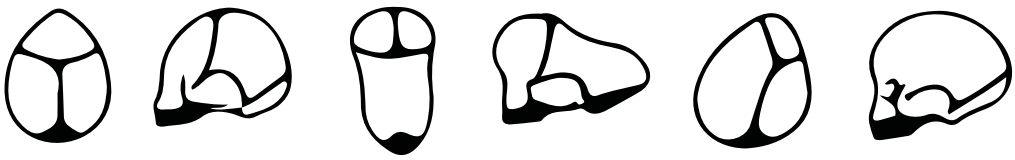
UNISUTURAL CRANIOSYNOSTOSIS

Simple or Complex?



Martijn J. Cornelissen

Unisutural craniosynostosis: simple or complex?

Martijn Johannes Cornelissen

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Unisutural craniosynostosis: simple or complex?

Unisuturale craniosynostose: simpel of complex?

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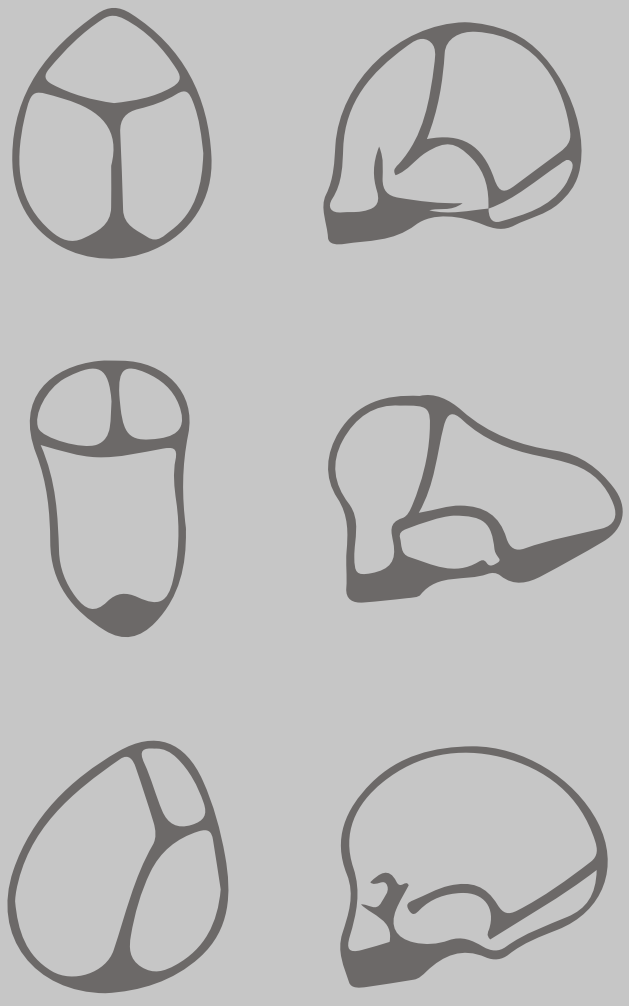

Chapter 1

General Introduction

CRANIOSYNOSTOSIS

Craniosynostosis is a congenital disorder in which one or more skull sutures fuse prematurely. This occurs in 3.1 - 6.4:10.000 births and affects skull growth (fig. 1).[1-5] As a result of the distorted skull growth, patients with craniosynostosis have an increased risk of intracranial hypertension, which may lead to problems with cognition, behavior and vision.[6-10] In approximately 21% of patients craniosynostosis is part of a syndrome, often affecting more than one suture. The remaining 79% are considered non-syndromic, isolated, craniosynostosis, in which only one suture is affected.[11, 12]

This thesis focuses on isolated craniosynostosis. It ranges from the first insights in prenatal detection of this congenital malformation to its treatment and prevalence of intracranial hypertension years after birth.

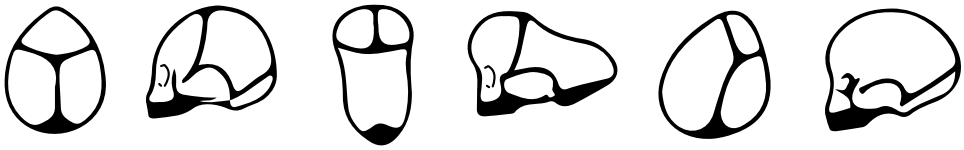

Figure 1. Metopic (m), sagittal (s) and unicoronal (c) suture synostosis cause a suture-specific skull shape.

EMBRYOLOGY

In human development all structures derive from three primary germ layers; the mesoderm, the endoderm and the ectoderm. These layers are formed at the 3rd week of gestation. Blood vessels, the lymphatic system and muscles are formed by the mesoderm, the endoderm is responsible for development of the inner epithelium. The ectoderm is the outer layer and is responsible for forming the nervous system, the retina, hair and the epidermis (among others). At 4 weeks of gestation the neural groove closes, forming the neural tube. At the same time, cells of the neural crest begin to separate from the neural tube. These cells are subject to specific differentiation pathways and eventually form neural and non-neural structures, such as bone and cartilage. Soon after the neural tube has taken shape, the region of the future brain can be distinguished and during the 5th week subdivision of the brain-forming region results in 5 vesicles (telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon).

The skull is formed by the viscerocranium (oral cavity, pharynx and upper respiratory passages) and the neurocranium, which surrounds the brain. The development of the

skull starts at 6 weeks of gestation when a layer of mesenchyme surrounds the brain. At this stage the skull is called the desmocranium. From ossification centers within the mesenchyme the growth of the neurocranium is initiated. The skull base is formed by chondrofication of the desmocranium. In contrast to the skull base, the rest of the skull is formed by intramembranous ossification. The occipital bones are part of the skull base and are therefore formed by enchondral ossification. However, their superior part is formed by intramembranous ossification, making it a combined structure. Bone centers within the membranous layer arise around the 10th week of gestation. Normally, skull suture formation starts at 15 weeks of gestation for the metopic suture, at 16 weeks for the coronal and lambdoid sutures and at 18 weeks for the sagittal suture.[13]

The neural crest, derived from the ectoderm, is responsible for the formation of the frontal bones and the meninges. The parietal and occipital bones are mostly derived from the mesoderm. However, Jiang et al have shown that a small patch of neural crest cells is situated at the anterior part of the parietal bones and at the central part of the occipital bone.[14] This implies that the metopic suture is completely located in the neural crest domain, while the lambdoid and sagittal sutures are partly mesoderm-partly neural crest derived. The coronal sutures are entirely located at the mesoderm-neural crest boundary. At this boundary different tissues meet, which results in a complex interaction between two developmental signaling systems. These signaling systems have been the subject of numerous genetic papers, studying the effect of the different active genes in calvarial development and suture formation.[15-18] In the past years genetic research has been growing exponentially, revealing various genes influencing sutural growth, of which *TWIST1* and *FGFR1*, *2* and *3* are the most famous.[12, 19, 20] In non-syndromic, isolated, craniosynostosis only 1 suture is affected and, in case of sagittal and metopic suture synostosis, known genetic malformations are often not present. In unicoronal synostosis, although only one suture is affected, genetic alterations are more often found.

