; FSS: Fatigue Severity Scale score; TMT-A and TMT-B: Trail Making Test A and B scores; SD: standard deviation.

DISCUSSION

Our results show disturbed cognitive and emotional outcomes in patients with PM-SAH, also found in other studies.[18,30,31] The cognitive task, TMT-A, indicates that patients with PM-SAH have no problems in processing and motor speed, in contrast with patients with A-SAH, which is in agreement with our hypothesis. However, the results on the more complex TMT-B task indicate that both groups of SAH patients perform worse than a normative sample. This implies that divided attention is affected in both the PM-SAH and A-SAH patients. This confirms the findings of Madureira et al. (2000), in which 72% of the patients with PM-SAH showed neuropsychological deficits and Hütter et al. (1994), who found similar cognitive deficits in non-A-SAH patients in comparison with A-SAH patients.[6,18]

Another notable finding in our study is that the proportion of patients with PM-SAH with fatigue did not differ significantly from that of patients with A-SAH, and it almost significantly differed from the normative scores. To our knowledge, fatigue was not investigated in other studies with validated questionnaires in patients with PM-SAH. This finding suggest that patients with PM-SAH, like those with A-SAH, do experience fatigue, which is described as a common complaint after SAH.[24]

Contrary to our expectations, none of the patients with PM-SAH in our study reached the CES-D cut-off score of 16, which indicates clinical depression. This finding differs from earlier literature in which, besides the cognitive deficits symptoms of depression in PM-SAH patients are also reported.[9,18,30] A possible explanation is that, in our study, the majority of patients with PM-SAH was male. Gender is a known predictor for symptoms of depression, and could therefore have influenced the outcome of the CES-D.[32] In the study of Madureira et al. (2000), for example, 66% of the patients with PM-SAH with depression were female. Of the patients with A-SAH in our study, 44.4% had clinical depression.[1,15,18] The difference between A-SAH and PM-SAH might be explained by the different prospects of both groups. Patients with PM-SAH do not require surgical or radiological treatment and get an excellent clinical prognosis without the risk of a re-bleed and without follow-up treatment, whereas A-SAH patients are faced with complex treatment, high complication rates, a survival chance of only 50%, a high risk of recurrence and many of them face months of rehabilitation.[1,15]

Although the results of this study of impaired complex cognitive functioning and fatigue in patients with PM-SAH confirm previous research findings, not much has changed in terms of follow-up treatment for patients with PM-SAH in the Netherlands. Patients with PM-SAH often are discharged from hospital without long-term follow-up because of their good prognosis. Based on our results, this policy should be questioned.

This study has some limitations. The first is that there were only 8 PM-SAH and 59 A-SAH patients enrolled in the study. Even with this small number of PM-SAH patients we did find significant cognitive deficits compared with a normal population. In terms of percentage, this number fits the incidence of 10% of all SAH patients. In further research a larger sample is required to confirm that PM-SAH patients experience fatigue. Another limitation might be that the measurement time, within the first year after the haemorrhage, was not the same for all patients, and no follow-up measurements were done. In recent research it was found that cognitive complaints may diminish within 3 years of follow-up.[9] Finally, cognitive testing was limited to the TMT test, which is a good test to measure processing speed and mental flexibility. In future studies other domains of cognitive functioning, such as long-term memory and sustained attention, should be measured in a larger sample over a longer follow-up.

In conclusion, contrary to the assumed favourable outcome, patients with PM-SAH may experience impaired complex cognitive functioning and fatigue. In this respect patients with PM-SAH have similar sequelae as those with A-SAH, which may interfere with daily activities and social participation. These findings are of clinical relevance, as patients with PM-SAH often are discharged from hospital without long-term follow-up. Based on our results this policy should be questioned.

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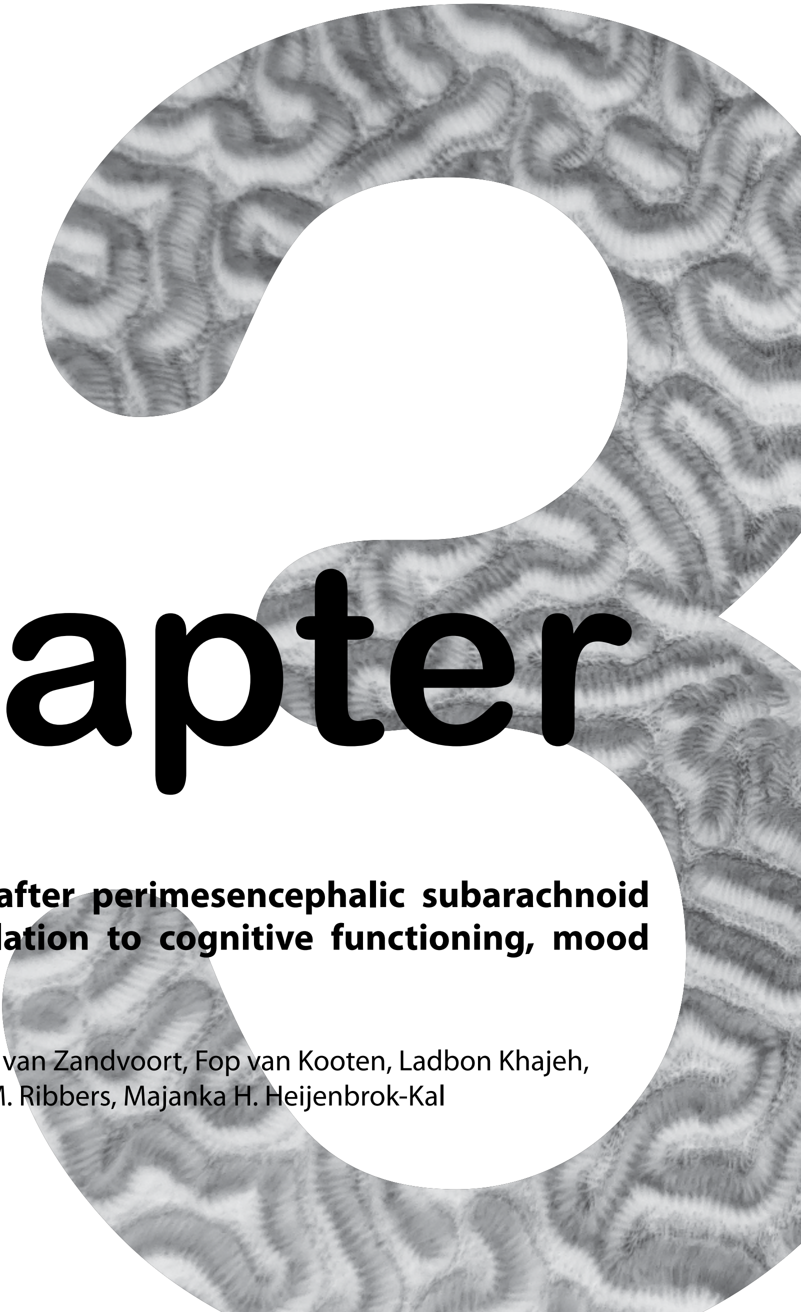

Chapter

Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity

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Submitted

ABSTRACT

Purpose: To study relationships between fatigue and objective and subjective cognitive functioning, mood, and comorbidity in the long term after perimesencephalic subarachnoid haemorrhage (PM-SAH).

Methods: Cross-sectional study. Objective cognitive functioning was measured with: Trail Making Test; Symbol Substitution; D2; Verbal and Semantic Fluency; Tower Test; Digit Span; 15-Words Test; Rey Complex Figure. Subjective cognitive functioning: Cognitive Failure Questionnaire. Fatigue: Fatigue Severity Scale. Mood: Hospital Anxiety and Depression Scale.

Results: Forty-six patients, mean age 50.4 (SD 9.4), mean time after PM-SAH 4.7 (SD 1.6) years participated. Patients with fatigue (33%) had significantly lower scores than patients without fatigue on most objective cognitive functioning tests ($p<0.05$). Fatigue score was significantly associated with subjective and objective cognitive functioning, mood, and comorbidity. After adjustment for mood and comorbidity, fatigue remained associated with attention and executive functioning.

Conclusions: This study supports our previous findings that a third of patients with PM-SAH experience fatigue and problems of cognitive functioning, also in the long term. Future research should investigate whether these patients would benefit from long-term follow-up and/or cognitive rehabilitation programs.

INTRODUCTION

In about 10% of the cases of subarachnoid haemorrhage, patients are diagnosed with a perimesencepahlic subarachnoid haemorrhage (PM-SAH). This means that no aneurysm is found and the haemorrhage is restricted to the cisterns surrounding the brainstem and the suprasellar cistern, combined with a negative angiogram.[1,2] Although this type of subarachnoid haemorrhage (SAH) is often described as a benign form of SAH with favourable outcomes, we found that patients with PM-SAH may experience problems in executive functioning and fatigue.[3]

The long-term relationship between fatigue and cognitive functioning after PM-SAH has not extensively been studied. Most of the long-term outcome studies focus on clinical outcomes or quality of life.[4-7] Despite good clinical outcome[7], quality of life outcomes are contradictory. Two studies[4,6] reported long-term complaints or reduced vitality and general health, whereas one study reported no long-term reduction in quality of life.[5] Hütter et al. (1994), Madureira et al. (2000), and Krajewski et al. (2014) did focus on cognitive outcomes in patients with PM-SAH or other types of non-aneurysmal SAH (broader group).[8-10] They determined minor cognitive deficits in their patients, but did not study fatigue in relation to cognitive functioning. Passier et al. (2011) described various factors such as physical and cognitive impairments, mood disturbances like anxiety and depression, and a passive coping style to be associated with fatigue after aneurysmal SAH.[11] In an earlier study we found that 38% of the subgroup of patients with PM-SAH (*n*=8) suffered from fatigue 3.2 (SD 2.5) months post-onset.[3] In view of the expected favourable outcome in patients with PM-SAH, we considered this a surprising outcome that asked for replication in a larger population. The data registries of two university medical centres were used to obtain a larger group of patients with PM-SAH that could be tested extensively on cognitive functioning. We were interested whether the experienced cognitive problems that were found around 3 months after PM-SAH also exist in the long term. The aim of this study was to investigate the relationships between fatigue, cognitive functioning, and mood in the long term after PM-SAH. The second aim was to determine whether cognitive functioning differs between patients with and without fatigue after PM-SAH. If fatigue is related to problems in cognitive functioning, than this should be taken into account in tailoring (cognitive) rehabilitation programs for these patients.[12]

METHODS

Participants and Procedures

All patients diagnosed with PM-SAH, hospitalized between 2006 and 2012 at the neurology and neurosurgery departments from the Erasmus University Medical Center Rotterdam or the University Medical Center Utrecht, were screened for participation in this study. PM-SAH was defined by accumulation of blood around the mesencephalon on CT and a normal 4-vessel angiogram. Inclusion criteria were: PM-SAH, and at least 18 years of age. Exclusion criteria were: all other types of stroke or SAH, serious (neurological) comorbidity and insufficient mastering of the Dutch language. All patients who were willing to participate provided informed consent. The Medical Ethics Committee of the Erasmus MC and UMC Utrecht approved the study.

Data collection

The staff of the neurology and neurosurgery departments in both hospitals identified all patients diagnosed with PM-SAH from a data registry of all SAH patients hospitalized between 2006 and 2012. Patients received an information letter from their neurologist and were invited to participate in the study. After informed consent was obtained from eligible patients, a research psychologist visited the patients at home to collect various outcome measures. A structured interview was used (patient characteristics and pre- and post-injury employment status), and validated questionnaires for depression, fatigue, comorbidity and subjective cognitive functioning. Furthermore, objective tests were used for multiple domains of cognitive functioning, which included memory, executive functioning, attention, concentration, speed of information processing and visuoconstruction.

Measurement instruments

Questionnaires

Fatigue was assessed using the Fatigue Severity Scale (FSS). The questionnaire contains 9 statements on fatigue in daily life. The patients scored these statements on a 7-point Likert scale ranging from 1 to 7, with 1 indicating “strongly disagree” and 7 indicating “strongly agree”. Patients with fatigue are distinguished from healthy controls if the mean score over the 9 items is 4 or higher.[13]

The Cognitive Failure Questionnaire (CFQ) measures self-perceived cognitive failures in daily life. It consists of 25 items for which participants indicate on a 5-point scale (range 0-4) how often they experience cognitive failures in daily life. A sum score is calculated (range

0-100) in which higher scores indicate an increased experience of cognitive problems.[14] 'Normal' scores range from 21 to 43 (mean 31.8; SD 11.1), a cut-off score >43 is used to distinguish normal scores from abnormal scores.[15]

To measure the degree of depression and anxiety in patients, the Hospital Anxiety and Depression Scale (HADS) was used. This questionnaire exists of 7 questions related to anxiety and 7 related to depression. The answers are given on a 4-point scale (range 0-3) and a total sum score is calculated. A higher sum score indicates more emotional problems. The scores 0-7 are defined as no anxiety or depression, 8-10 as probable cases and 11-21 as definite cases.[16,17]

Comorbidity was measured with the Cumulative Illness Rating Scale (CIRS). This list consists of 14 disorders and diseases (including SAH), which are rated on a 5 point rating scale, ranging from 0 (disorder/disease not present) to 4 (life-threatening disorder/disease present).[18] Patients were classified as having symptoms of comorbidity if they had a score above 5.[19]

Neuropsychological tests

The Trail Making Test (TMT), was used to measure cognitive functioning on the domains speed of information processing (part A) and divided attention, which was classified as a task of executive functioning (part B). The measured time to complete the task (with a maximum of 180 sec.), including extra time for correcting potential errors, was recorded to calculate a time score.[20,21] Norm scores by age group and education were obtained from Tombaugh (2004).[22]

The D2 test of attention and concentration was used to measure visual selective attention, processing speed and concentration. A total performance score and a concentration performance score was determined. The total performance score was calculated from the total of processed items minus total missed items and total wrong items; the concentration performance score is based on the total identified correct items minus total identified wrong items.[23]

The Digit Span is a subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III), and was used to measure attentional span and working memory. The maximum scores for the forwards and backwards series are 16 and 14, respectively.[24]

The Symbol Substitution task (SS) is a subtest of the WAIS-III, and was used to measure speed of information processing. The total number of correctly completed items is counted.[24]

The Fifteen Word Task (15WT, Dutch version) was used to measure learning, delayed recall and recognition. Raw scores were calculated for the immediate total (15WT-TRS) recall (range 0 to 75), delayed (15WT-DRS) recall (range 0 to 15) and for the recognition task (15WT-rec) (range 0-30). A cut-off score ≤26 is used to distinguish normal scores from abnormal scores for the recognition task.[25]

To measure semantic memory (category fluency) and executive functioning (phonological fluency) the Word Fluency task (WF) was used. The total score consists of the total correct items named per task in respectively 2 and 1 minute.[26]

The Tower Test (TT) from the Delis-Kaplan Executive Functioning System (D-KEFS) measures executive functions like planning and problem-solving abilities. A total performance score is calculated taking time and total amount of moves into account.[27]

The Rey Complex Figure Task (RCFT) was used to measure visuoconstructional skills (copy) and incidental memory (recall). Patients receive points for correctly placed lines, the total score for both copies is used.[25]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (SPSS Inc, Chicago, USA). Descriptive statistics were used to describe the study population characteristics. Means and standard deviations were calculated for interval variables and numbers and percentages for categorical variables. Differences in patients, SAH characteristics and cognitive outcomes between fatigued and non-fatigued patients were tested with independent samples *t*-tests. Dichotomous or categorical variables were calculated with a χ^2 or Fisher's Exact test in case of small groups. Relationships between subjective and objective cognitive test outcomes, fatigue, depression scores, and comorbidity scores are expressed in Pearson correlations. Relationships between fatigue and cognitive functioning were adjusted for depression and comorbidity using partial correlations. *T*-scores were calculated based on clinical reference scores, adjusted for age and education level for each individual. *T*-scores in the range of 40 to 60 are considered normal.[23-27] The mean scores of TMT and CFQ were also compared with published norms using independent samples *t*-tests.[15,22] A significance level of $p<0.05$ was used for all analyses. Bonferroni corrections were performed to correct for multiple testing for the comparisons between patients with and without fatigue, resulting in a significance level of $p<0.003$.

RESULTS

Study population

From a total of 109 patients with PM-SAH, 46 agreed to participate in the study, 20 from Erasmus MC Rotterdam and 26 from University Medical Center Utrecht. The flow of patients is shown in Figure 1. The mean age of the total group was 50.4 (SD 9.4) years, and 63% were men. An overview of the patient- and clinical characteristics is displayed in Table I. In this study sample 33% suffered from fatigue (mean 3.4; SD 1.3). The differences between fatigued and non-fatigued patients are also presented in Table I. Although not significant, patients with fatigue were less likely to have a paid job after PM-SAH. Furthermore, patients with fatigue had significantly higher scores on the CIRS comorbidity scale and the HADS depression scale.

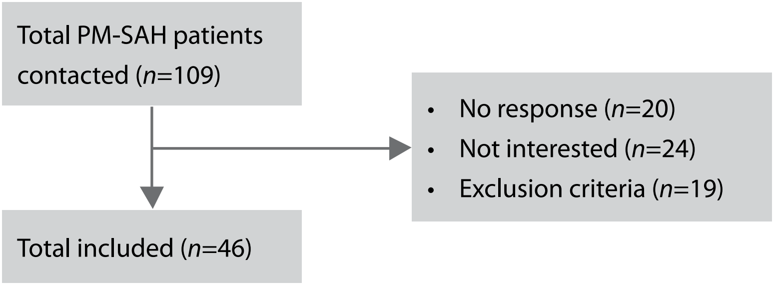

Figure 1. Flow of patient inclusion.