CAUSES OF UNISUTURAL CRANIOSYNOSTOSIS

Although largely unknown, there are several theories on the cause of premature suture closure. Over the past decades several factors influencing the onset of unisutural craniosynostosis have been described. Some chromosomal abnormalities in relation to metopic suture synostosis have been identified, such as deletions at chromosomes 22q, 9p and 11q.[21-25] Despite thorough genetic screening studies more subtle genetic alterations have only sporadically been reported, such as the P250R mutation in the FGFR3 gene for metopic suture synostosis and a missense mutation TWIST mutation for sagittal suture synostosis.[26-28] This suggests that only a fractional part of unisutural synostosis can be explained by a genetic alteration. Consequently, as the diagnostic yield of genetic testing

in isolated sagittal and metopic synostosis is close to zero, the referral of these patients for genetic testing is discouraged by Wilkie et al.[29] However, for unicoronal synostosis, several genetic factors have been described. Approximately in 30% of all unicoronal synostosis patients a genetic mutation can be identified.[11, 12, 29] This illustrates the difference in etiology between unicoronal synostosis and metopic/sagittal suture synostosis.

Other factors that have been proven to cause unisutural craniosynostosis are mostly pharmaceutical: thyroid hormone replacement therapy and valproate use during pregnancy have both been described in relation to metopic suture synostosis of the child.[30-33] Additionally, SSRI's have been suggested to induce craniosynostosis.[34]

Another theory on the etiology of craniosynostosis is a mechanical one: constraint of the fetal head during the last phase of pregnancy would lead to the onset of craniosynostosis. This theory has been described by Graham and Smith, showing two cases of fetal head constraint and metopic suture synostosis.[35] Smartt et al. have proven this principle in a mouse model, showing changes in morphology and cell biology as a result of fetal head constraint.[36] However, the onset of craniosynostosis has been shown to occur in the first trimester of pregnancy, before fetal head constraint would occur, which disproves the 'constraint-theory'.[13]

POSTNATAL GROWTH

The fact that surgery, commonly performed during the first year of life, does not uniformly provide satisfying results and revision surgery is needed in some cases, suggests that processes of postnatal growth work against the morphological correction achieved by the surgeon. Consequently, understanding prenatal and postnatal craniofacial development and growth is critical to the treatment planning with regard to timing and type of surgery of these patients.

Increase in size of the cranial vault is primarily stimulated by growth of the brain.[37, 38] The brain reaches two-thirds of its adult size within the first 2 years of life, eventually reaching most of its adult size between 6 and 10 years of age.[39] In the first 6 years of life the sutures function as growth centers: at the site of the suture proliferating osteoprogenitor cells differentiate into bone-matrix secreting osteoblasts resulting in growth of the skull.[15, 19, 40] After the age of six years this effect stops and skull growth is solely achieved by resorption of bone on the inside of the skull and appositional growth.[41] When a cranial suture fuses prematurely, growth arrest occurs at the fused suture and further growth occurs at still-patent sutures, altering growth trajectories and producing changes in cranial vault shape. It is assumed that the rapidly growing brain experiences localized compression and corresponding local perfusion-related problems when a suture closes prematurely. This may result in increased intracranial pressure (ICP), especially in patients with multiple prematurely-closed sutures.[6, 42]

During normal development, the metopic suture is known to fuse the earliest, at around 8-12 months of age.[43] This is probably a consequence of its different embryological origin, compared to the other sutures.[40] The sagittal, coronal and lambdoid sutures close during adulthood, between the ages of 22 and 26 years.[43]

PRENATAL DETECTION

In the Netherlands all pregnant women are offered the possibility of a 20 week anomaly ultrasound scan as part of a national screening program. This ultrasound scan aims to detect anatomical anomalies, particularly neural tube defects and other anomalies such as cleft lip/palate and congenital heart defects.[44-46] In total, 95% of all pregnant women choose to participate. Craniosynostosis is known to commence at around 15-18 weeks of gestation.[13] Consequently, the 20-week anomaly scan would in theory be the ideal tool to detect craniosynostosis prenatally. However, isolated craniosynostosis is detected prenatally only sporadically and most often not until the third trimester.[47-50] A number of causes may attribute to this lack of recognition. The skull shape at 20 week's gestation is not yet altered such that differentiation from a normal head shape is possible and although open coronal and lambdoid sutures are straightforward to recognize prenatally due to the positon of the fetal head in utero, the sagittal and metopic sutures are not easily accessible. Additionally, craniosynostosis is a rare disease and not well known within the obstetric/gynecologic community. Most primary care ultrasonographers have never come in contact with this anomaly before, leading to low awareness and correspondingly a lower chance of detection. It could also be due to the fact that the standard measurements performed at the 20-week anomaly scan do not discriminate enough between healthy fetuses and fetuses with craniosynostosis.

Advantages of prenatal detection are numerous. When there is a suspicion of craniosynostosis following prenatal screening an advanced ultrasound scan in combination with 3D ultrasound may provide information on the type and extend of the craniosynostosis. Invasive prenatal diagnostic testing may be offered to discriminate between an isolated craniosynostosis and a syndromic craniosynostosis. A relatively early diagnosis provides the clinician with enough time to properly counsel and prepare the parents, but also to arrange a timely referral to a specialized center. Craniosynostosis care in the Netherlands has been the subject of centralization. Nowadays, only 2 centers are equipped to treat children with isolated craniosynostosis. A referral to one of these 2 centers would benefit the patient greatly. For scaphocephaly patients, for instance, referral before 6 months of age provides the possibility to perform a minimally invasive operation, using springs to correct the deformity. This results in less blood loss, a shorter operative time and hospital stay.[51]

Besides enabling skull growth the skull sutures also enable moulding of the skull when passing through the birth canal during labour.[52] Due to the premature fusion of skull sutures fetal head moulding is restricted. Consequently a higher rate of maternofetal trauma, such as secondary caesarean sections, compared to healthy controls is found.[53, 54] When craniosynostosis is detected prenatally, problems during labor may be anticipated.

TREATMENT

The first report of surgical correction for craniosynostosis dates back to 1888. Dr. L.C. Lane, professor of Surgery at the Cooper Medical College in San Fransisco performed a removal of the fused sutures in a case of microcephaly.[55] Although the procedure went according to plan, the child died the day after surgery due to complications of the anesthetic agent. After this report the operative correction for craniosynostosis was abandoned for over 30 years, until Dr. Mehner published his technique of removal of the fused suture.[56] The surgical technique for correction of craniosynostosis has evolved tremendously since then. This is also illustrated by the amount of research on craniosynostosis that has been performed in the past century (fig 2). A clear rise in number of research papers is noted, showing the increasing knowledge we have gathered in this field over the past decades.

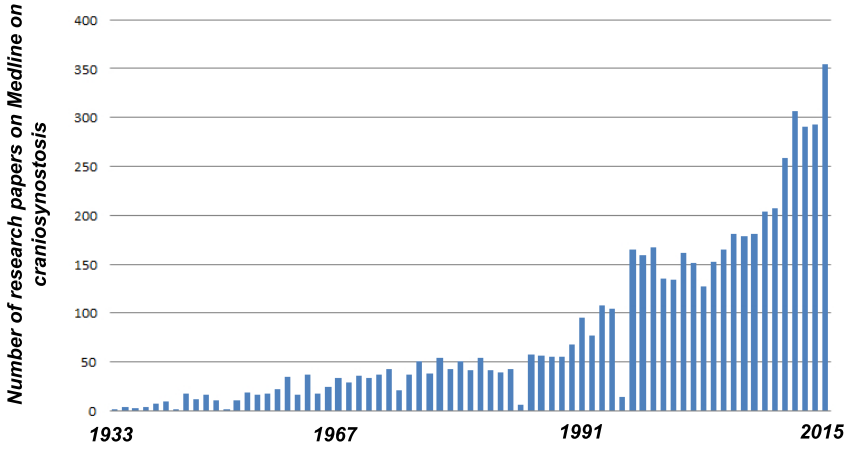

Figure 2. A graph showing the amount of published papers on craniosynostosis from 1933 until 2015.

Treatment of craniosynostosis nowadays has two main aims. Firstly to correct the apparent deformation and normalize the patient's appearance. Secondly, treatment aims to treat or prevent intracranial hypertension.[57, 58]

Treatment differs among the different types of isolated craniosynostosis: In our center unicoronal and metopic synostosis are treated by a fronto-orbital advancement and remodellation, a technique that addresses the frontal bone and supraorbital bar (fig 3).[59] The supraorbital bar is taken out at the level of the frontozygomatic sutures and reshaped using an open-wedge osteotomy at the midline and insertion of a bone graft at this site, while the lateral curves are created through closed wedge osteotomies. The frontal bone is split at the midline, both bone pieces are turned through 180˚, and the resulting bone fragments are adjusted to the best position, with a particular focus on restoring the temporal depressions. The supraorbital bar is corrected in a unilateral (unicoronal) or bilateral (unicoronal and metopic) fashion.

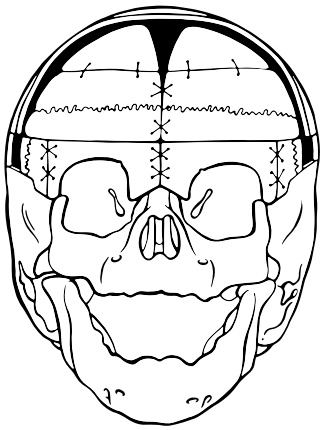

Figure 3. Bilateral fronto-orbital advancement and remodellation to treat metopic synostosis

In our center treatment for scaphocephaly has evolved over the past decades, from an extensive total cranial vault remodeling to a strip craniectomy with or without parietal wedges.[60, 61] Nowadays, a spring-assisted cranioplasty is performed, resulting in less blood loss and operative time(fig. 4).[51] Future long-term follow up studies will have to determine the effect on long term results concerning intracranial hypertension and cosmesis.

Timing of treatment differs among the different types of isolated craniosynostosis as well. At our center, unicoronal synostosis patients are treated at around 9 months of age, trigonocephaly is corrected between 9 and 12 months of age. For scaphocephaly the spring-assisted cranioplasty is performed at 4-6 months, when a patient is referred at a later age a (fronto) biparietal correction is performed at around 9 months. Age at surgery has been a subject of various recent papers, especially for scaphocephaly patients.[7, 9] These papers show that in case of scaphocephaly neurocognitive outcome benefits from early

surgery, before the onset of intracranial hypertension. For unicoronal or metopic synostosis this has not been shown to date.

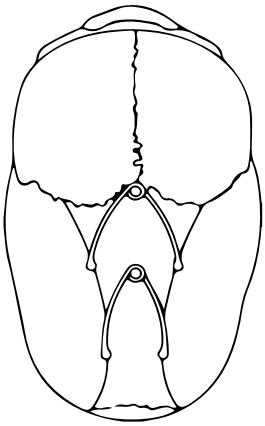

Figure 4. Spring-assisted surgery to treat sagittal synostosis

INTRACRANIAL HYPERTENSION

In 1783 Alexander Monro published his study on intracranial pressure.[62] His findings were later confirmed by his former protégé, George Kellie.[63] The result of their combined studies is now known as the Monro-Kellie doctrine. It stated that the cranium was a 'rigid box' filled with a 'nearly incompressible brain' and that its total volume tends to remain constant. The doctrine states that the cranial content consists of cerebrospinal fluid (CSF), blood and brain tissue and that any increase in the volume of the cranial contents will elevate intracranial pressure. Further, if one of these three elements increases in volume, it must be at the expense of volume of the other two elements. CSF and to a lesser extent blood volume are the main buffers for increased volumes.[64]

An important distinction should be made in the type of intracranial hypertension. Intracranial hypertension as a result of a traumatic injury is characterized by a sudden rise of ICP, due to swelling of the brain tissue. This endangers cerebral blood flow and therefore cerebral oxygenation. The intracranial hypertension that is found in craniosynostosis patients is not characterized by a sudden rise of ICP, but a slow rise, providing the CSF and cerebral blood flow the chance to compensate to some extent. The rise of ICP found in craniosynostosis patients is most often observed during rapid eye movement (REM) sleep.[6] During this period, in which active dreaming takes place and brain activity peaks, the intracerebral blood-volume is increased by intracerebral vaso-dilatation.[65] This leads to increased ICP and shows that the compensatory mechanism described above has its

boundaries. Prolonged intracranial hypertension may lead to swelling of the optic nerve and eventually loss of nerve fibers and a loss of vision. Intracranial hypertension is thought to negatively affect sleep quality, cognition and behavior, possibly leading to a lower IQ, learning disabilities and behavioral disturbances in single-suture craniosynostosis patients.[6, 7, 9, 66]

FACTORS OF INFLUENCE ON INTRACRANIAL PRESSURE

Historically the occurrence of raised ICP in craniosynostosis patients was solely attributed to a growth restriction of the skull.[6] However, since then, evidence was found that other factors influence the occurrence of raised ICP as well.[67-71] Nowadays, the following factors are thought to influence ICP, apart from cranio-cerebral disproportion: venous outflow obstruction, ventriculomegaly (or hydrocephalus if progressive), tonsillar herniation or Chiari I malformation and obstructive sleep apnea (OSA).