Table I. *Demographic and clinical characteristics for Fatigued (Fatigue Severity Scale (FSS) ≥4) vs Non-Fatigued (FSS<4) patients with PM-SAH.*

	Total group *N*=46	**Fatigued *n*=15 (32.6%)**	**Non-Fatigued *n*=31 (67.4%)**	**Fatigued vs Non-Fatigued *p*-value**
Age of onset (years), mean ± SD	50.4 ± 9.4	50.5 ± 9.3	50.3 ± 9.6	0.936
Gender (men), *n* (%)	29 (63.0)	10 (66.7)	19 (61.3)	0.723
Partner (yes), *n* (%)	39 (84.8)	15 (100)	30 (96.8)	1.000
Education (high), *n* (%)	19 (41.3)	4 (26.7)	15 (48.4)	0.161
Hypertension (yes), *n* (%)	12 (26.1)	7 (46.7)	5 (16.1)	**0.038**
CIRS total score (mean) ± SD	4.0 ± 3.0	6.5 ± 3.5	2.8 ± 1.7	**0.001**
Pre-morbid employment status, *n* (%)				0.733
Employed	36 (78.3)	11 (73.3)	25 (80.6)	
Retired	4 (8.7)	2 (13.3)	2 (6.5)	
Unemployed	6 (13.0)	2 (13.3)	4 (12.9)	
Current employment status, *n* (%)				0.075
Employed	29 (63.0)	6 (40.0)	23 (74.2)	
Retired	7 (15.2)	4 (26.7)	3 (9.7)	
Unemployed	10 (21.7)	5 (33.3)	5 (16.1)	
Hospital discharge destination, *n* (%)				0.674
Home	45 (97.8)	15 (100)	30 (96.8)	
Inpatient rehabilitation	1 (2.2)	0 (0.0)	1 (3.2)	
Time post-onset (years), mean ± SD	4.7 ± 1.6	4.9 ± 1.5	4.6 ± 1.7	0.597
HADS (depression score), mean ± SD	3.6 ± 3.6	6.4 ± 3.0	2.1 ± 3.0	**<0.001**
Probable depression HADS ≥8, *n* (%)	7 (15.2)	5 (33.3)	2 (6.5)	**0.029**
FSS (fatigue score), mean ± SD	3.4 ± 1.3	5.0 ± 0.6	2.7 ± 0.7	**<0.001**

CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale, FSS: Fatigue Severity Scale

Table II. *Mean scores and differences in Cognitive Test outcomes; Fatigued (Fatigue Severity Scale (FSS) ≥4) vs Non-Fatigued (FSS<4) patients with PM-SAH.*

	Total group *N*=46 mean ± SD	**Fatigued *n*=15 mean ± SD**	**Non-Fatigued *n*=31 mean ± SD**	**Fatigued vs Non-Fatigued *p*-value**
Subjective cognitive functioning				
CFQ, Total score	36.3 ± 14.6*	42.2 ± 15.4*	33.5 ± 13.5	0.056
CFQ Score >43, *n* (%)	12 (26.1)	7 (46.7)	4 (12.9)	**0.024**
Attention and concentration				
D2, Concentration performance	166.4 ± 41.9	137.2 ± 39.9	179.6 ± 31.1	**0.001**[#]
Digit Span, Forward	8.6 ± 1.7	7.6 ± 1.2	9.0 ± 1.8	**0.007**
Speed of information processing				
D2, Total performance	420.1 ± 96.3	353.2 ± 99.8	450.3 ± 79.2	**0.001**[#]
TMT-A (max. 180 sec.)	32.0 ± 10.9	39.1 ± 11.6*	28.6 ± 8.8	**0.001**[#]
Symbol Substitution, Total good	69.5 ± 17.3	56.5 ± 17.6	75.8 ± 13.3	**<0.001**[#]
Memory				
15 WT, Total score	44.0 ± 9.8	38.5 ± 10.1	46.6 ± 8.6	**0.007**
15 WT, Total recall	9.2 ± 2.9	7.3 ± 3.0	10.1 ± 2.4	**0.001**[#]
15 WT, Total recognition	29.0 ± 1.3	28.3 ± 1.2	29.3 ± 1.2	**0.006**
Rey Complex Figure, Recall score	19.9 ± 5.7	17.5 ± 6.5	21.0 ± 5.0	0.051
WF, Semantic	34.7 ± 7.8	31.4 ± 7.9	36.4 ± 7.3	**0.042**
Digit Span, Backward	6.5 ± 2.2	5.6 ± 1.5	6.9 ± 2.4	0.061
Digit Span, Total score	15.1 ± 3.5	13.3 ± 2.5	15.9 ± 3.6	**0.014**
Executive functioning				
Tower Test, Total performance	17.3 ± 4.6	15.4 ± 4.4	18.2 ± 4.5	0.067
WF, Phonological	23.2 ± 7.3	19.5 ± 5.0	25.1 ± 7.6	**0.014**
TMT-B (max. 180 sec.)	75.2 ± 30.9*	87.8 ± 40.3*	69.0 ± 23.5	0.052
Visuoconstruction				
Rey Complex Figure, Copy score	33.1 ± 2.5	33.1 ± 2.7	33.1 ± 2.5	0.939

Missings: D2: *n*=1; Tower Test: *n*=1

CFQ: Cognitive Failure Questionnaire; TMT: Trail Making Test; 15 WT: 15 Words Task; WF: Word Fluency.

* Mean scores worse than healthy individuals ($p<0.05$)

[#] Significant after Bonferroni correction ($p<0.003$)

Table III. *Proportions of patients with abnormal test results (T-scores<40, adjusted for age and education level) for Fatigued (Fatigue Severity Scale (FSS) ≥4) versus Non-Fatigued (FSS<4) patients with PM-SAH.*

	Fatigued **n=15** **% abnormal**	**Non-Fatigued** **n=31** **% abnormal**	**Fatigued vs Non-Fatigued** ***p*-value**
D2, Concentration performance	28.6	0.0	**0.007**
D2, Total performance	50.0	6.5	**0.002**[#]
Digit Span, Total score	20.0	6.5	0.311
15 WT, Total score	33.3	9.7	0.092
15 WT, Total recall	33.3	12.9	0.127
15 WT, Total recognition	6.7	6.5	0.704
Rey Complex Figure, Copy score	20.0	9.7	0.375
Rey Complex Figure, Recall score	46.7	22.6	0.170
Symbol Substitution, Total good	20.0	0.0	**0.030**
TMT-A (max. 180 sec.)	33.3	0.0	**0.002**[#]
TMT-B (max. 180 sec.)	20.0	6.5	0.311
Tower Test, Total performance	13.3	0.0	0.101
WF, Semantic (1 min.)	26.7	12.9	0.414
WF, Phonological	26.7	23.3	1.000

15 WT: 15 Words Task; TMT: Trail Making Test; WF: Word Fluency.
Missings: D2: n=1; Tower Test: n=1
[#] Significant after Bonferroni correction (p<0.003)

Comparison between fatigued and non-fatigued patients and norms

Patients with fatigue did not differ significantly from patients without fatigue in subjective cognitive functioning, but they did have significantly poorer scores on the objective cognitive functioning domains of attention and concentration, speed of information processing, and memory (Table II).

Comparing the *T*-scores, which were adjusted for age and education level, we found that the proportion of patients with abnormal test results was significantly larger in the fatigued group than in the non-fatigued group for the D2 Concentration performance, D2 Total performance, TMT-A and SS (Table III).

Further, in the fatigued group, total mean scores on TMT-A (t=2.3; p=0.023) in the speed of information processing domain, TMT-B (t=3.3; p=0.002) in the executive functioning domain, and CFQ (t=3.6; p<0.001) in subjective cognitive functioning were significantly worse than those from healthy individuals.[22]

Relationships between fatigue, depression, comorbidity and cognitive functioning

In Table IV the correlations between fatigue, subjective and objective cognitive functioning, depression and comorbidity scores are presented. Strong correlations were found among fatigue, depression, and comorbidity. Higher fatigue scores were related to poorer cognitive functioning on all domains (subjective and objective), except for visuoconstruction. Depression score was associated with poorer scores of subjective cognitive functioning, attention and concentration, and memory. Comorbidity score was negatively associated with the domains of processing speed, attention and concentration, and memory. Subjective cognitive functioning (CFQ) was not associated with any domain of objective cognitive functioning. Partial correlations showed that the relationships between fatigue and Digit Span (forward) (p=0.032), Symbol Substitution (total good) (p=0.041), 15WT (total score) (p=0.041), Word Fluency (semantic) (p=0.021) and Word Fluency (phonological) (p=0.011) remained significant, adjusted for depression. These variables still covered all the domains of objective cognitive functioning, except the domain visuoconstruction. Adjusting for both depression and comorbidity, revealed that relationships between fatigue and Digit Span (forward) (p=0.019) and Word Fluency (phonological) (p=0.010) remained significant.

Table IV. *Pearson correlations between fatigue, subjective and objective cognitive test outcomes, depression score, and comorbidity score.*

	FSS Total score *p*-value	**HADS Depression *p*-value**	**CIRS Total score**	**CFQ Total score *p*-value**
FSS, Total score	1	0.597 (<0.001)	0.473 (0.001)	0.405 (0.005)
HADS, Depression	0.597 (<0.001)	1	0.419 (0.004)	0.372 (0.011)
CIRS, Total score	0.473 (0.001)	0.419 (0.004)	1	-
Subjective cognitive functioning				
CFQ, Total score	0.405 (0.005)	0.372 (0.011)	-	1
Attention and concentration				
D2, Concentration performance	-0.351 (0.018)	-	-0.371 (0.012)	-
Digit Span, Forward	-0.545 (<0.001)*‡	-0.353 (0.016)	-	-
Speed of information processing				
D2, Total performance	-0.326 (0.029)	-	-0.387 (0.009)	-
TMT-A (max. 180 sec.)	0.369 (0.012)	-	-	-
Symbol Substitution (Total good)	-0.454 (0.002)*	-	-0.413 (0.004)	-
Memory				
15 WT, Total score	-0.408 (0.005)	-0.383 (0.009)	-0.334 (0.023)	-
15 WT, Total recognition	-0.314 (0.034)	-0.427 (0.003)	-0.467 (0.001)	-
15 WT, Total recall	-0.410 (0.005)	-0.327 (0.026)	-0.324 (0.028)	-
Rey Complex Figure, Recall score	-0.399 (0.006)	-	-	-
WF, Semantic	-0.371 (0.011)	-	-0.406 (0.005)	-
Digit Span, Backwards	-0.335 (0.023)*	-	-	-
Digit Span, Total score	-0.476 (0.001)	-0.352 (0.017)	-	-
Executive functioning				
Tower Test, Total performance	-0.368 (0.017)	-	-	-
WF, Phonological	-0.453 (0.002)*‡	-	-	-
TMT-B (max. 180 sec.)	-	-	-	-
Visuoconstruction				
Rey Complex Figure, Copy score	-	-	-	-

CFQ: Cognitive Failure Questionnaire; TMT: Trail Making Test; 15 WT: 15 Words Task; WF: Word Fluency; FSS: Fatigue Severity Scale; CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale.

* Significant partial correlations adjusted for depression $p<0.05$

‡ Significant partial correlations adjusted for depression and comorbidity $p<0.05$

DISCUSSION

The main finding in this study was that 1 in every 3 patients suffered from fatigue in the long term after onset of PM-SAH. Fatigue was strongly related to poorer scores on both subjective and objective cognitive functioning, depression, and comorbidity. Higher depression and comorbidity scores were also related to reduced objective cognitive functioning. However, only fatigue was associated with the domain of executive functioning, also after adjustment for depression and comorbidity. This is in line with the results from our previous study.[3]

Fatigue after A-SAH is often described in the literature. The review of Kutlubaev et al. (2012) mentioned pituitary dysfunction as a potential predictor for post A-SAH fatigue. Also relationships between fatigue and factors like anxiety, depression, PTSD, memory difficulties, personality changes, sleep disturbances and cognitive and physical impairment after A-SAH are described.[28,29] In this study, relationships of fatigue with cognitive functioning and depression are also found in PM-SAH patients. Pihlaja et al. (2014) presented similar associations of fatigue with negative cognitive outcomes, and lower rates of return to work 3-6 months after stroke.[30] The employment rate of patients with fatigue in our study was relatively low (40.0%) compared to patients without fatigue (74.2%), although not significantly different. The total employment rate in patients with PM-SAH (63.0%) was comparable to the return-to-work rate after A-SAH (61.4%), despite the presumed favourable outcome.[31]

Comparing the proportions of abnormal test scores between the fatigued and non-fatigued group we found significant differences in subjective cognitive functioning, attention and concentration, and speed of information processing. Furthermore, patients with fatigue experienced more subjective cognitive complaints and underperformed healthy individuals on the TMT-A and TMT-B tasks for speed of information processing, and executive functioning.[15,22] These results support the findings from our previous work in a relatively small group of patients with PM-SAH (*n*=8), in which fatigue and executive functioning were affected.[3] Krajewski et al. (2013) also found tendencies of memory impairment and slower cognitive processing in PM-SAH groups 2 years after discharge, but found no significant differences compared with norm data.[10] However, they did not perform subgroup analyses in patients with fatigue.

Because of the good prognosis, in terms of no risk of re-bleeds and unaffected survival rates, patients with PM-SAH are mostly discharged home without follow-up. Moreover, this group of patients is often excluded from scientific research, because of the assumed good prospects. The outcomes of our study questions this assumption. Patients with PM-SAH could be followed in outpatient rehabilitation clinics to screen for problems of cognitive functioning, fatigue, and mood. There are simple screening questionnaires like the FSS and HADS available as a starting point for screening. Subjective cognitive functioning appeared not to be related to objective cognitive functioning.[15] Our results suggest that screening for subjective cognitive problems using the CFQ may not be sufficient in detecting specific problems of cognitive functioning.

This study has some limitations. Despite the fact that with a larger number of patients we confirmed the results of our previous study, the sample size is still small. Also the absence of short-term measurements and follow-up measurements can be considered a limitation of this study, because no causal relationships could be studied. Furthermore, not all patients that were contacted responded or were interested in taking part in this study, which may have resulted in selection bias.

In conclusion, this study supports our findings from previous research that the consequences for patients with PM-SAH are underestimated. These patients may be left with fatigue, have less than optimal cognitive functioning, and relatively low employment rates. Patients with PM-SAH should be screened for these problems in outpatient clinics, just as patients with aneurysmal SAH. Future research should investigate whether these patients would benefit from long-term follow-up and/or rehabilitation programs incorporating fatigue management and/or cognitive rehabilitation.

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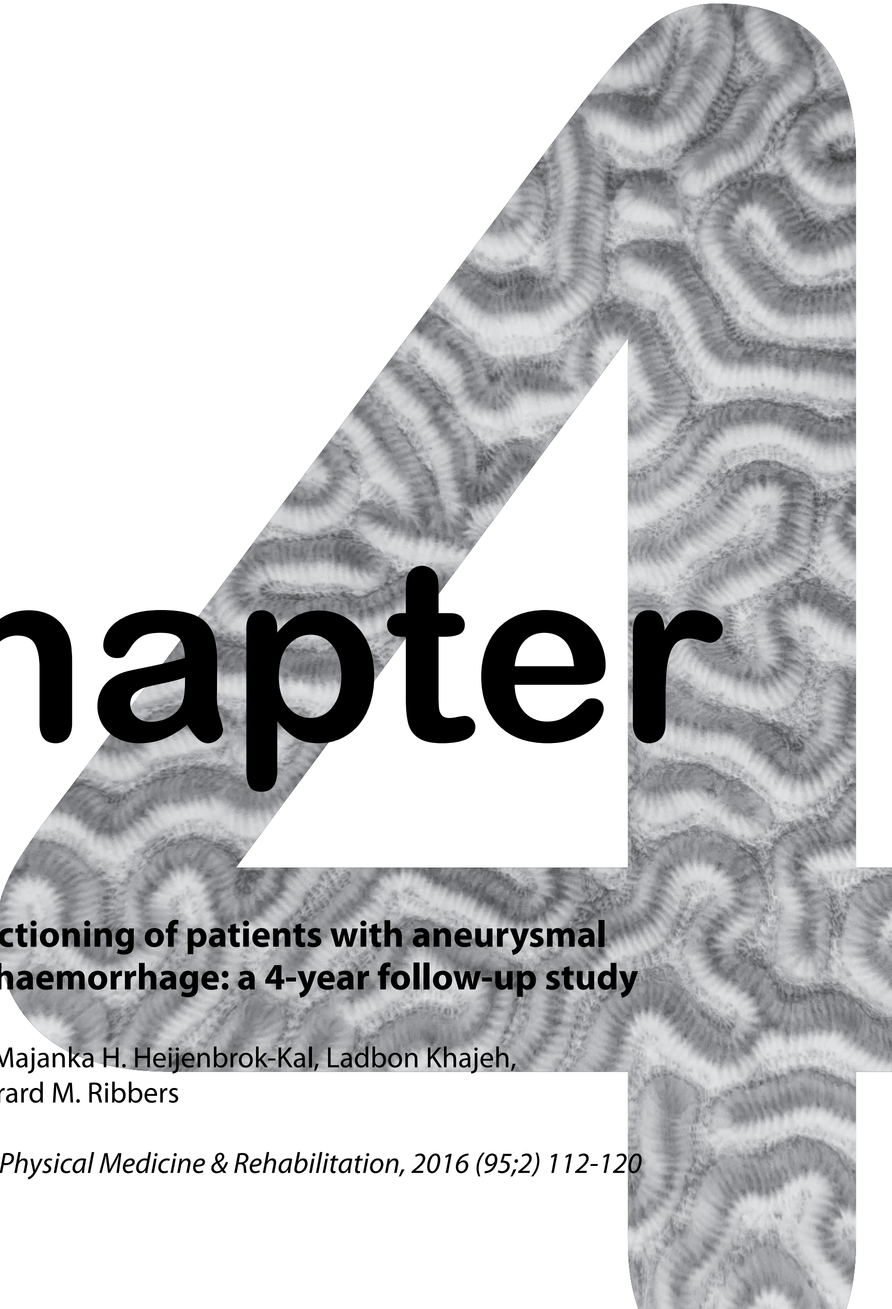

Chapter 4

Long-term functioning of patients with aneurysmal subarachnoid haemorrhage: a 4-year follow-up study

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ABSTRACT

Objectives: The aim was to study changes over time for multiple outcomes based on the International Classification of Functioning, Disability, and Health in patients with aneurysmal subarachnoid haemorrhage and to compare long-term outcomes with norms.
Design: A prospective cohort study with 4-year follow-up was conducted. Main outcome measures were as follows: Center for Epidemiologic Studies Depression-Scale, Fatigue Severity Scale, Trail Making Test A and B, Barthel Index, Sickness Impact Profile-68, Impact on Participation and Autonomy Questionnaire, Social Support List-12, Multidimensional Health Locus of Control Scales, COOP-WONCA Charts, and Short Form-36 Health Survey.
Results: Seventy-six patients with aneurysmal subarachnoid haemorrhage were included. Measurements were done at T1=0.4 years (SD 0.3) and T2=3.9 years (SD 0.7) after onset. Significant improvements over time were found for Barthel Index (T1=18.5; T2=19.5; *p*=0.023), Trail Making Test B (T1=119.4; T2 = 104.6; *p*=0.025), Social Support List-12 total score (T1=31.1; T2=32.7; *p*=0.042) and esteem support (T1=10.2; T2=10.9; *p*=0.027), Multidimensional Health Locus of Control Scales (physician-orientation) (T1=21.8; T2=19.2; *p*=0.020), and Short Form-36 Health Survey (role-emotional) (T1=54.6; T2=73.9; *p*=0.048). Center for Epidemiologic Studies Depression Scale, Fatigue Severity Scale, Sickness Impact Profile-68, and Short Form-36 Health Survey scores remained stable over time. A decline was found for COOP-WONCA (overall-health) (T1=2.3; T2=2.7; *p*=0.021). At 4-year follow-up, proportions of depression (27%) and fatigue (60%) were larger and scores on the Fatigue Severity Scale (mean [SE], 4.3 [0.2]), Trail Making Test A (mean [SE], 51.3 [3.9]), and Trail Making Test B (mean [SE], 104.4 [0.2]) were significantly worse than norm scores.
Conclusions: Many patients with aneurysmal subarachnoid haemorrhage had fairly good long-term outcomes, but problems in executive functioning, mood, and fatigue still exist at long-term follow-up.

INTRODUCTION

Aneurysmal Subarachnoid Haemorrhage (A-SAH) accounts for 85% of all cases of subarachnoid haemorrhage (SAH). Compared with ischemic stroke, A-SAH occurs at a relatively young age, when patients are in the most productive stage of their life, in which work and family are important responsibilities.[1,2] This is why even minor sequelae of A-SAH can have a major and long-lasting impact on quality of life.

Al-Khindi et al. (2010) showed that deficits in memory, executive functioning, and language are common after A-SAH and may persist until 2 to 3 years after onset. Furthermore, mental slowness and attention deficits are known long-term consequences of A-SAH.[2,3] Patients who do regain independence for activities of daily life may not be able to resume work, experience difficulties in maintaining and establishing relationships, and report mood disturbances and impaired quality of life with long-term anxiety complaints, symptoms of depression, and fatigue.[4-7]

However, studies that evaluate the outcomes of SAH survivors beyond the horizon of 1 year after onset are scarce. Furthermore, most studies have a retrospective design and focus on single outcomes.[8,9] Thus, prospective studies with long-term follow-up and evaluating multiple outcomes over time are lacking.

Therefore, a prospective study was designed to assess multiple outcomes for patients with A-SAH over a follow-up period of 4 years. Outcomes were evaluated based on all domains of the International Classification of Functioning, Disability, and Health (ICF) model and related to normative values. As such, an overview of long-term consequences of A-SAH was created, which may help rehabilitation services to adapt their programs to long-term needs.

METHODS

Participants and Procedures

Patients were included if they were hospitalized between 2006 and 2009 at the neurology or neurosurgery department from the Erasmus University Medical Center Rotterdam with a diagnosis A-SAH determined by computed tomography, and if negative, by a lumbar puncture followed by a computed tomography angiography or digital subtraction angiography to detect the aneurysm.[10] Other inclusion criteria were at least 18 years of age and survival of

A-SAH at least until hospital discharge. Exclusion criteria were neurologic comorbidity, serious comorbidity resulting in a life expectancy less than 1 year and insufficient knowledge of the Dutch language. Patients who agreed to participate were asked to sign an informed consent form. The study was approved by the Medical Ethics Committee of the Erasmus MC.