For unisutural craniosynostosis cranio-cerebral disproportion and venous outflow obstruction seem to be the most plausible causes of raised ICP, as ventriculomegaly, tonsillar herniation and OSA are rarely seen in these patients.

Cranio-cerebral disproportion

One can conclude from the Monro-Kellie doctrine that when cranio-cerebral disproportion is larger than the possible compensation of CSF and blood, intracranial pressure will rise. This would mean that intracranial volume is inversely related to the occurrence of increased intracranial pressure. In other words, one would assume that a decrease in intracranial volume would mean a higher incidence of increased intracranial pressure. However, this is contradicted by a combination of several recent articles. Maltese et al have shown that patients with trigonocephaly show equal intracranial volumes compared to controls before operation, but end up with a significantly smaller intracranial volume after surgery at three years of age.[72] In contrast, scaphocephaly patients show no difference in intracranial volume before or after surgery compared to controls.[73, 74] Nevertheless, scaphocephaly patients are known to be at higher risk of developing intracranial hypertension.[75] This suggests that besides cranio-cerebral disproportion other factors influence intracranial pressure too.

Venous outflow obstruction

The relation between venous hypertension and hydrocephalus has been a subject of study since the 1980's when Sainte-Rose et al. reported on 14 cases with craniosynostosis.[68] They described the role of increased pressure in the sagittal sinus and its effect on intracranial pressure: a fixed obstruction of the venous outflow resulted in elevated pressures of the

sagittal sinus leading to increased intracranial pressure and dilatation of the ventricles. The sagittal sinus is the largest vein transporting venous blood from the brain to the jugular and sigmoid sinuses. Its impact on intracranial pressure was most dramatically shown by a case reported by Thompson et al.[76] They described a case with an enormous transosseous venous channel emerging above the sagittal sinus. After transecting the vein and stopping the bleeding the child's intracranial pressure rose sharply and although surgery was terminated, the patient died shortly after. Autopsy showed that most pathways for intracranial venous drainage were severely narrowed and the patient must've mainly relied on the transosseous venous channel for venous drainage. These abnormal patterns of venous drainage have been described by several studies mainly focusing on syndromic or complex craniosynostosis.[69, 77] Mursch et al. performed transcranial Doppler ultrasound studies in unisutural craniosynostosis patients, showing a difference in blood flow velocity profile in the sagittal sinus with normalization after surgery.[78] However, the effect of the altered venous drainage on the occurrence of increased intracranial pressure in unisutural craniosynostosis has not been studied to date. The risk of increased intracranial pressure in unisutural craniosynostosis varies from 5.6% in trigonocephaly to 9.6% in scaphocephaly.[75] This difference could be due to the involved skull suture and its effect on the drainage of the sagittal sinus. Venous outflow obstruction could thus play a role in the occurrence of increased intracranial pressure in unisutural craniosynostosis.

Ventriculomegaly, tonsillar herniation and obstructive sleep apnea

As stated before, ventriculomegaly, tonsillar herniation and obstructive sleep apnea influence intracranial hypertension.[67-71] The relation between intracranial pressure and obstructive sleep apnea was first shown by Renier et al.[6] Later, Gonsalez et al. demonstrated elevation of intracranial pressure during rapid eye movement sleep, which was present in syndromic patients in particular.[79] Similarly, intracranial anomalies, such as ventriculomegaly and tonsillar herniation, are more frequent in syndromic craniosynostosis as well.[80] As these factors are rarely seen in unisutural craniosynostosis patients, their influence on intracranial pressure in these patients appears to be minimal.

Detection of intracranial hypertension

The prevalence of intracranial hypertension has been shown to be highly varying throughout literature. One of the factors responsible for this variance is the method of detecting intracranial hypertension. Florisson et al reported elevated intracranial pressure in approximately 6-10% of unisutural craniosynostosis patients.[75] In contrast, Shilito et al. reported the presence of intracranial hypertension in 7 – 19% of unisutural craniosynostosis patients and Thompson et al reported even higher percentages of up to 33%.[81, 82] However,

to compare these numbers, one must be aware of the study methods concerning timing and method of intracranial pressure monitoring that was used in that study. For instance, Shilito et al. described using several parameters, such as separation of uninvolved sutures by x-ray or cracked-pot percussion note of the skull, marked irritability and papilledema, to detect intracranial hypertension. In contrast, Florisson et al used fundoscopy exclusively to detect intracranial hypertension. Thompson et al used the gold standard: invasive intracranial pressure monitoring. This is a more invasive method, making it liable to selection bias when incorporated in a study.

Papilledema was first suggested as an indicator for increased intracranial pressure by Friedrich von Graefe in 1860. He reported his observations on optic nerve swelling in 4 patients with a brain tumor. Later his findings were further clarified by Hayreh, showing a clear relation between raised intracranial pressure and the presence of papilledema.[83-85] The theory behind it is that due to increased intracranial pressure the pressure in the optic nerve sheath is elevated. This causes swelling and edema of the optic nerve, which shows at the fundus, where the optic nerve fibers enter the orbit.

The relation between fundoscopy and intracranial pressure monitoring has been studied by Tuite et al.[86] This study demonstrated a high specificity, but a rather low sensitivity in young patients (22% in patients below 8 years). This suggests that fundoscopy in young patients may have a high rate of false negative results. However, this study, as with the majority of craniosynostosis studies, is limited by its numbers and its results should be interpreted with this in mind. Moreover, fundoscopy is a subjective method of monitoring and its results depend on the one who performs the investigation.

Another method to screen for intracranial pressure is to measure the occipitofrontal head circumference (OFC). Research in syndromic craniosynostosis patients has shown that occipitofrontal head circumference is closely related to intracranial volume and a deflection of the OFC growth curve is a major determinant of intracranial hypertension.[87, 88]

A new method to assess the optic nerve is optical coherence tomography (OCT).[89] OCT showed promising results compared to fundoscopy, providing the clinician with a standardized, objective measurement.[90] However, OCT is not possible in children younger than 3 years of age and its clinical use in a tertiary craniofacial center is currently studied in our center.

LONG TERM FOLLOW-UP

In our center postoperative follow-up is aimed at:

- Early detection of intracranial hypertension
- Early detection of cognitive or behavioral impairment
- Cosmetic satisfactory results

Intracranial hypertension

As stated before, screening for the occurrence of intracranial hypertension can be performed in various ways. In our center a combination of these tools is used. Firstly, patients are routinely seen by our ophthalmologist, who performs a fundoscopy to assess for papilledema, while correcting for ophthalmologic conditions such as hypermetropy. Secondly, the OFC growth curve is constructed at every out-patient clinic visit. Thirdly, the (new) presence of headaches, disturbed sleep or behavioral changes are considered possible indicators of the presence of intracranial hypertension. When one or more of these factors suggest the presence of intracranial hypertension an OCT is taken if possible and a CT or MRI scan is considered. Additionally, invasive intracranial pressure monitoring is considered when results are unclear or contradictory. When OSA is suspected a polysomnography is performed to test for the presence of OSA, which, if present, is treated accordingly. The consequence of increased intracranial pressure without OSA in the postoperative course would be a second decompressing craniotomy, aimed at enlargement of the skull.

Cognition and behavior

For a long time craniosynostosis was regarded as a condition that only affects the skull. In recent years more evidence is coming to light that craniosynostosis does not just affect the skull, but has a profound, primary, effect on the brain itself. In the late 1990's the first literature on cognitive impairment in unisutural craniosynostosis describe cognitive and behavioral abnormalities, especially in metopic suture synostosis patients.[91-93] Since then cognition and behavior have been the subject of various studies from different research collaborations.[8, 10, 94-101] Additionally, the influence of factors such as age at surgery and type of surgery on cognitive outcome have been evaluated.[7, 9] From all these studies, a few conclusions can be distilled:

- Visuomotor, language, learning and memory skills are impaired in unisutural craniosynostosis patients compared to healthy controls.
- Unisutural craniosynostosis patients, especially metopic synostosis patients, are more likely to score above a clinical threshold for behavioral problems compared to controls.
- IQ appears to be slightly less in children with unisutural craniosynostosis, especially in metopic suture synostosis.
- The presence of behavioral problems in metopic synostosis seems to be related to a lower IQ, which is related to the presence of additional congenital anomalies.
- Attention and executive function show no significant difference between unisutural craniosynostosis patients and controls.
- Early, extensive, surgery may improve neuropsychological outcome in sagittal synostosis.

Studying cognitive and behavioral impairment in children is complex and easily subject to bias. Moreover, the found differences in the above mentioned studies were limited and the clinical significance is yet to be determined. There is an ongoing discussion within the craniofacial community concerning all these factors. Future research using comparable groups, eliminating most bias, should clarify this matter further.

Cosmesis

After prevention of intracranial hypertension and prevention of possible neuropsychological deficits, cosmesis is the third reason to perform surgery in children with unisutural craniosynostosis. Although surgery seems to adequately address the first two goals, cosmetic results are variable and depend on what suture is affected. Sagittal suture synostosis is known for its elongated skull, typically accompanied by a bulging forehead and prominent occiput.[60] In contrast, metopic suture synostosis is characterized by a wedge-shaped forehead, supraorbital lateral retrusion and hypotelorism.[102] Surgery aims to address these suture-specific features and some degree of overcorrection is performed to account for residual growth of the surrounding structures.[103, 104]

Cosmetic outcome after craniofacial surgery is well documented for metopic and unicoronal suture synostosis especially. Both conditions are treated by fronto-orbital advancement and remodellation, a technique that addresses the forehead and supraorbital bar, aimed at correcting the contour deformity at the midline (metopic synostosis) and/or lateral supraorbital region (metopic and coronal synostosis). The most seen feature after this type of surgery is temporal hollowing and should be addressed accordingly at primary surgery, with future growth in mind.[102, 104-108] Temporal hollowing is suggested to be of bony origin, indicating diminished bony growth after operation.[59, 109] Whether the diminished bony growth is a negative sequelae of the osteotomies or due to the underlying condition is subject to research and further addressed in this thesis.

AIM OF THIS THESIS

This thesis covers several aspects concerning unisutural craniosynostosis and metopic and sagittal suture synostosis in particular. A number of uncertainties concerning unisutural craniosynostosis will be addressed. To summarize, the aims of this thesis are:

- to confirm reports on a rising prevalence of craniosynostosis and to provide evidence on the background of this increase.
- to enhance prenatal detection of unisutural craniosynostosis.
- to identify the effect of craniosynostosis on perinatal complications.
- to explore the relation between venous outflow obstruction and intracranial hypertension through transfontanellar Doppler ultrasound.
- to accurately establish the prevalence of intracranial hypertension in metopic suture synostosis.
- to clarify the background of temporal hollowing after correction of unicoronal synostosis.

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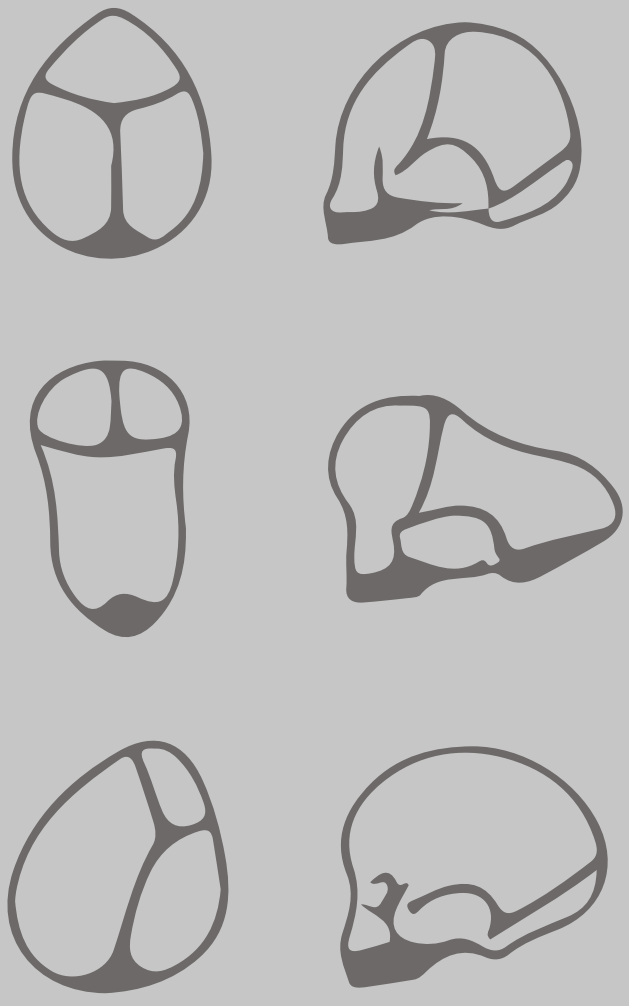