Data Collection

During hospitalization, baseline socio-demographic data and clinical characteristics were collected by the medical staff and prospectively entered into an anonymized database. The severity of the SAH is measured with the Glasgow Coma Scale and the World Federation of Neurosurgical Societies classification. Glasgow Coma Scale scores range from 3 to 15, where higher scores represent a higher level of consciousness, and World Federation of Neurosurgical Societies scores range from 1 (no symptoms) to 5 (severe symptoms).[11] Within 6 months after onset (T1), a research psychologist assessed the patients at home. To investigate long-term outcomes, a revisit was performed by a trained research psychologist 4 years after onset (T2).

Measurement Instruments and ICF Model

The measurement instruments in this research are categorized within the domains of the ICF model displayed in Figure 1. The extra category in the model is Health-Related Quality of Life (HR-QoL) as described in the review of Passier et al. (2013).[12]

Body Functions and Structures

The ICF domain body functions and structures refers to anatomical parts and physiologic functions of body systems and covers SAH characteristics, such as fatigue, mood, and neuropsychological impairments.[12,13] Within this domain, the study focused on cognition and mood. The Center for Epidemiologic Studies Depression scale (CES-D) is used to measure depressive symptoms over the previous week using a 20-item scale. This scale is validated in stroke patients. Scores range from 0 to 60, and the higher the score, the more depressive symptoms are present. Scores of 16 or higher are indicative of the presence of depression.[14] The Fatigue Severity Scale (FSS) measures fatigue by means of nine statements that must be scored on a 7-point Likert scale ranging from 1, “strongly disagree”, to 7, “strongly agree”. Mean scores of 4 or higher out of 9 are outside the range of healthy controls.[15] The Trail Making Test (TMT) parts A and B are sensitive to a wide range of neurocognitive deficits. Part A measures motor speed and processing speed, and part B measures processing speed and divided attention. The total time (with a maximum of 180 sec.) is recorded and includes the extra time for correcting potential errors.[16]

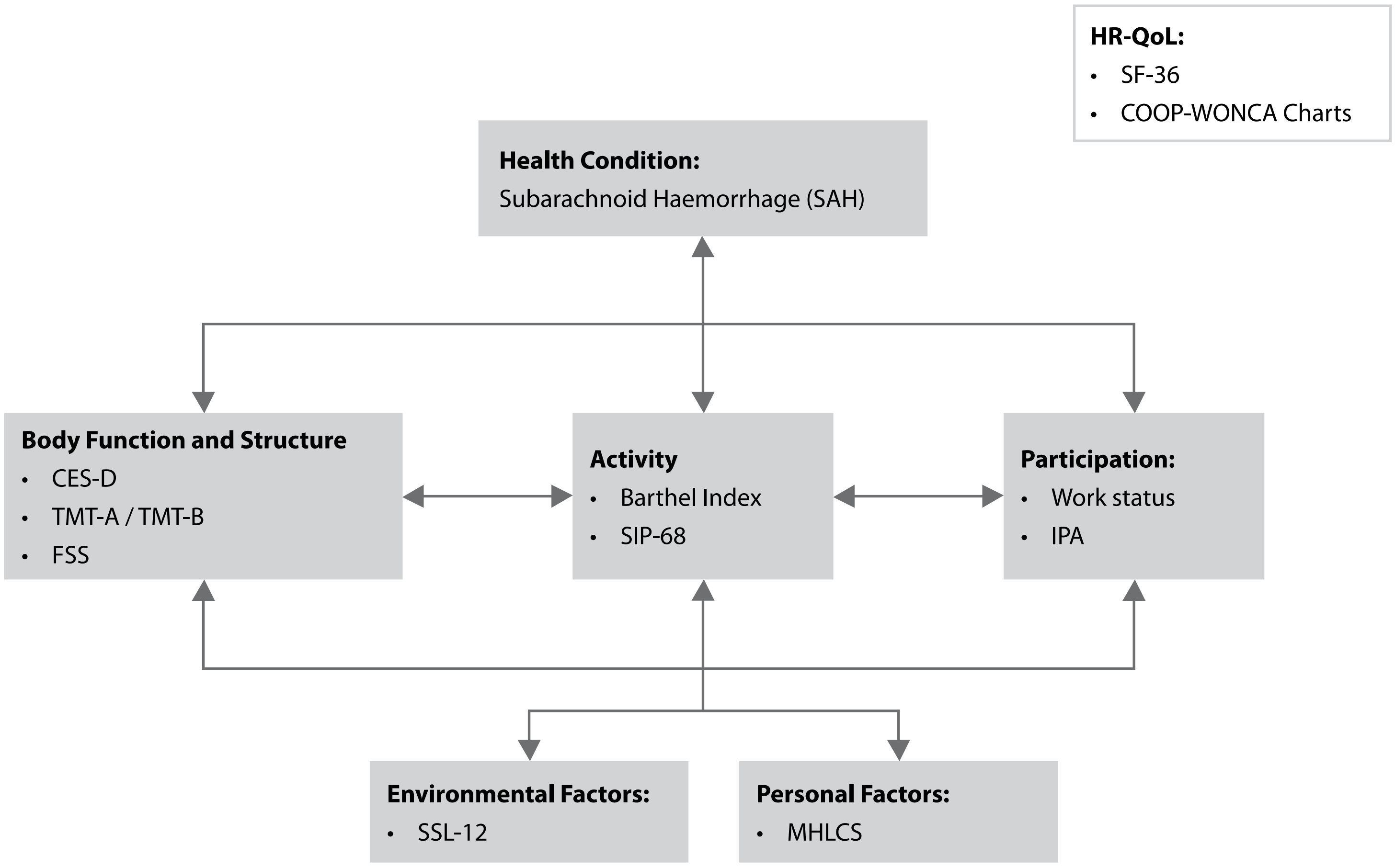

Figure 1. Measurement instruments for outcomes of subarachnoid haemorrhage divided over the ICF domains.

Activities

The ICF domain activities represents the execution of tasks or actions by an individual.[13] The Barthel Index (BI) is used to evaluate the patient's state of independence in activities of daily living, with total scores ranging from 0 to 20, in which 0 means completely dependent and 20 means completely independent.[17] The Sickness Impact Profile-68 (SIP-68) measures physical, mental, and social aspects of health-related functioning in six subscales: somatic autonomy, mobility control, mobility range, social behaviour, emotional stability, and psychological autonomy/communication. It contains 68 dichotomous (yes/no) items. The items reported as yes are used to calculate the total score. Higher scores indicate more health-related behavioural problems.[18]

Participation

The ICF domain participation refers to involvement in life situations, like return to work, social roles, and family life.[12] Participation was measured only at long-term follow-up (T2) using the Impact on Participation and Autonomy (IPA) and a description of the patients' work status, for patients who were younger than 65 years at the moment of the measurement. The IPA measures constraints in participation and autonomy. The questionnaire consists of 41 items divided over eight subscales: self-care and appearance, mobility, leisure, social relationships, work, education, family role, and financial independence. Each item was scored on a 5-point rating scale, ranging from 1 (excellent) to 5 (very poor). A higher sum score on a subscale indicates a greater perceived handicap on this specific subscale.[19]

Environmental Factors

Environmental factors are external features of physical, social and attitudinal environment in which people live and conduct their lives.[13] In this domain, the Social Support List (SSL-12) was used. This questionnaire measures the extent of received social support by means of social interactions with members of the primary social network. The questionnaire consists of 12 questions, which all start with "Does it ever happen to you that people…" The patient must answer the questions by choosing one of four options: (1) seldom or never, (2) now and then, (3) regularly, and (4) very often. Three subscores, everyday support, support in problem situations, and esteem support, and the total score can be calculated by the sum of the corresponding items. High scores indicate a high level of social support on the corresponding (sub)score.[20]

Personal Factors

Personal factors are features that can have impact on an individual's performance.[12] For this domain, the Multidimensional Health Locus of Control Scale (MHLCS) is used. The MHLCS measures the degree to which people perceive them-selves as having control over their own health. The scale consists of three dimensions: internal (the extent to which individuals perceive their own behaviour as responsible for their health), physician (the extent to which individuals perceive their physician as responsible for their health), and chance (the extent to which individuals perceive luck, fate, or chance as responsible for their health). Each subscale consists of six items with a 6-point Likert-type scale, ranging from “completely agree” to “completely disagree”. For each subscale, a total score is computed, with high scores indicating strong orientations.[21]

Health-Related Quality of Life

HR-QoL is not an official category of the ICF but an important concept to study in relation to SAH.[12] Questionnaires linked to the concept HR-QoL are the Short Form-36 Health Survey (SF-36) and the COOP-WONCA Charts. The SF-36 measures perceived health and contains 36 items in eight health-related domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The scores range from 0 to 100. Zero represents the worst imaginable health state, and a score of 100 represents perfect health.[22] The COOP-WONCA Charts is a measure for the patients’ assessment of his/her functional capacity at the given time. This scale consists of seven aspects of functional status: physical fitness, feelings, daily activities, social activities, change in health, overall health, and pain. The scores range from 1 to 5. Mean scores per aspect of functional status are calculated, and higher scores on an aspect indicate a more affected HR-QoL on that specific subject.[23]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (SPSS Inc, Chicago, USA). Descriptive statistics were used to describe the patient and clinical characteristics of the total group and subpopulations of T1 and T2. Linear mixed-model analyses were performed to study changes over time for each outcome, in which the covariance between measurements within patients is taken into account. This method is very flexible in handling missing values. Time was entered in each model as a predictor of the outcomes. A significance level of $p<0.05$ was used in all analyses. Comparisons of the long-term outcomes (T2) of the A-SAH group with norm values of healthy subjects were performed, by calculating Z-scores using the standard deviation of the norm group. A positive or negative Z-score indicates how many standard deviations the patient’s score deviates from the norm in positive or negative direction. A Z-score of 1.96 or higher is significantly different from healthy individuals. *P*-values were also calculated using independent-samples *t*-tests for interval variables and Fisher's exact tests for categorical variables, using a statistical internet tool (GraphPad Software Inc, La Jolla, CA). Norm scores of healthy individuals were obtained from the literature.[14-16,21-24]

RESULTS

Study Population

A total of 76 patients diagnosed with A-SAH agreed to participate in this study. One patient, in whom no aneurysm was found, was included in the study because this patient had an aneurysmal pattern of haemorrhage. The flow of patients is shown in Figure 2. A total of 76 patients were included, of which 59 completed T1 and 60 completed T2; the number of patients who completed both T1 and T2 was 43. The mean age of the total group was 53.8 years, and 31.6% were men. Twenty-five percent of the patients were treated in an inpatient or outpatient rehabilitation facility, and 14.4%, in a nursing home. The patient and SAH characteristics of the 76 patients are presented in Table I.

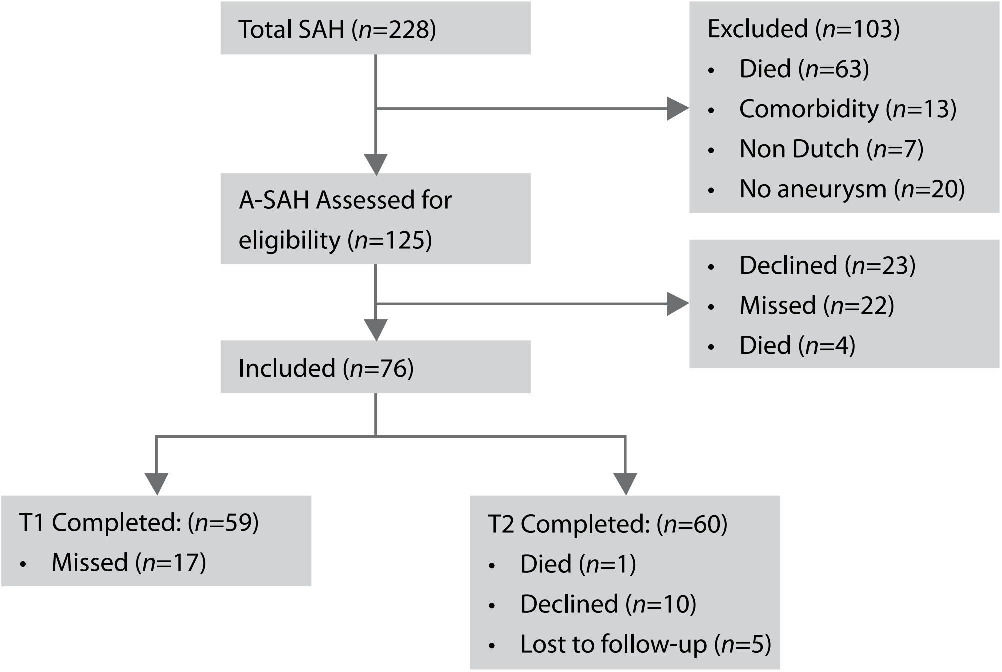

Figure 2. Flowchart of patient inclusion procedure.

Table I. *Patient and clinical characteristics (N=76).*

	Total A-SAH patients	T1 (*n*=59)	T2 (*n*=60)
Age, years	53.8 ± 11.5	53.6 ± 11.7	53.2 ± 10.9
Gender, men	24 (31.6)	19 (32.2)	22 (36.7)
Partner, yes	52 (68.4)	44 (74.6)	42 (70.0)
Education, high	14 (18.4)	10 (16.9)	14 (23.3)
Smoking, yes	32 (42.1)	25 (42.4)	28 (46.7)
Alcohol use, daily	17 (22.4)	12 (20.3)	19 (31.7)
Hypertension, yes	30 (39.5)	26 (44.1)	30 (51.7)
Employed, before SAH	-	34 (70.8)	-
Employed, after SAH	-	-	17 (31.5)
Length of Hospital stay, days	17.4 ± 10.5	16.4 ± 9.8	17.0 ± 10.3
GSC score at hospitalization	12.7 ± 3.7	13.0 ± 3.5	12.7 ± 3.8
WFNS grade at hospitalization			
Grade 1	39 (51.3)	31 (52.5)	31 (51.7)
Grade 2	16 (21.1)	12 (20.3)	13 (21.7)
Grade 3	3 (3.9)	3 (5.1)	3 (5.0)
Grade 4	8 (10.5)	7 (11.9)	5 (8.3)
Grade 5	10 (13.2)	6 (10.2)	8 (13.3)
Location of aneurysm, anterior	48 (66.7)	38 (67.9)	39 (68.4)
Treatment of aneurysm			
Clipping	21 (27.6)	17 (28.8)	15 (25.0)
Coiling	51 (67.1)	39 (66.1)	41 (68.3)
Hospital discharge destination			
Discharge home	46 (60.5)	36 (61.0)	34 (56.7)
Outpatient rehabilitation	8 (10.5)	7 (11.9)	9 (15.0)
Inpatient rehabilitation	11 (14.5)	7 (11.9)	14 (23.3)
Nursing home	11 (14.4)	9 (15.2)	3 (5)
Time post-onset, years	-	0.4 ± 0.3	3.9 ± 0.7

Data are presented as mean ± SD or *n* (%).

Missing data: hypertension, *n*=2; location of aneurysm, *n*=4; employed before SAH <65 years, *n*=11; employed after SAH >65 years, *n*=6.

IQR indicates interquartile range; GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies classification.

Table II. *Estimated mean [SE] of measurement 1 (T1) and measurement 2 (T2) and significance level of change over time (N=76).*

	T1	T2	*p*-value
Body functions and structure			
CES-D, total score	13.7 (1.2)	11.9 (1.2)	0.172
FSS, total score	4.4 (0.2)	4.3 (0.2)	0.546
TMT-A, seconds	50.3 (2.8)	51.3 (3.9)	0.688
TMT-B, seconds	119.4 (6.5)	104.6 (5.6)	0.025[a]
Activities			
BI, total score	18.5 (0.4)	19.5 (0.1)	0.023[a]
SIP-68	9.3 (1.5)	9.9 (1.4)	0.679
Environmental factors			
SSL-12, total score	31.1 (0.8)	32.7 (0.8)	0.042[a]
SSL-12, everyday support	11.0 (0.3)	11.1 (0.3)	0.684
SSL-12, support in problem situations	10.2 (0.3)	10.6 (0.3)	0.296
SSL-12, esteem support	10.2 (0.3)	10.9 (0.3)	0.027[a]
Personal factors			
MHLCS, physician-orientation	21.8 (0.7)	19.2 (0.6)	0.020[a]
MHLCS, chance-orientation	22.2 (0.7)	20.8 (0.7)	0.276
MHLCS, internal-orientation	20.4 (0.8)	20.5 (0.7)	0.911
Quality of Life			
COOP-WONCA, physical fitness	2.5 (0.2)	2.7 (0.1)	0.254
COOP-WONCA, mood	2.2 (0.2)	2.0 (0.1)	0.397
COOP-WONCA, daily activities	1.7 (0.2)	2.1 (0.2)	0.086

COOP-WONCA, social activities	1.8 (0.2)	1.7 (0.1)	0.767
COOP-WONCA, overall health	2.3 (0.2)	2.7 (0.1)	0.021[a]
COOP-WONCA, changes in health status	2.7 (0.1)	2.8 (0.1)	0.716
COOP-WONCA, pain	1.9 (0.3)	2.1 (0.2)	0.588
SF-36, physical functioning	77.5 (3.6)	74.7 (3.1)	0.250
SF-36, role limitation due to physical problems	50.3 (7.8)	64.8 (5.4)	0.072
SF-36, bodily pain	84.9 (4.3)	77.3 (3.4)	0.156
SF-36, general health perception	70.7 (3.5)	67.4 (3.0)	0.391
SF-36, energy vitality	59.1 (3.1)	57.8 (2.7)	0.701
SF-36, social functioning	73.6 (3.0)	70.4 (3.3)	0.410
SF-36, role limitation due to emotional problems	54.6 (9.1)	73.9 (5.2)	0.048[a]
SF-36, mental health	70.2 (3.1)	71.1 (2.4)	0.808
SF-36, mental component score	44.0 (2.1)	46.1 (1.5)	0.340
SF-36, physical component score	48.0 (1.3)	46.8 (1.3)	0.296

[a] Significant *p*-values

Table III. *Comparison of A-SAH with norm values at 4 years post-onset (T2).*

	A-SAH, Mean [SE], (*N*=76)	**Norm Values, Mean ± SD**	***N***	**A-SAH *vs.* Norm: *Z*-score**	**A-SAH *vs.* Norm: *p*-value**
Body functions and structure					
CES-D	11.9 (1.2)	8.2 ± 7.2	255	0.51	0.305
CES-D≥16, *n* (%) *N*=60	16 (26.7)	32 (12.7)	255	-	0.009^a
FSS	4.3 (0.2)	2.3 ± 0.7	20	2.86	0.002^a
FSS≥4, *n* (%) *N*=60	36 (60.0)	1 (5.0)	20	-	0.000^a
TMT-A	51.3 (3.9)	31.8 ± 9.9	41	1.97	0.024^a
TMT-B	104.6 (5.6)	63.8 ± 14	41	2.91	0.002^a
Personal factors					
MHLCS, internal-orientation	20.5 (0.7)	22.3 ± 5.7	10,302	-0.32	0.374
MHLCS, physician-orientation	19.2 (0.6)	17.5 ± 6.7	10,302	0.25	0.401
MHLCS, chance-orientation	20.8 (0.7)	18.8 ± 5.9	10,302	0.34	0.367
Participation					
Employed, *n* (%) *N*=54^b	17 (31.5)	7,873^c (71.6)	10,992^c	-	0.000^a
Quality of Life					
COOP-WONCA, physical fitness	2.7 (0.1)	2.2 ± 1.1	38	0.45	0.326
COOP-WONCA, mood	2.0 (0.1)	1.5 ± 0.7	38	0.71	0.239
COOP-WONCA, daily activities	2.1 (0.2)	1.5 ± 0.8	38	0.75	0.227
COOP-WONCA, social activities	1.7 (0.1)	1.4 ± 0.8	38	0.36	0.359

COOP-WONCA, overall health	2.7 (0.1)	2.8 ± 0.9	38	-0.11	0.456
COOP-WONCA, changes in health status	2.8 (0.1)	3.1 ± 0.3	38	-1.00	0.159
COOP-WONCA, pain	2.1 (0.2)	-	-	-	-
SF-36, physical functioning	74.7 (3.1)	85.2 ± 23.1	4,172	-0.45	0.326
SF-36, role limitation physical	64.8 (5.4)	79.5 ± 35.4	4,172	-0.42	0.337
SF-36, bodily pain	77.3 (3.4)	80.5 ± 24.4	4,172	-0.13	0.448
SF-36, general health perception	67.4 (3.0)	71.3 ± 20.8	4,172	-0.19	0.425
SF-36, energy vitality	57.8 (2.7)	68.6 ± 19.2	4,172	-0.56	0.289
SF-36, social functioning	70.4 (3.3)	85.1 ± 21.5	4,172	-0.68	0.248
SF-36, role limitation emotional	73.9 (5.2)	83.1 ± 32.7	4,172	-0.28	0.390
SF-36, mental health	71.1 (2.4)	75.9 ± 17.6	4,172	-0.27	0.394
SF-36, mental component score	46.1 (1.5)	50.0 ± 10.0	4,172	-	-
SF-36, physical component score	46.8 (1.3)	50.0 ± 10.0	4,172	-	-

[a] Significant *p*-values.
[b] Missing >65 years, *n*=6.
[c] Dutch total population (age 15-65 years) x 1,000.[24]

Changes over Time

All data of T1 and T2 were analysed to estimate the mean outcomes for the two measurement times, which are presented in Table II. Significant improvements were found in the domain body functions and structures for TMT-B (T1=119.4; T2=104.6; p=0.025), in the domain activities for BI (T1=18.5; T2=19.5; p=0.023), in the domain environmental factors for SSL-12 (T1=31.1; T2=32.7; p=0.042), and in the domain personal factors for MHLCS (physician-orientation) (T1=21.8; T2=19.2; p=0.020). For HR-QoL, the COOP-WONCA (overall health) (T1=2.3; T2=2.7; p=0.021) showed a significant decline, and the SF-36 (role limitation due to emotional problems) (T1=54.6; T2=73.9; p=0.048) showed a significant improvement. Scores on the CES-D, FSS, SIP-68, and the remaining scores on the COOP-WONCA and SF-36 remained relatively stable over time.