Chapter 2

Increase of prevalence of craniosynostosis

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ABSTRACT

Introduction Craniosynostosis represents premature closure of cranial sutures. Prevalence is approximately 3.1-6.4 in 10.000 live births, which is reportedly rising. This epidemiologic study aims to provide insight into this rise through an accurate description of the prevalence, exploring regional variation and change over time.

Methods The Dutch Association for Cleft Palate and Craniofacial Anomalies was consulted to identify patients with craniosynostosis born between 2008 and 2013. Data were verified using data provided by all hospitals that treated these patients. The following data were collected: date of birth, gender, diagnosis and postal code. Previously reported data from 1997 until 2007 were included to assess for change in prevalence over the years.

Results Between 2008 and 2013 759 patients with craniosynostosis were born in the Netherlands. Prevalence of craniosynostosis was 7.2 per 10.000 live births. Sagittal synostosis was the most common form (44%). Poisson regression analysis showed a significant mean annual increase of prevalence of total craniosynostosis (+12.5%), sagittal (+11.7%) and metopic (+20.5%) synostosis from 1997 to 2013.

Conclusion The prevalence of craniosynostosis is 7.2 per 10.000 live born children in the Netherlands. Prevalence of total craniosynostosis, sagittal and metopic suture synostosis has risen significantly from 1997 until 2013, without obvious cause.

INTRODUCTION

Craniosynostosis is defined as the premature closure of one or more cranial sutures, resulting in a characteristic distorted head shape and an increased risk of elevated intracranial pressure. The prevalence, according to the best available sources, ranges from 3.1-6.4 in 10.000 live births.[1-5] In 21% it is caused by a known genetic disorder, the remaining 79% are considered non-syndromic craniosynostosis.[6, 7]

The commonest single-suture craniosynostosis form is sagittal suture synostosis, comprising approximately 40-60% of single-suture craniosynostosis patients.[1, 3, 5, 6, 8-10] A rise of metopic suture synostosis has been reported, reflecting the changing demographics of craniosynostosis in both Europe and the United States.[3, 9-11]

Since 1991 the Dutch Association for Cleft Palate and Craniofacial Anomalies has kept record of all craniosynostosis patients born in the Netherlands. This continuous professional-based registry enables an accurate estimate of the prevalence of the different forms of craniosynostosis, assuming all cases are detected at some stage. Previous research at our center reported the prevalence of sagittal and metopic suture synostosis using this database and consulting the treating hospitals for the years 1997 – 2007.[3] Recently we notified a steady increase of the number of cases referred to our unit. This may reflect changing awareness of parents or caregivers, changing referral patterns, or may indeed reflect changing epidemiology. The epidemiologic study presented here aims to provide evidence on the background of this increase, through an accurate description of the prevalence of each type of non-syndromic and syndromic craniosynostosis, exploring regional variation and change over time.

METHODS

This study was approved by the institution's medical ethical board: MEC-2015-117. The approval included the use of registry data. As this was a retrospective study with an anonymous data-extract formal consent was not required.

The national registry of the Dutch Association for Cleft Palate and Craniofacial Anomalies (*Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen)*—the Dutch national registration authority for cleft lip/palate and craniofacial anomalies— was consulted to identify patients with craniosynostosis born between 2008 and 2013. This register contains anonymous data of all craniosynostosis cases coming under professional care. A data extract was provided containing birth date, gender, diagnosis and the registering center. The data obtained through this national register were verified at the local level i.e. the individual hospitals (all tertiary centers) where the patients were treated: Sophia Children's Hospital

– Erasmus Medical Center, Rotterdam; Radboud University Medical Center, Nijmegen; Maastricht University Medical Center, Maastricht; Academic Medical Center, Amsterdam; University Medical Center, Utrecht. Subsequently the postal codes of the included cases were supplied by the treating hospitals to enable epidemiological analysis.

Patients with the following diagnoses were included in the study:

- Single suture craniosynostosis: sagittal, metopic, coronal, lambdoid or fronto-sphenoidal synostosis.
- Syndromic craniosynostosis: Apert's, Crouzon-Pfeiffer's, Muenke's, and Saethre-Chotzen's syndrome, craniofrontonasal dysplasia (CFND) with craniosynostosis, Carpenter syndrome, TCF12-related craniosynostosis and all other known genetic mutations such as IL11RA, ERF and MSX2.
- Complex craniosynostosis: Multiple suture synostosis, without known genetic cause.

Data collected included: date of birth, gender, diagnosis and (crude) postal code. Four-digit postal codes enabled analysis of geographical epidemiology including variation in detection of craniosynostosis.

Only patients with primary craniosynostosis were included, i.e. cases were excluded with secondary craniosynostosis due to, for example, a VP-shunt or microcephaly. Additional exclusion criteria were: 1) patients with a metopic ridge only, a very mild form of trigonocephaly with no indication for surgical intervention; 2) patients with craniosynostosis born abroad, but treated in the Netherlands.

The Dutch perinatal registry registers all births in The Netherlands. The birth data for the years 2008 to 2013 were obtained from their annual public reports.[12, 13] A Poisson regression analysis was performed to assess for an increase or decrease in prevalence of the different subtypes of craniosynostosis. The total live birth count of the Netherlands from 2008 – 2013 was included in this analysis as offset.

Subsequently data derived from an earlier paper by Kweldam et al. covering 1997 – 2007 was included to assess for change in prevalence of total craniosynostosis and more specifically for metopic and sagittal synostosis.[3] For the other subtypes of craniosynostosis these data were not available in sufficient detail. For the combined dataset a Poisson regression analysis was performed.

The Netherlands is since 1960 subdivided into approximately 4000 4-digit postal codes. In the present study the 4-digit postal codes were grouped into 6 different regions, based on state boundaries and regional referral patterns (figure 1). To assess the regional evenness of prevalence the prevalence of craniosynostosis in these areas was related to the birth rate of these regions, provided by the Dutch Perinatal Registry, the online data of Statistics Netherlands, and reports relying on these sources. [14] The absence of regional prevalence differences was tested using a standard chi-square test.

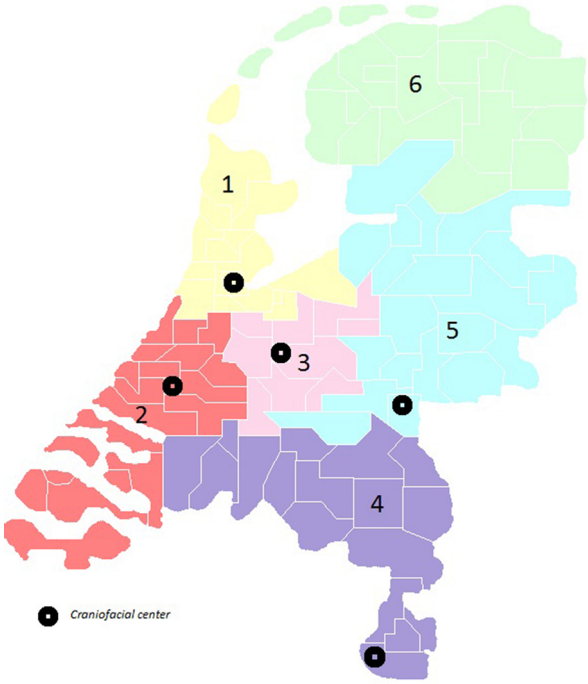

Figure 1 To assess regional spread the Netherlands was divided into 6 regions, based on state boundaries and location of regional referral centers.

RESULTS

Between January 1st 2008 and December 31st 2013, 759 patients with craniosynostosis were born in the Netherlands. Single suture craniosynostosis occurred in 666 patients (87.7%), while syndromic and complex craniosynostosis represented 93 of the cases (12.2%) (table 1, figure 2). The overall prevalence for craniosynostosis was 7.2 per 10.000 live births (about 1:1400). The male:female ratio was 2.2:1 for the whole study population, while this ratio was 2.5:1 in single suture craniosynostosis and 1:1.1 in syndromic cases.

To achieve the highest accuracy in the registered numbers of all subtypes the registry of the Dutch Association for Cleft Palate and Craniofacial Anomalies the data was cross referenced with the data provided by the treating hospitals. In total the hospitals reported 65 patients whom were not registered at the national registry.

Table 1 Craniosynostosis: absolute numbers and prevalence per 10.000 live births from 2008 to 2013 ([1] Abs = absolute)

	2008		2009		2010		2011		2012		2013		Total	
	Abs (%)[1]	Prevalence	Abs (%)	Prevalence	Abs (%)	Prevalence	Abs (%)	Prevalence	Abs (%)	Prevalence	Abs (%)	Prevalence	Abs (%)	Prevalence
Total	123 (100)	6.926	135(100)	7.520	107(100)	6.002	139(100)	7.826	128(100)	7.307	127(100)	7.515	759(100)	7.179
Single suture	106 (86.2)	5.698	112(83.0)	6.239	90(84.1)	5.049	124(89.2)	6.981	118(92.2)	6.736	116(91.3)	6.864	666(87.7)	6.300
Sagittal	61 (57.5)	3.435	61 (54.5)	3.398	43 (47.8)	2.412	64 (51.6)	3.603	56 (47.4)	3.197	51 (44.0)	3.018	336(50.5)	3.178
Metopic	36 (34.0)	2.027	39 (34.8)	2.172	36 (40.0)	2.019	41 (33.1)	2.308	45 (38.1)	2.569	44 (37.9)	2.604	241(36.2)	2.280
Unicoronal	7 (6.6)	0.394	10 (8.9)	0.557	8 (8.9)	0.449	17 (13.7)	0.957	13 (11.0)	0.742	18 (15.5)	1.065	73 (11.0)	0.691
Unilambdoid	0 (0.0)	0.000	2 (1.8)	0.111	3 (3.3)	0.168	1 (0.8)	0.056	4 (3.3)	0.228	2 (1.7)	0.118	12 (1.8)	0.114
Frontosphenoïdal	2 (1.9)	0.113	0 (0.0)	0.000	0 (0.0)	0.000	1 (0.8)	0.056	0 (0.0)	0.000	1 (0.9)	0.059	4 (0.6)	0.038
Syndromic	17 (13.8)	0.957	23 (17.0)	1.281	17 (15.9)	0.954	15 (10.8)	0.845	10 (7.8)	0.571	11 (8.7)	0.651	93 (12.2)	0.880
Complex	5 (29.4)	0.282	9 (39.1)	0.501	9 (52.9)	0.505	5 (33.3)	0.282	6 (60.0)	0.342	4 (36.4)	0.237	38 (40.9)	0.359
Apert	4 (23.5)	0.225	4 (17.4)	0.223	4 (23.5)	0.224	0 (0.0)	0.000	0 (0.0)	0.000	2 (18.1)	0.118	14 (15.1)	0.132
Muenke	1 (5.9)	0.056	3 (13.0)	0.167	3 (17.6)	0.168	1 (6.6)	0.056	2 (20.0)	0.114	1 (9.1)	0.059	11 (11.8)	0.104
Crouzon-Pfeiffer	2 (11.8)	0.113	3 (13.0)	0.167	1 (5.9)	0.056	2 (13.3)	0.113	1 (10.0)	0.057	1 (9.1)	0.059	10 (10.8)	0.095
Saethre-Chotzen	1 (5.9)	0.056	3 (13.0)	0.167	0 (0.0)	0.000	3 (20.0)	0.169	1 (10.0)	0.057	2 (9.1)	0.118	10 (10.8)	0.095
TCF12	3 (17.6)	0.169	0 (0.0)	0.000	0 (0.0)	0.000	1 (6.6)	0.056	0 (0.0)	0.000	1 (9.1)	0.059	5 (5.4)	0.047
IL11RA	1 (5.9)	0.056	1 (4.3)	0.056	0 (0.0)	0.000	2 (13.3)	0.113	0 (0.0)	0.000	0 (0.0)	0.000	4 (4.3)	0.038
CFND	0 (0.0)	0.000	0 (0.0)	0.000	0 (0.0)	0.000	1 (6.6)	0.056	0 (0.0)	0.000	0 (0.0)	0.000	1 (1.1)	0.009