Comparison of A-SAH Outcomes with Norm Values

Compared with norm scores of healthy individuals, clinically significant differences were found for FSS, TMT-A, and TMT-B scores in patients with A-SAH at 4-year follow-up (T2). The patients showed higher fatigue scores and needed significantly more time to complete the TMT-A and TMT-B tasks than did healthy individuals within their age group. The proportions of depressed and fatigued patients with A-SAH also were significantly higher than in healthy groups (Table III). The variables in the domain personal factors showed no significant differences compared with the norm scores. Also, the outcomes for the domain HR-QoL were not significantly different from the norm scores, but the outcomes in Table III showed a trend toward worse outcomes for patients with A-SAH compared with the norm scores in almost all subscales of HR-QoL. Norm scores of healthy individuals were found neither for BI and SIP-68 in the ICF domain activities nor for the IPA in the domain participation. For the BI, it was assumed healthy people to reach the maximum score of 20. With a mean BI score of 19.5, some restrictions in activities of daily living were found 4 years after A-SAH. Twenty-five percent of the patients with A-SAH did not reach the maximum score of 20; some problems were found in the activity of climbing stairs (13%) and some suffered from occasional urine incontinence (15%). In the same domain, the mean SIP-68 score was significantly different from zero (p<0.001), the score assumed for healthy subjects.[23] Eighty-two percent of the patients experienced one or more problems at the SIP-68. The highest percentages of patients with problems were found in the subdomains psychological autonomy and communication (60%) and social behaviour (62%).

IPA scores were relatively low, varying from 0.6 [SE 0.7] to 1.6 [SE 0.7], indicating reasonable to good participation. Employment proportions were 71% before A-SAH, which is comparable with the total Dutch population of working age (15-65 years). Four years after A-SAH, 34% of the patients younger than 65 years were employed (Tables I and III).

DISCUSSION

Improvement was found in at least one outcome in every measured ICF domain in this long-term prospective study of patients with A-SAH. Although improvement was found for the executive functioning task TMT-B, patients with A-SAH needed significantly more time to complete this task than norms of healthy individuals. TMT-A score was stable for T1 and T2 but also significantly worse compared with the norms. This outcome also applied for fatigue, where no improvement was found in the long-term, with scores above the norm scores and the cut-off score. Depression scores showed no significant improvement over time and no differences with a healthy norm group in the long term.

However, the proportion of depressed patients was significantly higher than in a healthy population.[14] This means that a relatively large number of patients with A-SAH experience fatigue, depressive symptoms, and problems in cognitive functioning, which may persist over the years. These problems are also found separately in other studies.[2,25,26] Whether rehabilitation professionals can adapt their programs to the long-term needs of these patients remains to be investigated. In this study, approximately one-third of the sample were treated in an inpatient rehabilitation centre or nursing home.

The BI showed significant improvement over time but is too rough a measure to detect small problems and suffers from a ceiling effect, especially in long-term outcome measurement.[2] Other measurement instruments, such as the Functional Independence Measure and the Functional Assessment Measure, may have been more specific.[27] In this study, some problems were found in the activity of climbing stairs and occasional problems of urine incontinence at long-term follow-up. Whether these problems were related to the SAH remains unknown. The SIP-68 is more sensitive for health-related behavioural problems in the long term.[27] Although patients with A-SAH had significantly worse scores than healthy individuals, they had better scores than patients with ischemic stroke.[18] In 25% of the patients, some problems in self-care (BI) were found in A-SAH patients, but in 82%, behavioural difficulties were found for more specific tasks (SIP-68) in the long run, such as psychological autonomy and communication and social behaviour.

In this study, 69% of the patients younger than 65 years were not working in the long-term after the A-SAH, which is a large proportion compared with the Dutch population of working age (28.4%).[24] Vilkki et al. (2012) found 56.4% of patients with A-SAH not working in the long term after the haemorrhage, of which 20% ascribed this to their SAH.[28] They also found a higher age as the most important long-term predictor for a poor work status after A-SAH.[28] In Passier et al. (2011), 1.4% of the subjects returned to work after A-SAH, of which only 35.2% completely resumed their previous position.[29] Cognitive functioning/attention and fatigue are known predictors of work status.[25,28,29] The long-term IPA-scores in this study were higher than zero, especially for the variables 'autonomy outdoors' and 'work and education'. However, the mean scores were all relatively low, representing the categories between good and reasonable. Thus, patients in this study sample did perceive some limitations in autonomy and participation but scored within normal ranges.

The physician-oriented locus of control scale showed a decline over time, representing a decreased attribution of one's health status to the physician. Either the patient's health status has improved or he/she has learned to cope with the long-term sequelae of the A-SAH. No differences were found on the locus of control scales compared with healthy individuals. In the domain environmental factors, an improvement in the experience of social support was found, especially in the esteem support domain, which implies that self-esteem and approval are improved by the support of others.[20]

Finally, a significant improvement in HR-QoL was found in the SF-36 domain role limitations due to emotional problems and a decrease for overall health on the COOP-WONCA charts. Compared with norm scores, no significant differences were found for HR-QoL in the long term, but a trend toward decreased HR-QoL scores can be seen in almost all domains compared with normative data. The findings in the literature are also mixed. Scharbrodt et al. (2009) found lower HR-QoL in the long term for patients with SAH, but Greebe et al. (2010) found an improved HR-QoL between 5 and 12.5 years after A-SAH, which may be due to psychological adaptation.[30,31] Another plausible explanation for these differences can be the differences in case mix. Al-Khindi et al. (2010) describes severity of A-SAH at hospital admission, depression, anxiety, fatigue, neuroticism, and a passive coping style as factors that could influence HR-QoL after A-SAH.[2]

Limitations

This study has some limitations. The moment of T1 was variable and covering a phase in which spontaneous recovery is an important factor. Participation was measured only at T2. No data were available for the premorbid situation or at T1. However, despite missing data, the mean outcomes of the total study population could be reliably estimated by using mixed-model analyses. Finally, a limited number of questionnaires was used to cover all domains of the ICF model. Other studies could have used other questionnaires to describe the ICF domains and possibly found other results per domain. The original ICF model has no specific domain for HR-QoL. According to Passier et al. (2013) the ICF model was therefore expanded, with HR-QoL as an additional domain to include outcomes of HR-QoL after A-SAH.[12,32]

CONCLUSIONS

Despite the fact that many patients with A-SAH had fairly good long-term outcomes, problems in executive functioning, depression, and fatigue still exist at long-term follow-up. Whether rehabilitation services can adapt their programs to long-term needs of these patients should be studied in future research.

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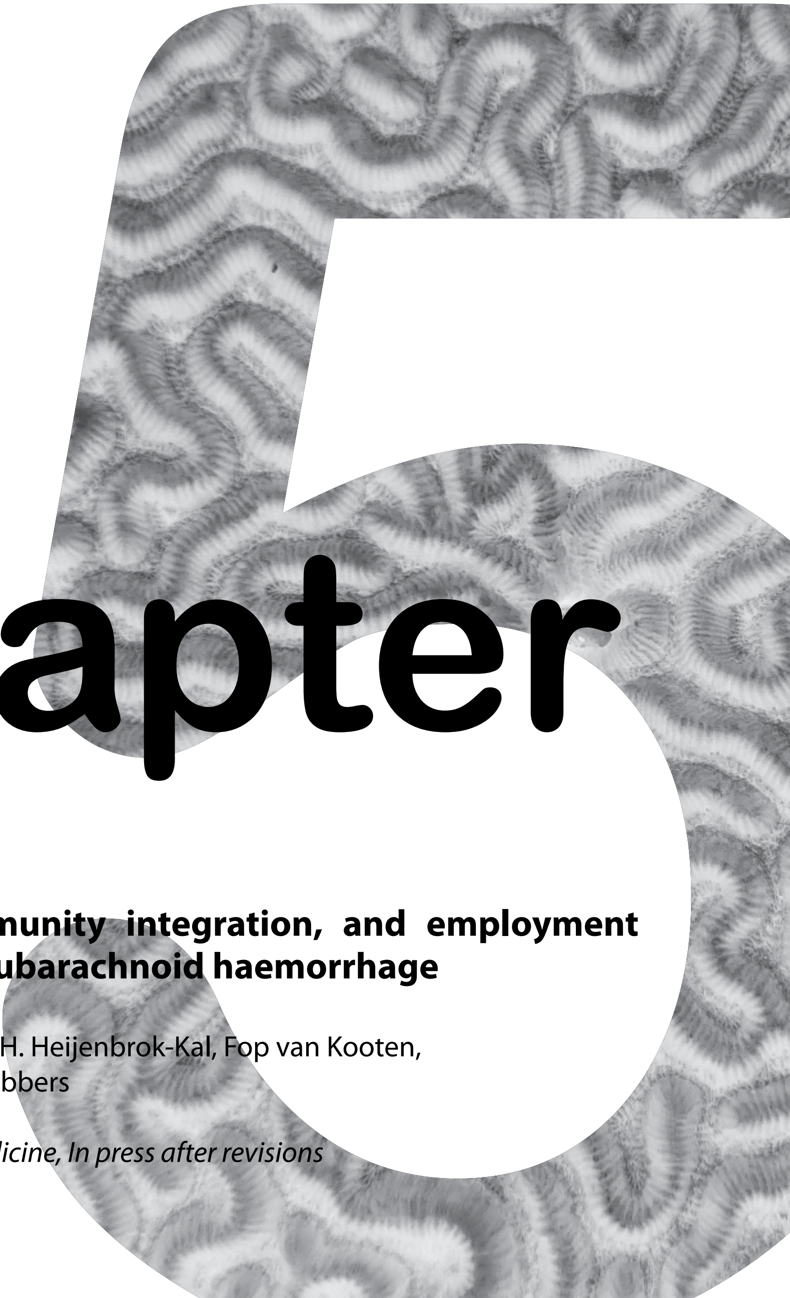
Chapter



Unmet needs, community integration, and employment status 4 years after subarachnoid haemorrhage

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ABSTRACT

Objective: To assess long-term unmet needs in relation to community integration and employment status 4 years after subarachnoid haemorrhage (SAH).
Design: Four-year follow-up of a prospective cohort.
Patients: Sixty-seven patients with SAH.
Methods: Employment status was assessed and the Community Integration Questionnaire-Revised and Southampton Needs Assessment Questionnaire were used.
Results: The mean age of SAH onset was 52.5 years (SD 10.7) and 39% were men. Four years after SAH, 23.9% had symptoms of depression, 43.3% had mild cognitive impairment, 67.2% was unemployed and 67.2% had one or more unmet needs. The need for information was mostly reported (59.7%). Unemployed patients had more unmet needs than employed patients (*p*=0.034), but no independent relationship was found. The community integration score was moderate (mean=15.1; SD=4.4). A higher level of unmet needs was independently related to a lower level of community integration (B=-0.25; *p*=0.018), adjusted for age and comorbidity.
Conclusion: The results of this study show a large proportion of patients with unmet needs and without employment 4 years after SAH, and also an inverse relation between unmet needs and community integration. Future research should investigate whether dealing with information needs during rehabilitation contributes to better community integration in these patients.

INTRODUCTION

Subarachnoid haemorrhage (SAH) accounts for 5% of all cases of stroke and is in approximately 85% of cases caused by a ruptured aneurysm in one of the cerebral vessels, called aneurysmal subarachnoid haemorrhage (A-SAH). In about 10% of the cases no aneurysm is found, and the haemorrhage is restricted to the cisterns surrounding the brainstem and the suprasellar cistern; called perimesencepahlic subarachnoid haemorrhage (PM-SAH). The remaining 5% is categorized as SAH of unknown origin.

After SAH, patients may face long-term impairments, like fatigue, cognitive disorders, mood disturbances and reduced quality of life.[3-7] The mean age of SAH onset is 50 years, which is relatively low compared to the other types of stroke which show a mean age of onset of 75 years.[8] Therefore, SAH may have a long-lasting and profound impact on social participation including return to work.[9,10] Several studies have addressed return to work (RTW) after SAH. The studies of Passier et al. (2011) and Harris et al. (2014) found that approximately 40% of the patients with A-SAH (*n*=141 and *n*=134) did not return to work 1 to 4 years after A-SAH.[10,11] Alfieri et al. (2011) found that more than 10% of the patients with non-aneurysmal SAH (a group without objective impairment) did not return to work 7 years after SAH.[12] RTW up to 8 years after different types of SAH was found to be related to marital status, age and depression.[10-12] In young stroke patients (mean age 55 years), Kersten et al. (2002) found that people unable to return to work and those with poorer mobility report most unmet needs.[13]

RTW is only one aspect of community integration. Community integration is described as participation in home, social and community activities.[14] Not much is known about community integration in patients with SAH. A recent study of Buunk et al. (2015) showed that resumption of previous leisure and social activities is seriously impaired 4 to 10 years after A-SAH. The presence of executive, cognitive and emotional problems, just as unemployment are associated with this outcome.[15] Also the study (*n*=10) by Ravnik et al. (2006) found that cognitive impairment, but also RTW were related to the level of community integration after SAH.[7] Whether patients with SAH face unmet needs in relation to RTW and community integration has not been studied before. SAH should be considered a lifelong condition rather than an incident. Therefore, more effort should be invested in optimizing long-term outcome, minimizing unmet needs and maximizing community integration.

The current study therefore focused on long-term outcome after SAH (4 years post-onset) with community integration, employment status, and the presence of unmet needs as outcomes of interest. The aim of this study was to evaluate whether patients face unmet needs 4 years after SAH onset, and whether these unmet needs are related to community integration and/or employment status.

METHODS

Participants and Procedures

All patients diagnosed with SAH, hospitalized between 2006 and 2009 at the neurology and neurosurgery department from the Erasmus University Medical Center Rotterdam, were approached for participation in a prospective cohort study with measurements within 1 and 4 years post-onset.[16] The current study focuses on the long-term outcome of this cohort. Inclusion criteria were: at least 18 years of age at onset and survival of SAH. Exclusion criteria were: serious comorbidity resulting in a short life expectancy less than 1 year and insufficient mastering of the Dutch language. Informed consent was obtained from all participants. The Medical Ethics Committee of the Erasmus MC approved the study.

Data collection

During hospitalization baseline socio-demographic data and clinical characteristics were collected by the staff of the neurology and neurosurgery departments, including origin of SAH and severity of SAH using the World Federation of Neurological Surgeons (WFNS) grading scale. A trained research psychologist visited the patients at home to collect additional measurements 4 years post-onset. A structured interview was performed to collect data on current employment status. Patients were classified as employed if they had a paid full-time or part-time job. Patients were defined as not employed if they did not have a paid job, only performed unpaid volunteer work, were students, or were retired.

Measurement instruments

The Community Integration Questionnaire (CIQ) measures community integration based on three subscales: Home competency, Social integration, and Productivity activity. We used the revisited CIQ scale with 13 questions based on the article of Sander et al. (1999).[17] Each question was scored on a three-point rating scale ranging from 0 to 2, with a total score range of 0-25. A high score indicates a high level of community integration.[17,18] The CIQ was originally developed for patients with traumatic brain injury, but the psychometric properties have also been evaluated in stroke patients with aphasia. The internal consistency (Cronbach's α=0.75) is good, and the test-retest reliability (Intraclass Correlation coefficient =0.96) is excellent.[19]

The summary section of the Southampton Needs Assessment Questionnaire (SNAQ) was used to assess the unmet needs of patients after SAH. Patients fill in which unmet need they face in dealing with the consequences of their SAH. The SNAQ consist of 66 items divided over 10 domains (information, mobility, social activities, work or training, family, voluntary organizations, finances, housing, formal health services, formal social services). Possible responses are yes (score 1) and no/not applicable (score 0). A total score is calculated. Higher scores indicate more unmet needs. The questionnaire is validated in a group of disabled people including patients with stroke.[20]

The Center for Epidemiological Studies Depression scale (CES-D) was used to measure symptoms of depression. The CES-D is a 20-item scale, and is validated in stroke patients.[21] Scores range from 0 to 60 and the higher the score, the more depressive symptoms are present. Scores of 16 or higher are an indication for the presence of depression.[21-23]

Comorbidity was measured with the Cumulative Illness Rating Scale (CIRS). This list consists of 14 disorders and diseases, rated on a 5 point rating scale, ranging from 0 (disorder/disease not present) to 4 (life-threatening disorder/disease present).[24]

The Coping Inventory for Stressful Situations (CISS) measures multidimensional coping, by asking the respondents how they generally react to stressful situations. The CISS exists of 48 items which can be answered on a 5-point scale from not at all to very strong. Scores can be calculated for three scales, each existing of 16 items with a maximum score of 80: task-oriented coping, emotion-oriented coping and avoidance-oriented coping.[25]

The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive dysfunction. It contains 11 tasks focused on the different domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum attainable score is 30 with a cut-off score of >26 considered as normal.[26] The following ranges may be used to grade severity: 18-26 = mild cognitive impairment, 10-17 = moderate cognitive impairment and less than 10 = severe cognitive impairment.[27]

The Trail Making Test (TMT), was used to measure cognitive functioning on the domains speed of information processing (part A) and divided attention (part B). The measured time to complete the task (with a maximum of 180 seconds), including extra time for correcting potential errors, was recorded to calculate a time score.[28]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (SPSS Inc, Chicago, USA). Descriptive statistics were used to describe the characteristics of the total study sample and subgroups of employed and unemployed patients. Means and standard deviations were calculated for interval variables and numbers and percentages for categorical variables. Independent-samples *t*-tests and χ^2 were used to test differences between the employed and the unemployed subgroups.

To investigate relationships between patient characteristics (age, gender, living with a partner, and education), clinical characteristics (SAH type, Length of Stay, and WFNS grade) and outcome variables (CIRS, CES-D, MoCA, CISS and SNAQ) with the dependent variable community integration (CIQ), univariable and multivariable regression analysis were performed. To investigate the same variables in relation to the dichotomous variable employment status, univariable and multivariable logistic regression analyses were performed. A significance level of $p<0.05$ was used to select variables from the univariable regression analyses, which were entered in the multivariable regression models using a forward selection procedure.

RESULTS

Study population

A total of 96 out of 228 consecutive patients with SAH, who were hospitalized in the neurology and neurosurgery departments of the Erasmus MC between April 2006 and August 2009 agreed to participate in the study. Of these, 67 patients participated in the 4-years follow-up measurement with a mean time of 3.9 (SD 0.8) years after SAH. The flow of patients is presented in Figure. 1. Three patients were excluded for the long-term follow-up for the following reasons: 1 patient did not comprehend the questionnaires, 1 patient moved abroad, and 1 patient recently had a recurrent stroke. Five patients were untraceable or could not be contacted and were considered lost to follow-up.

The mean age of the study population was 52.5 years (SD 10.7) and 39% were men. The majority of patients had an aneurysmal SAH (88%), and 23.9% was classified with a poor WFNS grade (grade 3-5). Patient characteristics for the total and subgroups are presented in Table I. Four years after SAH, 67.2% of the sample was unemployed. The subgroup of unemployed patients contained significantly more women, were older, had less years of education, had a longer length of hospital stay, and more surgical procedures compared to employed patients (Table I).

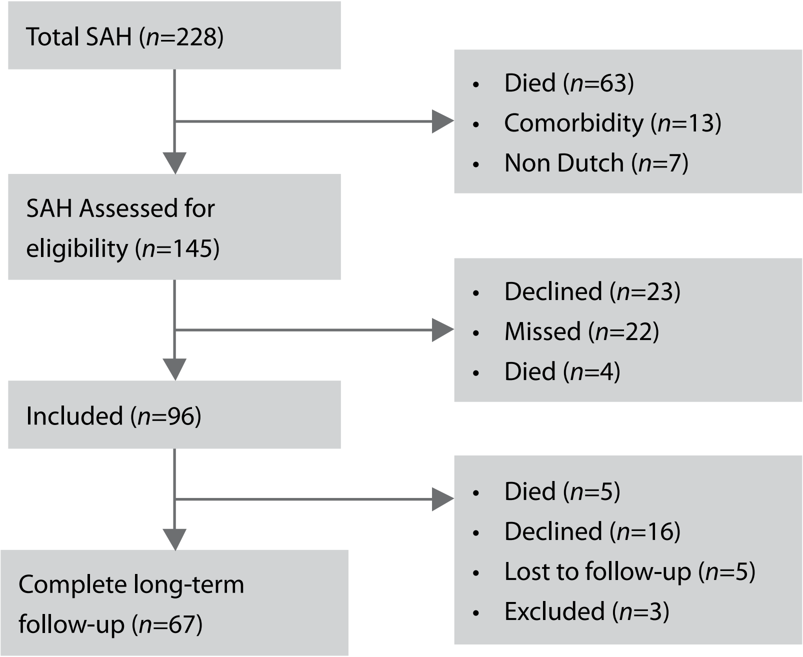

Figure 1. Flow of patient inclusion.

Table I. *Demographic and clinical patient characteristics for employed and unemployed patients (N=67).*

	Total group 67 (100%) *N%*	**Employed 22 (32.8%) *n%***	**Unemployed 45 (67.2%) *n%***
Age (years), mean ± SD	52.5 ± 10.7	45.0 ± 8.8	56.2 ± 9.6*
Gender (men)	26 (38.8)	14 (63.6)	12 (26.7)*
Living together with a partner (yes)	48 (71.6)	17 (77.3)	31 (68.9)
Education (years)	12.9 ± 3.9	14.4 ± 3.6	12.2 ± 3.8*
Employed before SAH (*n*=56)	37 (63.8)	15 (83.3)	22 (57.9)
SAH type (aneurysmal)	59 (88.1)	17 (77.3)	42 (93.3)
Length of hospital stay (days), mean ± SD	15.7 ± 10.4	10.9 ± 6.0	18.1 ± 11.3*
Severity of SAH (WFNS)			
Grade 1	36 (53.7)	15 (68.2)	21 (46.7)
Grade 2	15 (22.4)	4 (18.2)	11 (24.4)
Grade 3	3 (4.5)	1 (4.5)	2 (4.4)
Grade 4	5 (7.5)	0 (0.0)	5 (11.1)
Grade 5	8 (11.9)	2 (9.1)	6 (13.3)
SAH treatment			*
Coiling	41 (61.2)	13 (59.1)	28 (63.6)
Clipping	15 (22.4)	3 (13.6)	12 (27.3)
Other	2 (3.0)	0 (0.0)	2 (4.5)
No treatment	8 (11.9)	6 (27.3)	2 (4.5)
Discharge destination			
Home	40 (59.7)	17 (77.3)	23 (51.1)
Outpatient rehabilitation	10 (14.9)	3 (13.6)	7 (15.6)
Inpatient rehabilitation	14 (20.9)	2 (9.1)	12 (26.7)
Nursing home	3 (4.5)	0 (0.0)	3 (6.6)

SAH: Subarachnoid Haemorrhage; WFNS: World Federation of Neurosurgical Societies; CIRS: Cumulative Illness Rating Scale. Missings: Employed before SAH, *n*=11

* Significant difference between employed and unemployed subgroups (*p*<0.05)

Unmet Needs

Two-thirds of the patients (67.2%) experienced one or more unmet needs 4 years after SAH, with a mean number of unmet needs of 3.5 (SD 4.7). The unmet needs were divided into 10 domains, with the highest proportions of patients with unmet needs found in the domains information (59.7%), formal social services (20.9%), and mobility (19.4%). The proportions for each domain are presented in Figure 2.

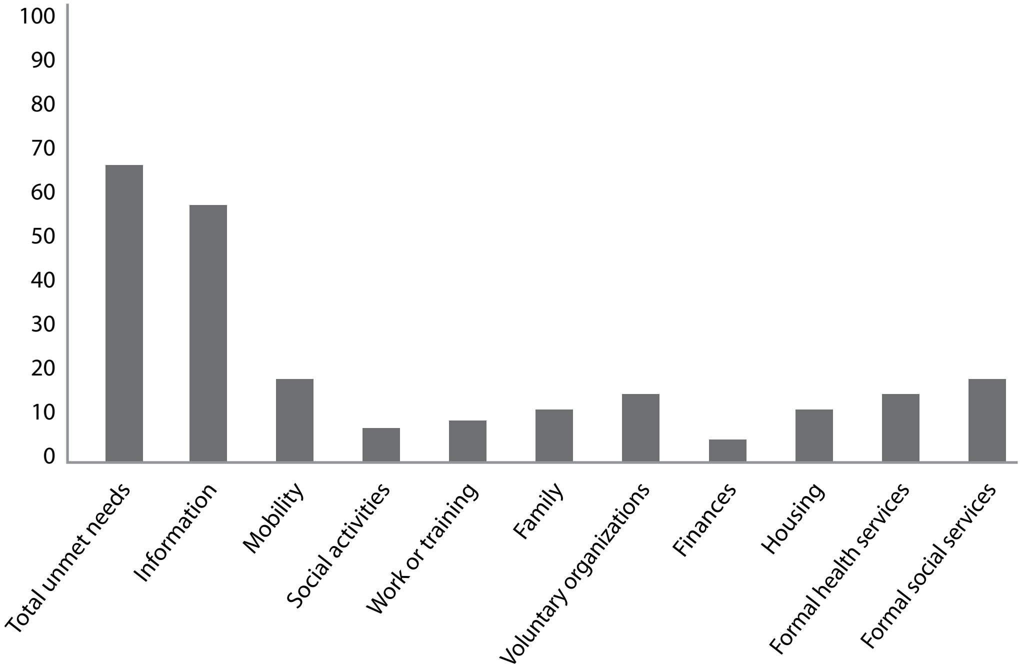

Figure 2. Proportions of patients with unmet needs for each domain.

Differences in outcome between employed and unemployed patients

After 4 years, depression was found in 23.9% and (mild) cognitive impairment in 43.3% of the total study sample. Unemployed patients had significantly more symptoms of depression (mean=13.0; SD=10.5 vs mean=6.2; SD=4.2) and used a more emotion-oriented coping style (mean=33.9; SD=10.1 vs mean=28.5; SD=8.2). Unemployed patients also scored worse on the cognitive screening test MoCA (mean=24.7; SD=2.9 vs mean=26.7; SD=2.8) than employed patients and needed more time to complete the cognitive functioning tasks of information processing TMT-A (mean=50.3; SD=29.8 vs mean=33.0; SD=12.3) and divided attention TMT-B (mean=110.9; SD=44.7 vs mean=73.7; SD=28.9). Moreover, unemployed patients had a lower community integration score (mean=14.0; SD=4.1 vs mean=17.5; SD=4.2), and more unmet needs (mean=4.3; SD=5.5 vs mean=2.2; SD=2.1) than employed patients. The subgroup outcomes are presented in Table II. Multivariable logistic regression analysis showed that female gender, higher age of onset, higher depression score (CES-D) and worse cognitive functioning (MoCA) were independently associated with unemployment 4 years after SAH (Table III).

Table II. *Demographic and clinical patient characteristics for employed and unemployed patients (N=67).*

	Employed ***n*=22** **Mean ± SD**	**Unemployed** ***n*=45** **Mean ± SD**	***p*-value**
Comorbidity			
Comorbidity score (CIRS)	5.3 ± 3.6	7.2 ± 4.8	0.098
Depression			
Depression score (CES-D)	6.2 ± 4.2	13.0 ± 10.5	**<0.001**
Depressed (CES-D >16), *n* (%)	1 (4.5)	15 (33.3)	**0.009**
Coping (CISS)			
Task-oriented coping	53.8 ± 9.7	50.4 ± 13.0	0.277
Emotion-oriented coping	28.5 ± 8.2	33.9 ± 10.1	**0.034**
Avoidance-oriented coping	38.1 ± 11.3	36.4 ± 11.0	0.560
Cognitive Functioning			
Cognitive Functioning score (MoCA)	26.7 ± 2.8	24.7 ± 2.9	**0.010**
Mild cognitive impairment (18-26), *n* (%)	10 (45.5)	34 (75.6)	**0.015**
Attention and Concentration			
Trail Making Test, part A	33.0 ± 12.3	50.3 ± 29.8	**0.002**
Trail Making Test, part B	73.7 ± 28.9	110.9 ± 44.7	**<0.001**
Community Integration (CIQ)			
Total score	17.5 ± 4.2	14.0 ± 4.1	**0.002**
Home Competency score	6.1 ± 3.0	6.4 ± 2.6	0.693
Social Integration score	7.7 ± 2.0	6.5 ± 2.3	**0.035**
Productive Activity score	3.6 ± 0.8	0.9 ± 1.5	**<0.001**
Unmet Needs (SNAQ)			
Total unmet needs	2.2 ± 2.1	4.3 ± 5.5	**0.034**

CIRS: Cumulative Illness Rating Scale; CES-D: Center for Epidemiological Studies Depression scale; CISS: Coping Inventory for Stressful Situations; MoCA: Montreal Cognitive Assessment CIQ: Community Integration Questionnaire; SNAQ: Southampton Needs Assessment Questionnaire;

Table III. *Variables associated with unemployment 4 years after SAH.*

	Unemployment			
	B	***p*-value**	**OR**	**95% CI**
Age (at onset)	0.169	0.008	1.184	1.20-1.31
Gender (women vs men)	2.567	0.002	13.030	1.96-86.70
Depression score (CES-D)	0.118	0.031	1.126	1.01-1.25
Cognitive Functioning score (MoCA)	-0.338	0.036	0.713	0.52-0.99

CES-D: Center for Epidemiological Studies Depression scale; MoCA: Montreal Cognitive Assessment; OR odds ratio; CI confidence interval.

Community integration

The mean Community Integration score was 15.2 (SD 4.4) out of a maximum score of 25. None of the patients reached the maximum score of 25, and 50% of the patients scored between 12 and 19. Highest scores were found in the subdomains Home Competency (mean=6.3; SD=2.7) and Social Integration (mean=6.9; SD=2.3) and a relatively low score was found in the subdomain Productive Activity (mean=1.8; SD=1.8). Table II presents the scores per subgroup of employment status.

Age, comorbidity score, depression score, divided attention score (TMT-B), and unmet needs score were significantly associated with community integration (Table IV). Multivariable linear regression analyses showed that an higher age of onset (B=-0.17; $p<0.001$), higher comorbidity score (B=-0.25; $p=0.023$), and more unmet needs (B=-0.25; $p=0.018$) were independently related to a lower community integration score ($R^2=0.32$).

Table IV. *Variables associated with community integration.*

	Community Integration score			
	Univariable		Multivariable	
	B	*p*-value	B	*p*-value
Age (at onset)	-0.16	**0.002**	-0.17	**<0.001**
Gender (men)	-0.14	0.200		
Living with a partner (yes)	-1.07	0.384		
Education (years)	-0.08	0.546		
SAH type (aneurysmal)	-1.23	0.463		
Length of stay (days)	-0.02	0.666		
WFNS grade (good vs poor)	0.83	0.529		
Comorbidity (CIRS)	-0.38	**0.001**	-0.25	**0.023**
Depression score (CES-D)	-0.15	**0.016**	-	ns
Cognitive Functioning score (MoCA)	0.31	0.104		
TMT-A	-0.29	0.161		
TMT-B	-0.33	**0.010**	-	ns
Task-oriented coping (CISS)	0.08	0.104		
Emotion-oriented coping (CISS)	-0.04	0.514		
Avoidance-oriented coping (CISS)	0.09	0.085		
Unmet Needs (SNAQ)	-0.24	**0.041**	-0.25	**0.018**

CIQ: Community Integration Questionnaire; CISS: Coping Inventory for Stressful Situations; SNAQ: Southampton Needs Assessment Questionnaire; CIRS: Cumulative Illness Rating Scale; CES-D: Center for Epidemiological Studies Depression scale; MoCA: Montreal Cognitive Assessment; ns: non-significant

DISCUSSION

Four years after SAH 67.2% of patients were unemployed, 67.2% reported unmet needs, and the mean score for community integration was 15.2 (SD 4.4). Unmet needs were inversely related to community integration. The high proportion of unmet needs is comparable to figures found in young stroke survivors >1 year after stroke.[13,29] The highest proportion was found for unmet information needs; almost 60% of the patients indicated one or more unmet needs in this category. Low et al. (2003) and Kersten et al. (2002) also found provision of information about strokes to be the most frequently reported unmet need in young stroke patients.[13,29] Despite the availability of patient information about stroke on websites, booklets and patient forums, specific information for the subgroup of patients with SAH may be lacking.[13] Because the general stroke group is older, the information given may not apply to younger SAH patients.[30] Therefore, future research should reveal whether tackling unmet needs, specifically with regard to information on the causes, consequences and prevention of SAH, may be beneficial for patients with SAH.

We showed that the unmet needs score was independently associated with community integration 4 years after SAH. The total community integration score of 15.2 (SD 4.4) in the current study is somewhat higher than for example the scores found in patients with TBI (mean=14.3; SD=5.52), brain tumours (mean=13.3; SD=5.54) and neurological/ neuropsychiatric disorders (mean=12.6; SD=4.23).[17,31,32] Equivalent scores were found on the Social Integration scale across these samples. On the Home Competency scale we found higher scores in SAH patients compared to TBI patients. This may possibly be explained by gender differences between the patient populations; 60% of SAH patients is female, whereas 75% of TBI patients is male. Women appear to have significantly higher scores on the Home Competency scale than men.[32] In our study, only 32.8% of patients were employed 4 years after SAH. Comparable proportions of long-term employment after SAH (35-44%) were found in other studies.[13,15,33] The employment proportion in our study cannot be compared with return-to-work proportions in some other studies, in which only previously employed persons are selected. For example, Passier et al. (2011) found that 61.4% of previously employed patients with SAH returned to work, of which only 35.1% had completely resumed their former work within 2 to 3 years follow-up.[10] In line with Kersten et al. (2002), we found that unemployed patients reported more unmet needs than employed patients.[13] Moreover, we showed that unemployed patients had worse cognitive functioning scores than employed patients, which is also in accordance to other studies.[7,33] Although we did not find an independent relationship between unmet needs and employment status, we did find that the level of unmet needs was independently related to the level of community integration.

Likewise, we found that older patients showed lower levels of community integration. A similar age effect was found in patients with TBI and adults with neurological/ neuropsychiatric disorders.[32,34] As patients with SAH are usually older than TBI patients, the total community integration score can be assumed to be fairly good. However, compared to controls or to retrospectively obtained pre-TBI total scores, patients with SAH do show restrictions in community integration.[18,34] Comorbidity score was also related to community integration. This is in line with Carter et al. (2000), who described depression and physical disability as important factors associated with impaired overall reintegration 1-6 years post SAH and with Baseman et al. (2010), who found that functional status, depression and overall stroke recovery were related to social integration >6 months after ischemic stroke.[35,36] These studies show that limitations both in physical and psychosocial health are barriers to community integration.[35]

Limitations

This study has some limitations. First of all, the lack of appropriate norm scores for CIQ-Revised made it difficult to draw conclusions from these scores. Further, no causal relationships could be established, because all outcome variables are measured at the same point in time. Finally, due to the relatively small number of patients, the number of variables that could be included in the regression analyses was limited.

CONCLUSION

The results of this study suggest that 4 years after SAH a large proportion of patients is unemployed and faces unmet needs with an inverse relationship between unmet needs and community integration. Future research should investigate if dealing with unmet needs, by for example expanding and improving information services, especially for patients with SAH, contributes to a better community integration of these patients.

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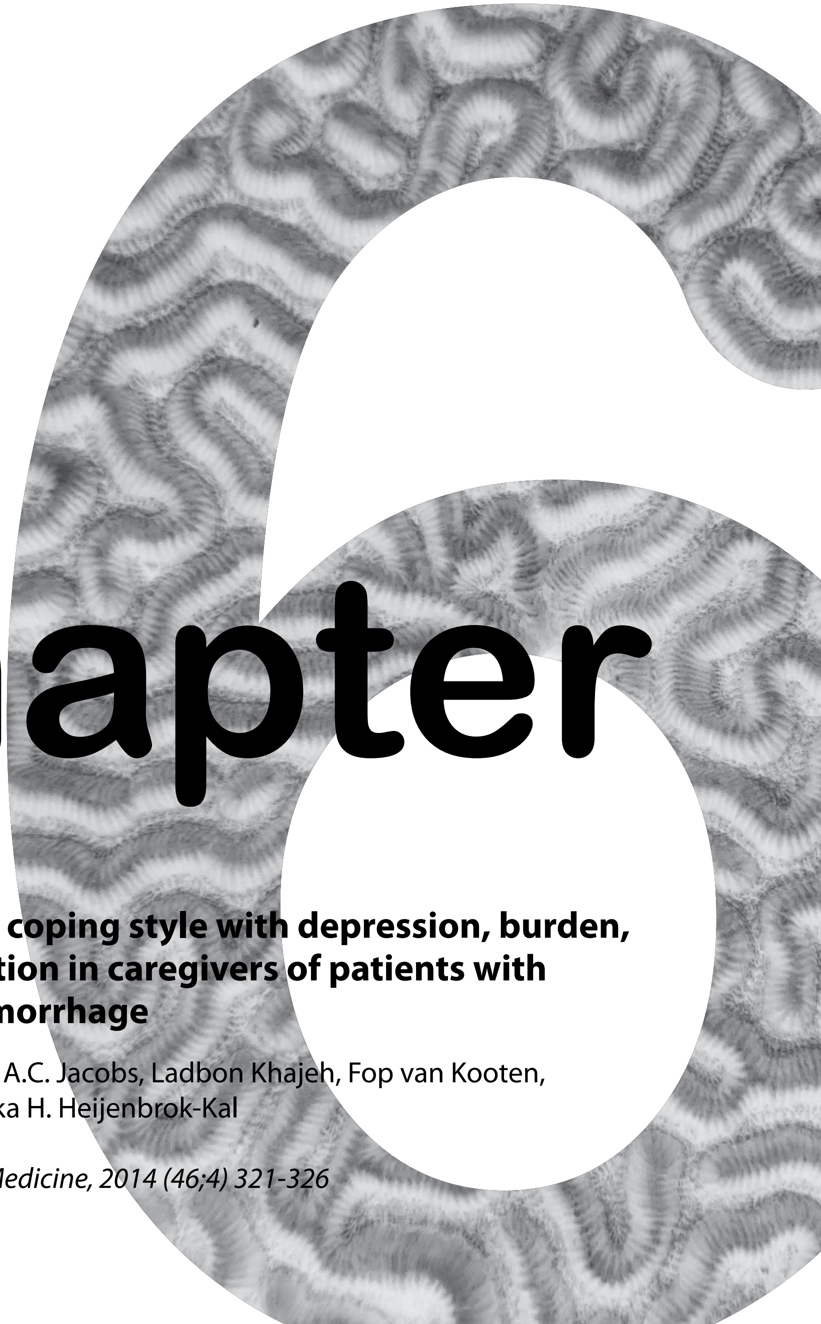

Chapter 6

The relationship of coping style with depression, burden, and life dissatisfaction in caregivers of patients with subarachnoid haemorrhage

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ABSTRACT

Objective: To assess the relationship of coping style with depression, burden and life satisfaction in caregivers of patients with subarachnoid haemorrhage.
Design: Cross-sectional study.
Participants: Forty-one primary caregivers of patients with subarachnoid haemorrhage.
Methods: Caregivers completed several questionnaires within the first year after subarachnoid haemorrhage. Coping style was assessed using the Utrecht Coping List, depression with the Goldberg Depression Scale (GDS), burden with the Sense of Competence Questionnaire, and life satisfaction with the Life Satisfaction Questionnaire.
Results: Caregivers had a mean burden score of 37.8 (SD 7.4) and a life satisfaction score of 5.0 (SD 0.6). Nine caregivers (23%) had depressive symptoms (GDS≥2). A palliative coping style was positively associated with the presence of depressive symptoms (OR=1.45; *p*=0.016). A passive coping style was positively related to burden (ß=1.61; *p*=0.024), adjusted for morbidity of the caregiver (ß=11.90; *p*=0.013), and inversely related to life satisfaction (ß=-0.10; *p*=0.025).
Conclusion: In caregivers of patients with subarachnoid haemorrhage palliative or passive coping styles are related to depressive symptoms, higher burden and life dissatisfaction. This implies that rehabilitation programmes for patients with subarachnoid haemorrhage should also include caregiver support programmes that focus on coping style.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is a subtype of stroke, which accounts for 5% of all cases of stroke. SAH is caused, in approximately 85% of cases, by a ruptured aneurysm in one of the cerebral vessels. The incidence of SAH in the Netherlands is 5.7 for men and 9.9 for women per 100,000 persons per year.[1,2] Compared with stroke in general, SAH occurs at a fairly young age: 50% of patients are younger than 55 years of age.[3] Three months after SAH, 47% of patients experience mild cognitive impairments, 25% severe cognitive deficits and 40% depressive symptoms.[4] One to 5 years after SAH, even in patients with good and fair recovery (Glasgow Outcome Score 5 and 4, respectively), there can still be cognitive deficits in all neuropsychological domains, with a high percentage of patients experiencing depression and reduced life-satisfaction.[5] In research SAH is often clustered with other forms of stroke, therefore it is difficult to distinguish the unique consequences of this subtype.[6]

Persistent psychosocial consequences are reported by the primary caregivers of patients with SAH, affecting quality of life, personal lives, family relations, financial situation and mood. Hop et al. (1998) and (2001) found that after 4 months, and even after 18 months, SAH had considerable impact on the quality of life of the partners.[7,8] Buchanan et al. (2000) studied patients with SAH who underwent surgery.[9] Their relatives reported psychological distress and 66% reported moderate or high levels of family burden.[9] Forty percent of caregivers found it easier to deal with the initial crisis than to cope with the consequences after hospital discharge.[10] Financial problems are reported by one-third of caregivers.[10] Two to 3 years after SAH, 54% of caregivers experienced social or emotional stress.[11] A study by Noble et al. (2008) showed that 3.5 months after SAH, almost 26% of caregivers had post-traumatic stress disorder (PTSD).[12] Because caregivers play an important role in the recovery of a patient with SAH (e.g. in maintaining treatment and emotional support), the consequences above imply that post-acute rehabilitation after SAH should focus not only on the patient but also on his or her caregiver.[7-11] To our knowledge there is no literature about specific caregiver support programmes for caregivers of patients with SAH.

Little is known about coping in relation to psychosocial functioning of the primary caregivers of patients with SAH. There is evidence that a passive coping style is related to quality of life and burden in acquired brain injury (ABI) in general, and more specifically, in stroke and traumatic brain injury (TBI) populations.[13-17] Only one study of caregivers of patients with SAH was found: Noble et al. (2008) concluded that maladaptive coping strategies seem to be a predictor of PTSD in caregivers of patients with SAH.[12] This study also suggests that these caregivers need greater attention and support, for example, by teaching them better coping strategies.

Another reason for studying caregivers of patients with SAH is that they differ from caregivers of patients with general stroke. Caregivers of patients with SAH are much younger and in different stage of life when the haemorrhage occurs compared with caregivers of patients with other types of stroke.[18] In order to improve caregiver support programmes, it is important to understand which caregivers are at risk of long-term psychosocial distress. If the coping style of the caregiver relates to psychosocial distress and quality of life, training active coping styles could be a target for improving caregiver support programmes. The current study therefore assesses the relationship of the caregiver's coping style with depression, burden and quality of life of primary caregivers of patients with SAH.

METHODS

Participants

Between May 2006 and May 2009 patients diagnosed with SAH, admitted to the neurology or neurosurgery department of the Erasmus University Medical Center Rotterdam (Erasmus MC), and their primary caregivers were asked to participate in a prospective cohort study on long-term functional outcome after SAH. This study in caregivers is a cross-sectional substudy of a longitudinal study in patients with SAH. Patients were included if they were diagnosed with SAH and were 18 years of age or older. Caregivers were included if they were the primary caregiver of the patient and if they were at least 18 years of age. Exclusion criteria for patients and caregivers were: inability to complete the questionnaires because of aphasia or cognitive impairment, no mastery of the Dutch language, or a short life expectancy (less than 1 year) due to comorbidity. Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the Erasmus MC.

Data collection

Clinical characteristics and socio-demographic data of the patients with SAH were collected during hospital stay by the staff of the neurology or neurosurgery department. Within one year post-onset, patients and their primary caregivers were visited at home by a trained research psychologist to complete a set of validated questionnaires. Data collected from the caregivers were: age, gender, education level and morbidity. Morbidity of the caregiver is designed as a dichotomous variable where the caregiver was asked if he or she had health problems and/or relational stressors requiring treatment. The outcome measures assessed with validated questionnaires included depression, quality of life, coping style, and burden.

Measurement instruments

Glasgow Coma Scale (GCS) scores were collected as a measure of the severity of the patients' SAH. The GCS score is composed of 3 components of impaired consciousness and coma: motor response, verbal response and eye opening. The total score ranges from 3 to 15, of which the higher scores represent a higher level of consciousness.[19] The GCS scores, in combination with absent or present motor deficits, are transformed into World Federation of Neurological Surgeons (WFNS) scales, which is a universal SAH grading scale in 5 categories, ranging from 1 (no symptoms) to 5 (severe symptoms).[20,21] The Barthel Index (BI) was used to measure physical functioning of the patient based on the independence of performing activities of daily living; it ranges from 1 (severe disabilities) to 20 (without disabilities).[22] The Mini-Mental State Examination (MMSE) was used to evaluate cognitive functioning of the patient.[23]

The Goldberg Depression Scale (GDS) was used to assess symptoms of depression in the primary caregivers of patients with SAH. This scale consists of 9 questions with yes/no answers and has a total score range of 0-9, with higher scores indicating more depressive feelings. A cut-off score of 2 or more has been found to yield good specificity (93%) and sensitivity (85%) in terms of assessing depression in a general population.[24]

The Sense of Competence Questionnaire (SCQ) was used to assess the burden of the caregivers. This questionnaire has been proven to be a reliable and valid instrument for assessing the burden of care-giving as experienced by caregivers of patients with stroke.[25] The SCQ consists of 27 items on 3 subscales: satisfaction with the patient as a recipient of care (7 items), satisfaction with one's own performance as a caregiver (12 items) and consequences of involvement in care for the personal life of the caregiver (8 items). Each item was graded on a 4-point rating scale, ranging from 1 to 4. The burden scores for the total and the 3 subdomains are represented as the sum of the item scores. The total score ranges from 27 to 108, with a higher score representing a higher level of perceived burden.[26] To differentiate between high and low burden, we used a cut-off score of >42 for high burden. This cut-off score is based on the description of normal cognitive functioning given by Scholte op Reimer et al. (1998).[25]

Life satisfaction was measured with the Life Satisfaction Questionnaire (LiSat-9). This questionnaire consists of 9 items: satisfaction with life as a whole, and 8 life domains. The scores range from 1 (very dissatisfying) to 6 (very satisfying). Scores of 1-4 depict degrees of dissatisfaction, and scores of 5-6 depict degrees of satisfaction. The total score consists of the mean of all 9 items scores and has shown good internal consistency and reliability (Cronbach's alpha coefficient = 0.82).[15,27,28] The Dutch version has been validated in an ABI population.[29]

Coping style was measured with the Utrecht Coping List (UCL), a questionnaire with an acceptable internal reliability and test-retest correlation. The UCL has 44 items in 7 subscales, each representing a coping strategy. Caregivers have to respond to the question "How often do the following behaviours apply to you?" by answering on a 4-point scale from never (1) to very often (4). The 7 subscales are: "Passive" (7 items), which includes isolating oneself from others, worrying about the past and taking refuge in fantasies; "Active confronting" (7 items), described as tackling a problem at once, seeing problems as a challenge and remaining calm in difficult situations; "Palliative" (8 items), which represents seeking distraction by trying to relax, going out or decreasing pressure by smoking or drinking alcohol; "Seeking social support" (6 items), which includes asking for help and sharing worries with someone; "Avoiding" (8 items), which means to let things take their course and wait to see which way the wind blows; "Expressing emotions" (3 items), which represents showing anger and letting off steam; and "Reassuring thoughts" (5 items) to encourage and telling oneself that everything will be alright. Sum scores were used per subscale.[30,31]

Data analysis

Statistical analyses were performed using SPSS version 19 (SPSS Inc, Chicago, USA). Descriptive analyses were used to express the patient and caregiver characteristics. The coping style mean scores were compared with the normal ranges in the norm tables (I and II) in the UCL manual.[30] Multivariate linear and logistic regression analyses were performed to estimate the relation of coping style with depression, burden and life satisfaction in caregivers of patients with SAH. The model assumptions of linearity, normality and homoscedasticity were checked. Because the residuals of the depression variable were not normally distributed, due to the high number of zero scores, this variable (GDS) was dichotomized into yes/no for the presence of depression, based on the cut-off score of 2. The relation of coping style with the presence of depression was assessed with a logistic regression analysis, and burden and life satisfaction were analysed using linear regression analyses. The following potential confounders were taken into account: the severity of SAH of the patient measured with the GCS, and age, gender, education level and presence of morbidity of the caregiver.

First, each variable was analysed separately with univariate regression analysis. If a significant relationship was found at a *p*-value<0.05, the variable was entered into a multivariate regression analysis using forward variable selection. If the *p*-value was >0.10 the variable was removed from the multivariate regression model.

RESULTS

Patient and caregiver characteristics

During the inclusion period, a total of 228 patients with SAH were admitted to the neurology or neurosurgery department of the Erasmus University Medical Center, of which, 63 patients died. All 165 surviving patients were asked to participate in the study before hospital discharge. Of these, 20 patients refused to participate, 30 did not meet the inclusion criteria and 48 were discharged before informed consent was obtained. A total of 67 SAH patients agreed to take part in the study. The primary caregiver of each included patient was also asked to participate in the study. Of these, 41 (61%) agreed to participate. The caregiver study population mainly consisted of spouses (*n*=35; 85%), with the remainder comprising of children (*n*=3; 7%) or parents (*n*=3; 7%) of the patients. The majority of the caregivers were men (59%). Ages ranged from 27 up to 79 years (mean=56.3; SD=13.4). The patient and caregiver characteristics are shown in Table I.

Outcomes of the caregivers

Caregivers were measured within 1 year after patients' SAH (mean=4.4 months; SD=3.8). Nine caregivers (23%) were classified as depressed (GDS≥2). The mean score on the LiSat-9 of 5.0 (SD 0.6) indicates that, in general, the caregivers were satisfied with life. Ten caregivers (28%) scored <5, indicating they were dissatisfied with life. Of the SCQ there were only 21 complete questionnaires, because this test was added later during the study. Of these 21 caregivers, 6 (29%) scored higher than 42, which indicates that they experienced high burden. All coping style subscores were in the normal ranges of age norm groups as described in the UCL manual.[30] All total mean scores and frequencies of these caregiver outcomes are shown in Table II.

Table I. *Patient and caregiver characteristics (n=41)*

	n (%)	Mean (SD)	Median (IQR)
Patient characteristics			
Age, years		54.8 (12.0)	
Gender, male	16 (39)		
Time post-SAH, months		6.8 (10.5)	
Type of SAH			
Aneurysmal	37 (90)		
Perimesencephalic	4 (10)		
WFNS grade			
Grade 1	22 (54)		
Grade 2	11 (27)		
Grade 3	0 (0)		
Grade 4	4 (10)		
Grade 5	4 (10)		
Treatment SAH			
Clipping	12 (29)		
Coiling	23 (56)		
Other	6 (15)		
Discharge destination			
Home	30 (73)		
Inpatient rehabilitation centre	6 (15)		
Nursing home	4 (10)		

Other	1 (2)		
GCS		13.2 (3.3)	15 (13-15)
Barthel Index		18.8 (2.2)	20 (19-20)
Depression Score (CES-D)		12.1 (9.2)	10 (4.8-17.8)
MMSE (total score)		26.7 (3.8)	28 (25.5-29.4)
Caregiver characteristics			
Age, years		56.3 (13.4)	
Gender, male	24 (59)		
Relation to the patient			
Partner	35 (85)		
Parent	3 (7)		
Child	3 (7)		
High education	12 (29)		
Employed	15 (37)		
Morbidity	5 (12)		

SAH: subarachnoid haemorrhage; WFNS: World Federation of Neurological Surgeons Scales; GCS: Glasgow Coma Scale score; CES-D: Center for Epidemiologic Studies - Depression Scale score; MMSE: Mini-Mental State Examination; SD: standard deviation; IQR: inter quartile range.

Table II. *Outcomes for caregiver depression, burden, life satisfaction and coping strategy (n=41)*

Outcome	*n* (%)	Mean (SD)	Median (IQR)
GDS (0-9)		1.0 (2.0)	0 (0-1)
Depression (GDS≥2)	9 (23)		
SCQ total (27-108)		37.8 (7.4)	35 (32-44)
Satisfaction as recipient (7-28)		9.1 (1.8)	9 (8-10)
Satisfaction with own performance (12-48)		16.4 (4.9)	15 (13-19)
Consequences of involvement (8-32)		12.3 (3.6)	12 (9-16)
Presence of burden (SCQ>42)	6 (29)		
LiSat-9 (1-6)		5.0 (0.6)	5.2 (4.9-5.4)
Dissatisfied (LiSat-9<5)	10 (28)		
UCL			
Active (7-28)		18.8 (3.4)	19 (16-21)
Palliative (8-32)		16.4 (2.9)	16 (14-17)
Avoiding (8-32)		14.4 (3.2)	14 (12-16)
Seeking social support (6-24)		12.7 (2.3)	12.5 (11-15)
Passive (7-28)		10.6 (2.3)	10 (9-12)
Expressing emotions (3-12)		5.6 (1.3)	6 (5-6)
Reassuring (5-20)		12.4 (1.9)	12 (11-14)

Missing data: GDS: *n*=2, SCQ: *n*=20, LiSat: *n*=5, UCL: *n*=1.
SAH: subarachnoid haemorrhage; UCL: Utrecht Coping List; GDS: Goldberg Depression Scale; SCQ: Sense of Competence Questionnaire; LiSat-9: Life Satisfaction Questionnaire; SD: standard deviation; IQR: inter quartile range.

Relationships between coping styles and outcomes

Results of the logistic and linear regression analyses are shown in Table III.

A palliative coping style was positively associated with the presence of depressive symptoms (OR=1.45; *p*=0.016). None of the potential confounders was significantly associated with the presence of depression.

Passive coping style (*p*=0.025), morbidity of the caregiver (*p*=0.010), and gender (*p*=0.024) were significantly related to burden in univariate analyses. In the multivariate model, a passive coping style was positively related to burden (ß=1.61, *p*=0.024), adjusted for morbidity of the caregiver (ß=11.90; *p*=0.013). Gender dropped out of the final regression model (R^2 change=5.0%; *p*=0.210).

Passive coping style was inversely related to life satisfaction (ß=0.10; *p*=0.025). None of the potential confounders was significantly associated with this outcome.

Table III. *Logistic and linear regression models for the 3 outcomes: presence of depression, burden score and life satisfaction score.*

	OR (95% CI)	ß (95% CI)	*p*-value	*R^2 change (%)*	R^2 total (%)
Presence of depression					34.3[a]
Palliative coping style	1.45 (1.07; 1.97)		0.016		
Burden					48.3
Morbidity of caregiver		11.90 (2.84; 20.97)	0.013	29.8	
Passive coping style		1.61 (0.24; 2.99)	0.024	18.5	
Life satisfaction					14.3
Passive coping style		-0.10 (-0.18; -0.01)	0.025		

[a] R^2 Nagelkerke.
95% CI: 95% confidence interval; OR: odds ratio.

DISCUSSION

In this study, we found that maladaptive coping styles, such as passive coping and palliative coping, are related to depression, burden and life dissatisfaction in caregivers of patients with SAH. This is in line with the results of other studies among the caregivers of patients with ABI, which concluded that psychosocial functioning is related to caregiver coping styles.[13-15,17,31] In particular, a passive coping style of the caregiver has been associated with lower family functioning, lower quality of life and higher strain.[17] Visser-Meily et al. (2005) found that the passive coping style of the caregiver was the most important predictor of quality of life 1 year after stroke.[15] In addition, 3 years after stroke, caregiver coping style seemed to be related to their psychosocial functioning: a passive coping style was related to negative outcomes, whereas an active coping style was related to positive outcomes.[16] In caregivers of patients with TBI, a similar correlation was found between coping style and perception of burden and increased emotional distress.[13,14,31] Surprisingly, in our study no significant associations were found between active coping styles and the caregiver outcomes, as in Visser-Meily et al. (2005) and (2009).[15,16] This may be explained by the problem of a small sample size in our study or by the different outcome measures that were used.

Our finding, about the correlation between coping style and caregiver outcomes, is important for the development and improvement of specific SAH caregiver support programmes in rehabilitation services and to target those persons who might benefit from such programmes. If it is possible to change maladaptive coping styles into effective coping styles through an intervention programme, both patients and caregivers might benefit from such a programme. A study analysing the burden of caregivers of chronic neurological patients showed that approximately 66% of the caregivers requested interventions aimed at reducing their burden.[32] In order to select persons for caregiver support programmes, questionnaires could be used that measure the preference for certain coping styles. Our study shows that caregivers with high scores on palliative or passive coping styles may benefit the most from such programmes. Several intervention studies for patients with stroke or TBI and their caregivers have focused on improving emotional functioning and reducing caregiver burden after TBI or stroke.[33,34] Backhaus et al. (2010) found that a Coping Skills Group intervention in a population of patients with TBI and their caregivers resulted in improved perceived self-efficacy directly after participating in the group.[35] This result is promising for our population of patients with SAH and their caregivers. Although 23% of caregivers of patients with SAH seemed to be depressed in this study, we also found that, in general, the primary caregivers of patients with SAH were satisfied with life, had low depression and burden scores, and showed adequate coping styles. Only 28% of caregivers were dissatisfied with life. These numbers are much better than those reported for caregivers of patients with ABI. For these caregivers, Wolters Gregório et al. (2011) found that 39% experienced high levels of strain and 38% reported a low quality of life.[17] In spouses of patients with stroke, 52% reported depressive symptoms, 50% dissatisfaction with life and 54% strain.[15] An explanation for this discrepancy might be that the studies of caregivers of stroke or ABI patients contained cohorts of patients that were more severely affected, both physically and mentally, by the injury in comparison with our cohort, in which the majority of the patients had maximal GCS scores and Barthel Index scores.[13,16,31,36] If a patient is severely affected by the injury this will have a greater impact on caretaking tasks and burden for their caregivers.[34] Differences in injury severity can also be explained by the fact that our sample is a hospital-based cohort of patients with SAH, whereas other ABI cohorts are often rehabilitation cohorts and thus more severely affected. From our cohort only 25% were referred to inpatient rehabilitation centres or nursing homes and 75% were discharged directly to their homes.

Finally, the high scores on the GCS and low scores on WFNS in this study might be partly explained by the fact that patients with perimesencephalic SAH were not excluded (10% of the study population). The prognosis of these patients is considered much better compared with patients with aneurysmal SAH.[18]

Study limitations

The study has some limitations. The first is that the sample size is relatively small. However, even with this small number, we did find significant differences in outcomes based on coping styles of caregivers. In further research a larger sample is required to confirm that palliative or passive coping styles in caregivers of patients with SAH are related to depressive symptoms, higher burden and life dissatisfaction. Another limitation is that the study has a cross-sectional design, which prevents us from drawing conclusions about causal relationships. No follow-up measurement was performed in this group of caregivers, and as such the change over time in coping styles, mood and life satisfaction was not studied. Finally, no distinction was made between the types of caregivers. All types of caregivers were grouped together, because the sample size in this study was too small to subdivide the group of caregivers into partners, parents and children. Further studies are required to determine whether there are different outcomes for these subgroups.

CONCLUSION

In conclusion, palliative and passive coping styles are related to depressive symptoms, burden, and life dissatisfaction in caregivers of patients with SAH in the first year post-onset. To develop specific rehabilitation programmes for patients with SAH and their caregivers, more studies assessing the relationship between coping style, depression, burden and life dissatisfaction in caregivers of patients with SAH are required, with a longitudinal study design.

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Chapter 7

General discussion

Wendy Boerboom

The main objective of this thesis was to evaluate long-term consequences 4 years after subarachnoid haemorrhage (SAH), and to define which patients are in need of long-term professional support. Research on long-term problems experienced by patients with SAH is of growing importance, because in recent years, survival rates of SAH have increased.[1] To investigate these long-term outcomes, it was necessary to study a wide range of factors which are possibly connected to the outcomes in this group of patients. A distinction is made between perimesencephalic subarachnoid haemorrhage (PM-SAH) and aneurysmal subarachnoid haemorrhage (A-SAH), partners/caregivers are involved in the study, and different variables like cognitive functioning, physical and social functioning are studied. This chapter will discuss the main findings, strengths and limitations of this study in the context of the published literature. Finally, directions for future research and possible implications for rehabilitation programs are described.

MAIN FINDINGS

Perimesencephalic Subarachnoid Haemorrhage

In terms of clinical outcomes, PM-SAH is described as a benign subtype of SAH. Patients do not need surgery, they are not at risk for the serious complications of SAH, re-bleeding or delayed cerebral ischemia and do not have a higher mortality rate than healthy people.[2,3] However, based on the results of this thesis, we concluded that the outcomes for these patients are not that favourable. Our short term findings (Chapter 2) regarding the presence of fatigue in 37.5% of patients and the problems in complex cognitive functioning compared to norm values are confirmed in the long term (Chapter 3). Four years after PM-SAH, 33% of the patients experienced fatigue and 37% did not return to work. Furthermore, we found indications for problems in complex cognitive functioning, especially in the group of fatigued patients with PM-SAH. The review of Kapadia et al. (2014) gives a broad description about clinical, functional and cognitive outcomes in patients with PM-SAH.[4] We confirm their findings about the difficulties with returning to work and deficits in several cognitive domains. Fatigue is known to be related to negative cognitive outcomes and lower rates of return to work 3-6 months after stroke.[5] Although fatigue appears to be a long-term consequence of PM-SAH, it has received little attention in scientific research. Supported by the personal stories of the participants in our research, further research into the origin and consequences of fatigue after SAH seems warranted.

Aneurysmal subarachnoid haemorrhage

Studies that evaluate outcomes of A-SAH survivors more than 1 year post-onset are scarce, and rehabilitation programs for patients with SAH usually do not expand beyond the scope of one year post-onset. We found that patients with A-SAH improve over time and in general their outcomes on all ICF domains are fairly good (Chapter 4). However, compared to healthy subjects, patients with A-SAH experience more fatigue, depressive symptoms and problems in cognitive functioning. Furthermore, 25% of the patients show problems in self-care and 82% have behavioural difficulties in the long term on domains of 'psychological autonomy and communication' and 'social behaviour'. Just as in the patients with PM-SAH, a large percentage of A-SAH patients are unemployed, even 4 years after SAH. Our findings are consistent with the reviews of Al-Khindi et al. (2010) and Rinkel et al. (2011).[1,6]

Fatigue, cognitive functioning and mood

In patients with A-SAH, as well as in patients with PM-SAH, we found fatigue and disturbances in cognitive functioning and mood in the long term after SAH (Chapters 2, 3, 4 and 5). These variables are described in the literature as the 3 most common consequences of stroke in general with significant impact on the lives of the patients.[7] Relationships between fatigue and anxiety, depression, Post-traumatic stress disorder, memory difficulties, personality changes, sleep disturbances and cognitive and physical impairment after A-SAH are described.[6,8] The review of Abd-Elfattah et al. (2015) describes fatigue as a decrease in physical performance associated with an increase in the real/perceived difficulty of a task or exercise.[9] In patients with stroke, Wu et al. (2015) makes a distinction in early fatigue, which may be triggered by biological factors, and late fatigue which may be more attributable to psychological and behavioural factors.[10] Our study also established relations between fatigue, cognitive functioning and depression in patients with PM-SAH (Chapter 4). However, causal attributions cannot be made. It is not clear whether fatigue causes cognitive dysfunction and mood problems or if the relationship is the other way around. What we can tell from this research is that these problems co-exist and that follow-up studies and intervention studies are needed to find out whether these variables change in the same direction or can be influenced by therapy.

Unmet needs

Four years after SAH, 67% of all patients reported one or more unmet needs and patients experienced less than optimal community integration (Chapter 5). A higher number of unmet needs is associated with a lower score on community integration. Unemployed patients reported more unmet needs and had lower cognitive functioning scores than employed patients. The high proportion of patients with unmet needs in our study is comparable to the proportions found in young stroke survivors >1 year after stroke.[11,12] The highest proportion unmet needs in our study was found for the category unmet information needs; almost 60% of the patients indicated one or more unmet needs in this category. Despite the availability of patient information about stroke on websites, booklets and patient forums, specific information for the subgroup of patients with SAH may be lacking.[11]

STRENGTHS AND LIMITATIONS

A major strength of this study is that it provides an extensive description of long-term outcome in patients with SAH. Studies evaluating the outcomes of SAH survivors longer than 1 year post-onset are scarce, most studies have a retrospective design and focus on a single outcome.[13,14] In line with Lezak (1988), who determined that brain damage not only is of negative influence on the patients' quality of life, but also affects the well-being of patients' families,[15] we involved caregivers in our study, which is another important strength.

In addition, we studied long-term cognitive functioning and fatigue in patients with PM-SAH (Chapter 3). This group of patients is considered to have a favourable outcome and is often excluded from outcome studies. Earlier studies on non-aneurysmal or PM-SAH patients concerned small numbers of patients.[16-19] In our collaboration with Utrecht Medical Center, we managed to study a relatively large group of PM-SAH patients (N=46).

Our study has several limitations too. First of all, due to the small sample size the number of variables that could be included in regression analyses was limited. However, even with small numbers, we did find significant differences between patients with PM-SAH and A-SAH and between our sample and norm values of healthy people. Especially in our studies on patients with PM-SAH and caregivers of patients with SAH, the absence of short-term measurements and follow-up measurements is considered a limitation of this study, because causal relationships could not be studied. At T1 we also had to deal with missing data, due to incomplete questionnaires, variety of research assistants and the capacity of some of the participants. Despite this, the mean outcomes of the total study population could be reliably estimated by using modern statistical methods.

RECOMMENDATIONS FOR FUTURE RESEARCH

In general, more long-term, longitudinal studies on larger groups of patients with SAH are necessary to draw further, and more accurate conclusions on the long-term outcomes of these patients involving caregivers and patients with both A-SAH and PM-SAH.

As fatigue is an important factor throughout this thesis, future research aimed at unravelling the underlying mechanisms is necessary if we are to come to an individually tailored treatment for patients with SAH. To evaluate fatigue is difficult, and the best manner of measuring fatigue is subject to discussion. In our studies we used the Fatigue Severity Scale (FSS), a simple scale which is often used in TBI research.[20] However, the FSS items are more related to behavioural consequences of fatigue, rather than fatigue characteristics. Other questionnaires could be used, such as the Multidimensional Fatigue Inventory (MFI), which makes a distinction between several types of fatigue for a better understanding of the origin of fatigue.[21]

Furthermore, because patients with SAH still experience problems 4 years after onset, it should be questioned if rehabilitation services can adapt their programs to incorporate long-term needs of patients with SAH.

Finally, future research should include patients with PM-SAH. These patients are under-represented in the scientific literature.

CLINICAL IMPLICATIONS

With fatigue being a recurring theme throughout this thesis, and possibly related to other problems in long-term outcomes, screening for fatigue, and long-term fatigue management in the treatment for patients with SAH can be advised.[1,6] Furthermore, as cognitive problems may remain in the long term, not only in patients with A-SAH but also in PM-SAH, these should be anticipated by health care professionals and communicated to patients and their caregivers. Finally, many patients pointed out a need for more information specific to SAH, so this topic deserves more emphasis both in patient associations and in rehabilitation institutes.

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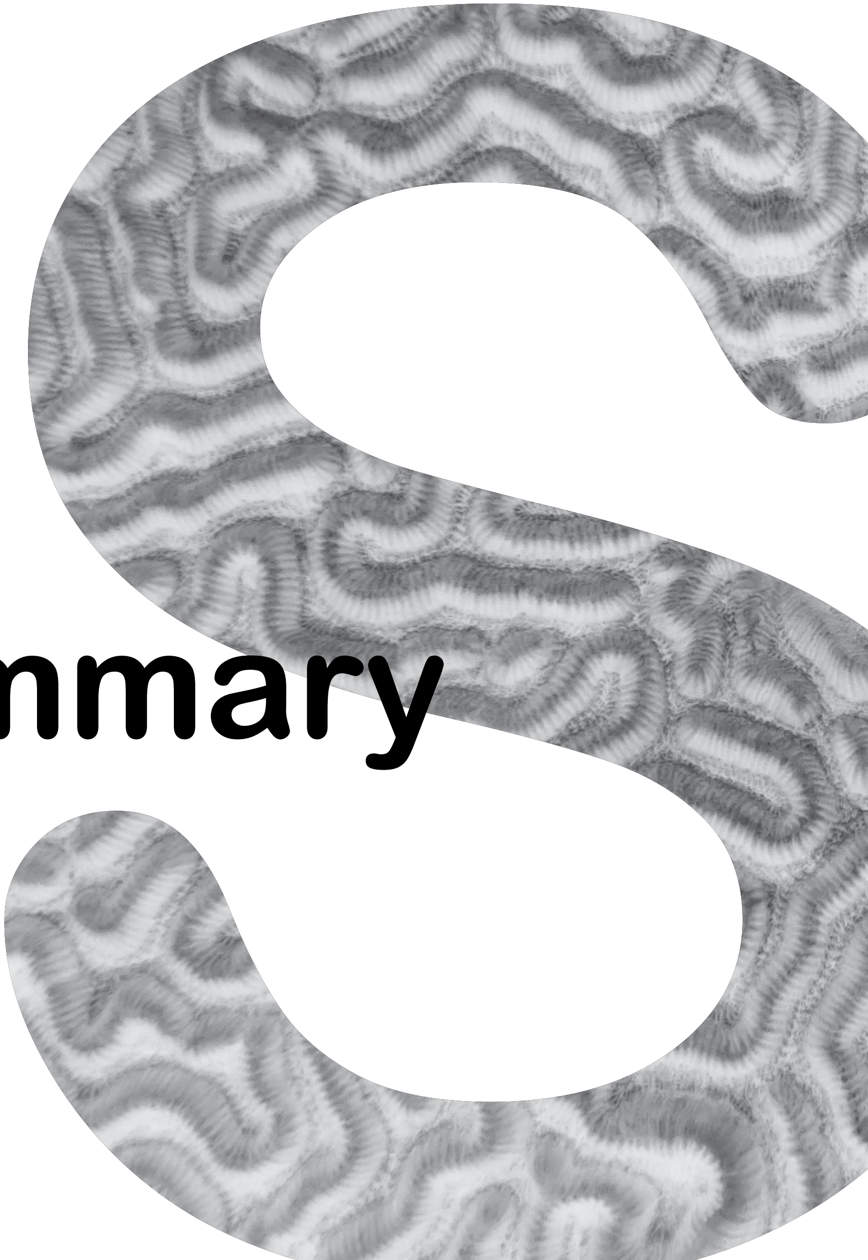
Summary



The introductory **Chapter 1** provides background information about subarachnoid haemorrhage (SAH) and gives a short overview of the current knowledge of its long-term impact on the lives of patients. The chapter explains the main objective of this thesis, which is to gain more knowledge about the long-term consequences four years after subarachnoid haemorrhage, and to define which patients are in need of long-term professional support.

Compared to aneurysmal SAH (A-SAH), perimesencephalic SAH (PM-SAH) often is considered to have a more favourable outcome. The aim of **Chapter 2** is to compare outcome between patients with A-SAH and PM-SAH in the first year post-onset. The results indeed showed that patients with PM-SAH had less depression and fatigue, and were faster on the cognitive task for motor speed and processing speed, than patients with A-SAH. Compared with norm scores, patients with A-SAH scored worse on all tests, while patients with PM-SAH scored worse on the TMT-B, used to measure complex cognitive functioning, and had higher fatigue scores measured with the FSS. These results suggest that patients with PM-SAH may also suffer from long-term consequences that interfere with daily activities and social participation. We conclude that one year post-onset, both patients with A-SAH and PM-SAH may be in need of professional support. More research is needed to confirm these findings.

In **Chapter 3** we subsequently studied fatigue and cognitive functioning in a larger group of patients with PM-SAH in collaboration with the University Medical Center in Utrecht. Four years after PM-SAH, 33% of patients with PM-SAH experienced fatigue and experienced problems in the cognitive functioning domains: attention and concentration, speed of information processing, and memory. The fatigue score was found to be significantly associated with subjective and objective cognitive functioning, mood and comorbidity. Even after adjustment for mood and comorbidity, fatigue remained associated with attention and executive functioning. These results underscore that even four years post-onset patients may face the negative impact of PM-SAH.

Chapter 4 is focused on patients with A-SAH with a four-year follow-up. Multiple outcomes for depression, fatigue, cognitive functioning, independence, health-related functioning, participation, social support, locus of control, and quality of life were tested, based on the International Classification of Functioning, Disability and Health. Changes over time were assessed and the four-year outcomes were compared with norm scores. We found that the scores for Barthel Index, TMT-B, SSL-12 (total score and esteem support), MHLCS physician-orientation, and SF-36 (role emotional) improved over time, whereas scores for CES-D, FSS, SIP-68 and SF-36 (remaining scores) remained the same. At four-year follow-up, patients were slower on the cognitive functioning task TMT-A and TMT-B, had higher fatigue scores, and a higher proportion of depression than norm scores. Furthermore, we found that 69% of patients were unemployed and 82% experienced difficulties on the domains psychological autonomy and communication, and social behaviour of the SIP-68. We therefore conclude that four years post-onset, problems in executive functioning, mood and fatigue were present.

In **Chapter 5** we assessed whether patients with A-SAH and PM-SAH experience unmet needs in relation to community integration and employment status four years after SAH. The results of this study show 67.2% of patients with unmet needs and 67.2% with unemployment. Almost 60% of patients reported a need for more information; unemployed patients had more unmet needs than employed patients. Finally, an inverse relation between unmet needs and community integration was found. It was concluded that future research is necessary to investigate whether expanding and improving information services may contribute to a better community integration in patients with SAH.

In **Chapter 6** we focussed on the impact of PM-SAH and A-SAH on the caregivers seven months post-onset. The relationships of coping style with depression, burden and life satisfaction in these caregivers was studied. Overall we found that the caregivers were satisfied with life, had low depression and burden scores and showed adequate coping styles. Caregivers with a preference for more palliative or passive coping styles had more depressive symptoms, higher burden and life dissatisfaction.

Chapter 7 is the general discussion of this thesis, which describes the main findings, discusses the relations between fatigue, cognitive functioning and mood, and points out the importance of unmet needs in relation to community integration. Further, the strengths and limitations of this study are discussed, recommendations for future research are made and clinical implications are addressed.

Samenvatting

Het inleidende **hoofdstuk 1** geeft achtergrondinformatie over subarachnoïdale bloedingen (SAB) en geeft tevens een kort overzicht van de huidige kennis van de langetermijngevolgen voor het leven van de patiënt. Dit hoofdstuk beschrijft de belangrijkste doelstelling van dit proefschrift, namelijk het verkrijgen van meer kennis over de langetermijngevolgen vier jaar na een SAB en om te bepalen welke patiënten langdurige professionele ondersteuning nodig hebben.

Vergeleken met een aneurysmatische bloeding (A-SAB), wordt de perimesencefale bloeding (PM-SAB) vaak beschouwd een gunstiger uitkomst te hebben. Het doel van **hoofdstuk 2** is om de uitkomsten in het eerste jaar na het ontstaan van een SAB te vergelijken tussen patiënten met A-SAB en PM-SAB. De resultaten toonden inderdaad aan dat patiënten met PM-SAB minder last hadden van depressie en vermoeidheid en dat ze sneller waren dan patiënten met A-SAB op de cognitieve taak voor het meten van motor- en verwerkingssnelheid (TMT-A). Vergeleken met normscores scoorden patiënten met een A-SAB slechter op alle testen, terwijl patiënten met PM-SAB langzamer waren op de complex cognitief functioneren taak (TMT-B) en meer last hadden van vermoeidheid, gemeten met de FSS. Deze resultaten suggereren dat ook patiënten met een PM-SAB op de lange termijn last kunnen hebben van gevolgen die interfereren met dagelijkse activiteiten en sociale participatie. We kunnen hieruit concluderen dat zowel patiënten met A-SAB als patiënten met een PM-SAB één jaar na de bloeding mogelijk behoefte hebben aan professionele ondersteuning. Meer onderzoek is nodig om deze resultaten te bevestigen.

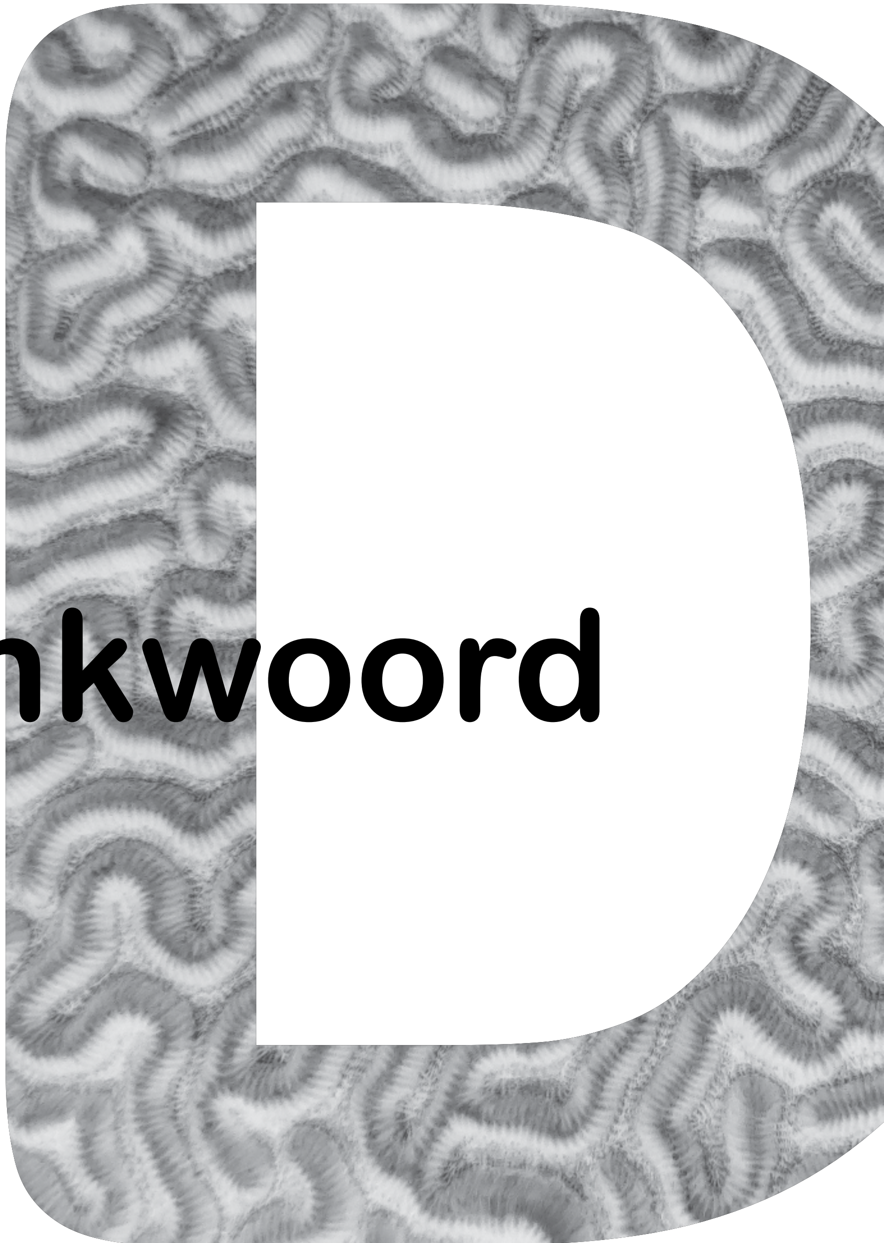
Vervolgens hebben we in **hoofdstuk 3** bij een grotere groep patiënten met PM-SAB vermoeidheid en cognitief functioneren onderzocht in samenwerking met het Universitair Medisch Centrum Utrecht. Na vier jaar ondervond 33% van de patiënten met een PM-SAB vermoeidheid en problemen met cognitief functioneren op de domeinen aandacht en concentratie, snelheid van informatieverwerking en geheugen. De vermoeidheidsscore was significant geassocieerd met subjectief en objectief cognitief functioneren, stemming en co-morbiditeit. Zelfs na correctie voor stemming en co-morbiditeit, bleef vermoeidheid geassocieerd met aandacht en executieve functies. Deze resultaten benadrukken dat patiënten, zelfs vier jaar na het ontstaan van de bloeding, geconfronteerd kunnen worden met de negatieve gevolgen van een PM-SAB.

Hoofdstuk 4 richt zich op patiënten met een A-SAB die vier jaar gevolgd werden. Verschillende uitkomstmaten voor depressie, vermoeidheid, cognitief functioneren, onafhankelijkheid, gezondheid-gerelateerd functioneren, participatie, sociale steun, locus of control en kwaliteit van het leven werden getest op basis van het ICF-model (International Classification of Functioning, Disability and Health). Veranderingen in de tijd werden gemeten en langetermijnresultaten werden vergeleken met normscores. We vonden vooruitgang op de scores van de Barthel Index, TMT-B, SSL-12 (totale score en waarderingssteun), MHLCS (arts-oriëntatie), en SF-36 (emotionele rol), terwijl de scores op de CES-D, FSS, SIP-68 en SF-36 (overige scores) gelijk bleven. Na vier jaar follow-up vonden we dat patiënten met een A-SAB slechter scoorden op de cognitief functioneren taken (TMT-A en TMT-B), hogere vermoeidheid scores (FSS) hadden, en dat een groter percentage patiënten depressieve klachten had dan norm groepen. Daarnaast vonden we dat 69% van de patiënten niet werkten en dat 82% problemen ondervond op de domeinen psychologische autonomie en communicatie en sociale participatie (SIP-68). Uit deze resultaten kunnen we concluderen dat vier jaar na het ontstaan van de bloeding, patiënten problemen ervaren met executieve functies, stemming en vermoeidheid.

In **hoofdstuk 5** onderzochten we of patiënten met A-SAB en PM-SAB onvervulde behoeften (unmet needs) ervaren met betrekking tot integratie in de samenleving en arbeidssituatie vier jaar na SAB. De resultaten van deze studie laten zien dat 67.2% van de patiënten werkloos is en 67.2% onvervulde behoeften heeft. De belangrijkste onvervulde behoefte blijkt de behoefte aan informatie te zijn en wordt door bijna 60% van de patiënten gerapporteerd. Daarnaast hebben werkloze patiënten meer onvervulde behoeften dan patiënten die wel werk hebben. Tenslotte vinden we een inverse relatie tussen onvervulde behoeften en integratie in de samenleving. Hieruit kunnen we concluderen dat er verder onderzoek nodig is om te bekijken of uitbreiding en verbetering van informatievoorzieningen bijdraagt aan betere integratie in de samenleving van patiënten met een SAB.

In **hoofdstuk 6** hebben we ons gericht op de gevolgen van een A-SAB en een PM-SAB op de mantelzorgers van de patiënten. We hebben de relatie van coping stijl met depressie, belasting en tevredenheid met het leven bij deze mantelzorgers onderzocht. Over het algemeen waren de mantelzorgers in deze studie tevreden met het leven, hadden ze lage depressie- en belasting scores en lieten ze adequate coping stijlen zien. Tevens laten de resultaten zien dat een voorkeur hebben voor palliatieve of passieve coping stijlen gerelateerd is aan meer depressieve symptomen, hogere belasting en ontevredenheid met het leven binnen de groep mantelzorgers van patiënten met SAB.

Hoofdstuk 7 is de algemene discussie van dit proefschrift, welke de belangrijkste bevindingen beschrijft, de relatie tussen vermoeidheid, cognitief functioneren en stemming bespreekt en wijst op het belang van het hebben van onvervulde behoeften in relatie tot integratie in de samenleving. Verder worden de sterke- en zwakke punten van deze studie besproken, doen we aanbevelingen voor toekomstig onderzoek en geven we enkele klinische implicaties aan die voortvloeien uit dit onderzoek.



Dankwoord

Nadat ik ongeveer een jaar in Rijndam werkte als onderzoeksassistent, werd mij gevraagd of ik misschien een artikel wilde schrijven. Op zich leek dat me wel leuk, maar ja is dat nou wel helemaal iets voor mij? Twijfelen, denken en uiteindelijk toch maar besloten er een gesprek met Gerard aan te wagen. Echter, mijn eerste echte kennismaking met Gerard werd toch wel iets anders dan verwacht. "Dag Wendy, leuk dat je dat artikel gaat schrijven, maar als je er nou gelijk 5 schrijft, dan heb je een proefschrift en kun je promoveren." Dit had ik niet aan zien komen en dat merkte hij ook gelijk op. Dus vandaar zijn advies: "Neem vanavond een goed glas wijn en ik hoor volgende week wel of je dat wat vindt."

Beste Gerard, nu liggen die 5 artikelen hier voor je, mijn proefschrift is klaar. Ontzettend bedankt voor het vertrouwen dat je mij al had gegeven voordat ik dat zelf gevonden had en voor deze enorme kans, iets waarvan ik nooit had gedacht dat ik dat in mijn leven zou bereiken.

Natuurlijk is dit proefschrift niet alleen tot stand gekomen met behulp van vertrouwen en kansen. Een heleboel mensen hebben mij daarbij geholpen op diverse manieren. Allereerst natuurlijk Majanka in de rol van copromotor, maar bovenal als dagelijks begeleider, luisterend oor, corrector, data-analist en gewoon een fantastische collega. Ik vond het heel fijn om met je te mogen samenwerken!

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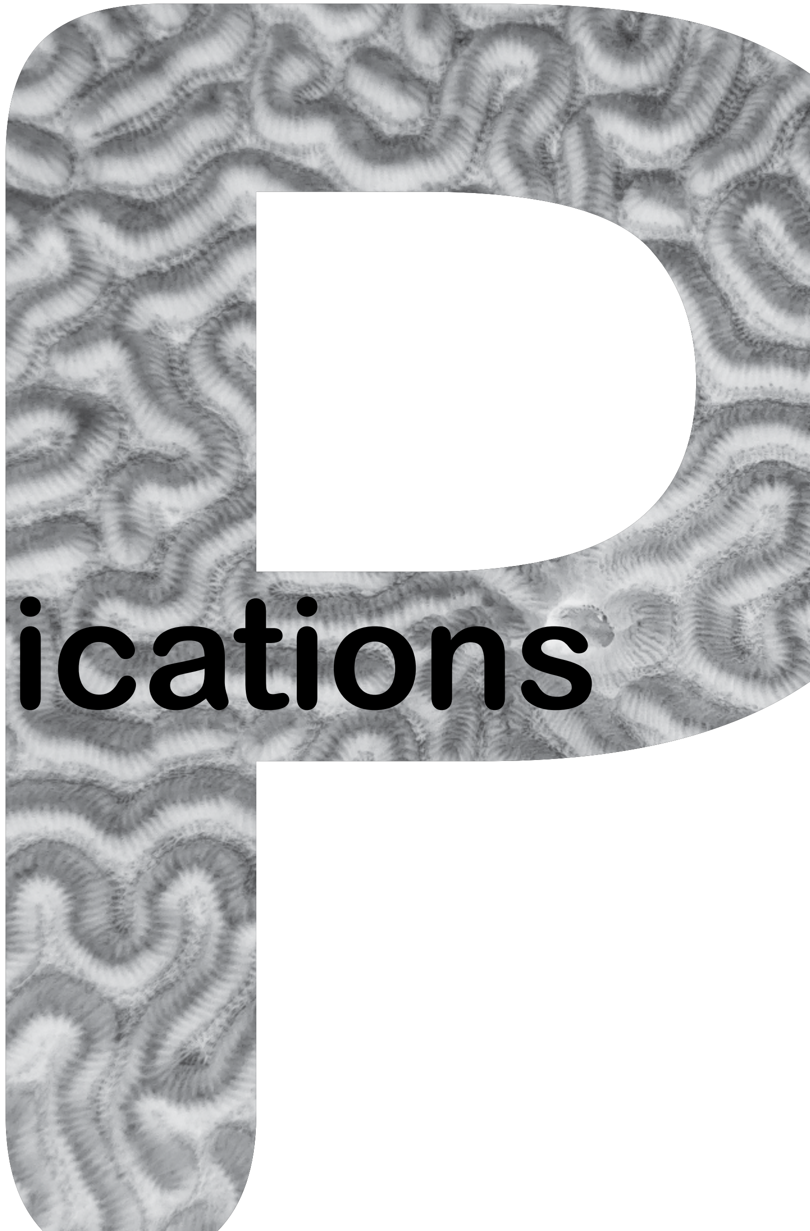
About the author

Wendy Boerboom was born in Alkmaar (the Netherlands) on the 26th of October 1984. She attended secondary school at College Hageveld (Atheneum) in Heemstede, where she graduated in 2003. After obtaining her first-year certificate Media Entertainment Management in 2004 at Inholland Haarlem, she continued with studying Psychology at Leiden University. She obtained her masters degree in Social and Organizational Psychology in 2009. After four months of travelling, she started working as a research assistant in Rijndam Rehabilitation Center in 2010. She assisted in several PhD projects aimed at patients with stroke. In April 2011 she was asked to take over a research project at Rijndam Rehabilitation Center as part of the research line of Rotterdam Neurorehabilitation Research (RoNeRes) and the department of Rehabilitation Medicine of the Erasmus MC, Rotterdam, resulting in this PhD thesis. During her PhD, she also worked as a policy advisor for the newly initiated 'Innovation Center Rehabilitation' at the Research and Development department of Rijndam Rehabilitation Center.



Publications

Boerboom, W.; Heijenbrok-Kal, M.H.; Khajeh, L.; van Kooten, F.; Ribbers, G.M. Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage. *Journal of Rehabilitation Medicine, 2014 (46;1) 28-32.*

Boerboom, W.; Jacobs, E.A.C.; Khajeh, L.; van Kooten, F.; Ribbers, G.M.; Heijenbrok-Kal, M.H. The relationship of coping style with depression, burden, and life dissatisfaction in caregivers of patients with subarachnoid haemorrhage. *Journal of Rehabilitation Medicine, 2014 (46;4) 321-326.*

Boerboom, W.; Heijenbrok-Kal, M.H.; Khajeh, L.; van Kooten, F.; Ribbers, G.M. Long-term functioning of patients with aneurysmal subarachnoid haemorrhage: a 4-year follow-up study. *American Journal of Physical Medicine & Rehabilitation, 2016 (95;2) 112-120.*

Boerboom, W.; van Zandvoort, M.J.E.; van Kooten, F.; Khajeh, L.; Visser-Meily, J.M.A.; Ribbers, G.M. Heijenbrok-Kal, M.H. Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning and mood. *Submitted*

Boerboom, W.; Heijenbrok-Kal, M.H.; van Kooten, F.; Khajeh, L.; Ribbers, G.M. Unmet needs in relation to community integration and employment status 4 years after Subarachnoid Haemorrhage. *Journal of Rehabilitation Medicine, In press after revisions*

PhD portfolio

Summary of PhD training and teaching activities

Name PhD student:	Wendy Boerboom	PhD period:	2011 - 2015
Erasmus MC Department:	Rehabilitation Medicine	Promotor:	G.M. Ribbers
Research School:	-	Supervisor:	M.H. Heijenbrok-Kal

1. PhD training

	Year	Workload
General academic skills		
• Endnote (Medical Libary)	2011	2 hours
• BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2011-2012	46 hours
• Minicursus Methodologie van Patiëntgebonden Onderzoek (CPO)	2012	8 hours
• Research Integrity	2013	56 hours
Research skills		
• Writing a scientific Article (Talencentrum, VU)	2012	64 hours
• Inleiding Biostatistiek en Epidemiologie (EpidM)	2011	48 hours
• Biostatistical Methods 1: Basic prinicples (CC02, NIHES)	2012	159,6 hours
• Cohort Studies (ESP39, NIHES)	2013	15 hours
In depth courses		
• English 4 (Talencentrum, Universiteit Leiden)	2011	84 hours
• English 5 (Talencentrum, Universiteit Leiden)	2011	84 hours
• Preventing Failed Interventions (try out) (NIHES)	2012	39,2 hour
Presentations		
• Oral presentation: “Prognostic factors and long-term outcome of Subarachnoid Haemorrhage”. Research meeting, dept. of Rehabilitation Medicine and Physiotherapy, Erasmus MC (Rotterdam, NL)	2011	20 hours
• Poster presentation: “Differences in cognitive and emotional outcomes after perimesencephalic subarachnoid haemorrhage and aneurysmal subarachnoid haemorrhage”. IBIA congress, (Edinburgh, UK)	2012	20 hours

	Year	Workload
• Oral presentation: “Differences in cognitive and emotional outcomes after perimesencephalic subarachnoid haemorrhage and aneurysmal subarachnoid haemorrhage”. Research meeting, department. of Rehabilitation Medicine and Physiotherapy, Erasmus MC (Rotterdam, NL)	2012	10 hours
• Poster presentation: “Langetermijngevolgen en prognostiche determinanten bij subarachnoïdaal bloedingen”. Rijndam 100 jaar Symposium (Rotterdam, NL)	2012	10 hours
• Oral presentation: “Differences in cognitive and emotional outcomes after perimesencephalic subarachnoid haemorrhage and aneurysmal subarachnoid haemorrhage”. Regionale refereeravond, Rijndam (Rotterdam, NL)	2013	10 hours
• Poster presentation: “Differences in cognitive and emotional outcomes after perimesencephalic subarachnoid haemorrhage and aneurysmal subarachnoid haemorrhage”. INS congress (Amsterdam, NL)	2013	10 hours
• Oral presentation: “Coping style predicts depression, high burden and life dissatisfaction in caregivers of patients with subarachnoid haemorrhage”. Research meeting, department of Rehabilitation Medicine and Physiotherapy, Erasmus MC (Rotterdam, NL)	2013	10 hours
• Datablitz presentation: “Social participation in patients with SAH: Long-term outcome”. 11th Conference of the World Federation for NeuroRehabilitation (WFNR) Special Interest Group (Limassol, Cyprus)	2014	20 hours
• Oral presentation: “Long-term Functioning of Patients With Aneurysmal Subarachnoid Haemorrhage: a 4-year Follow-up Study”. Research meeting, department of Rehabilitation Medicine and Physiotherapy, Erasmus MC (Rotterdam, NL)	2014	15 hours
• Oral presentation: “Long-term Functioning of Patients With Aneurysmal Subarachnoid Haemorrhage: a 4-year Follow-up Study”. American Congress of Rehabilitation Medicine (ACRM) Annual Conference (Toronto, CA)	2014	20 hours
• Poster presentation and pitch: “Long-term functioning 4 years after aneurysmal subarachnoid haemorrhage”. Dutch Congress of Rehabilitation Medicine (DCRM 2014) (Rotterdam, NL)	2014	15 hours

	Year	Workload
• Oral presentation: "Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning and mood". Dutch Congress of Rehabilitation Medicine (DCRM 2015) (Rotterdam, NL)	2015	20 hours
(Inter)national conferences		
• American Congress of Rehabilitation Medicine (ACRM) Annual conference (Atlanta, VS)	2011	32 hours
• International Brain Injury Association (IBIA) 9th World Congress on Brain Injury (Edinburgh, UK)	2012	24 hours
• World Federation for NeuroRehabilitation (WFNR) 10th Conference of the Neuropsychological Rehabilitation, Special Interest Group (Maastricht, NL)	2013	16 hours
• International Neuropsychological Society (INS) 2013 Mid-Year Meeting (Amsterdam, NL)	2013	28 hours
• VRA Annual Congress 2013 (Noordwijkerhout, NL)	2013	16 hours
• World Federation for NeuroRehabilitation (WFNR) 11th Conference of the Neuropsychological Rehabilitation, Special Interest Group (Limassol, Cyprus)	2014	16 hours
• American Congress of Rehabilitation Medicine (ACRM) Annual Conference (Toronto, CA)	2014	24 hours
• Dutch Congress of Rehabilitation Medicine (DCRM 2014) (Rotterdam, NL)	2014	8 hours
• Dutch Congress of Rehabilitation Medicine (DCRM 2015) (Rotterdam, NL)	2015	8 hours
Seminars and workshops		
• Workshop Endnote (Medische Bibliotheek EMC, Rotterdam)	2011	2 hours
• PhD Day 2011 (Erasmus MC, Rotterdam)	2011	6 hours
• Pre-conference workshop and Focus Group, Early Career Development (ACRM, Atlanta USA)	2011	10 hours
• PhD Career Day (Erasmus University, Rotterdam)	2012	5 hours
• PhD Day 2013 (Erasmus MC, Rotterdam)	2013	6 hours

	Year	Workload
• Workshop: Cognitive Assessment at the Stroke Unit: From bedside testing to full Neuropsychological Assessment (Martine van Zandvoort), (INS 2013 Amsterdam)	2013	2 hours
• Workshop: Attentional Disorders and their Rehabilitation (Ian H. Robertson) (INS 2013 Amsterdam)	2013	2 hours
• Pre-conference Instructional course: Fatigue in Traumatic Brain Injury: Current State of Knowledge and Future Direction (ACRM, Toronto CA)	2014	4 hours
• National PhD day (Den Haag)	2014	5 hours
• Research Seminar of the MSH Research Program EMGO+, Missing data analysis (VU, Amsterdam)	2015	2 hours
Other		
• Participating in research meetings, department of Rehabilitation Medicine, Rotterdam	2011-2015	160 hours
• Participating in research meetings, dept. of Medical Psychology and Psychotherapy (Rotterdam)	2012- 2015	10 hours
• Participating in RoNeRes Journalclubs, department Rotterdam Neurorehabilitation Research	2013-2015	17 hours

2. Teaching activities

Supervising practicals and excursions, Tutoring		
• Supervising 2nd year medical students with review assignment (Erasmus MC, Rotterdam	2011	2 hours
• Supervising master student psychology with patient measurements (UMCU, Utrecht)	2011-2012	46 hours
Total		***1233 hours***