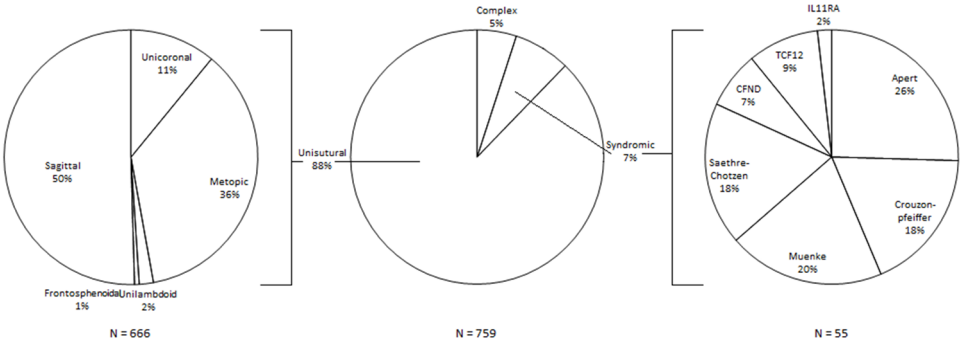

Figure 2 Proportions of all subtypes of craniosynostosis. Cohort 2008 – 2013.

Single suture craniosynostosis

In total, 666 patients with single suture craniosynostosis were identified. The prevalence of single suture craniosynostosis was 6.3 per 10.000 live-births. Absolute numbers and prevalence of all subtypes during the complete study period are shown in table 1 and figure 3.

Male:female ratios were 3.9:1 for sagittal, 3.0:1 for metopic, 1:3.6 for unicoronal and 3:1 for unilambdoid synostosis. All frontosphenoidal synostosis patients (n=4) in this study were male.

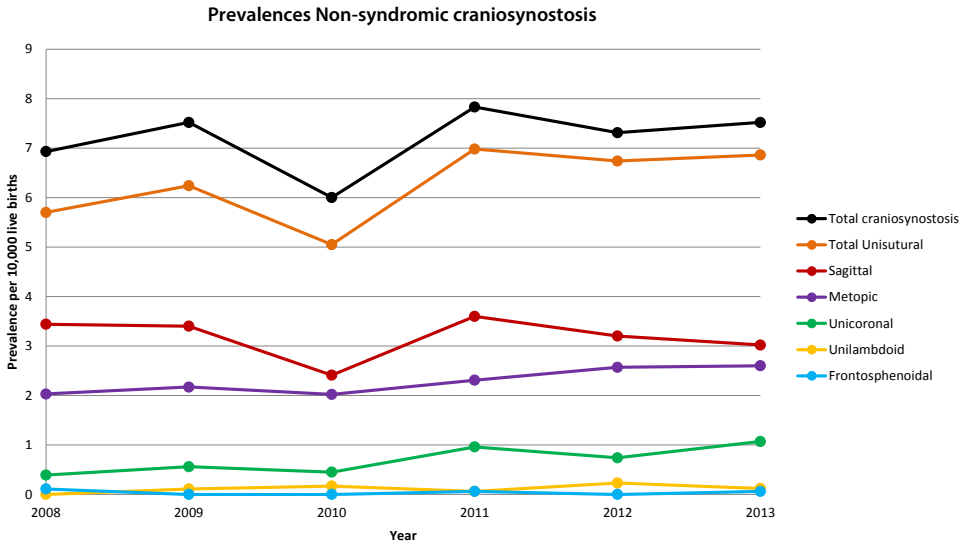

Figure 3 Prevalence of total and single suture craniosynostosis during 2008 – 2013.

The 73 patients with unicoronal synostosis were coded as apparently non-syndromic, based on clinical evaluation. In 43 of these patients (59%) this clinical evaluation was confirmed by negative genetic tests. In the remaining 30 patients no genetic testing was performed.

Syndromic and complex craniosynostosis

This study identified 55 syndromic and 38 complex craniosynostosis cases. This resulted in a prevalence of 0.9 per 10.000 live births. Absolute numbers and prevalence of all syndromic subtypes are shown in table 1 and figure 4.

Male:female ratio was 2.2:1 for complex craniosynostosis, 1.3:1 for Apert, 1:1.8 for Muenke, 1:1.5 for Crouzon-Pfeiffer and 1:8 for Saethre-Chotzen. All CFND and TCF12 related craniosynostosis patients in this study were female. The single IL11RA patient was male.

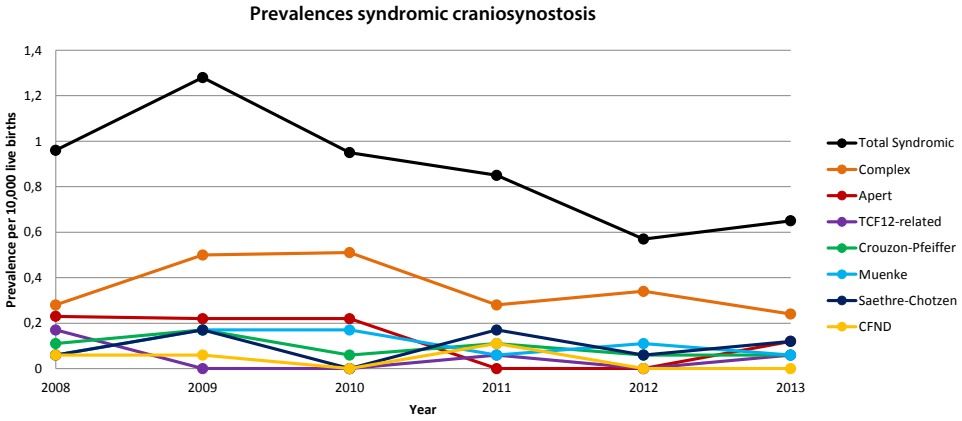

Figure 4 Prevalence of syndromic and complex craniosynostosis during 2008 – 2013.

Trend over time

Poisson regression analysis did not show a significant increase or decrease of any of the subtypes within this study period. (Table 2)

A subset analysis with Poisson regression on the total craniosynostosis count and more specifically metopic and sagittal synostosis, combined with the data from Kweldam et al., was performed. This showed a significant annual 12.5% increase of total craniosynostosis ($p<0.0001$). For trigonocephaly the annual increase was 20.5% per year ($p<0.0001$), for scaphocephaly 11.7% ($p<0.0001$). (Figure 5, Table 3)

Table 2 Poisson regression analysis for all craniosynostosis subtypes seen from 2008 until 2013. α = 0.003 after Bonferroni correction.

Diagnosis	Beta	P-value
Scaphocephaly	-0.019	0.56
Trigonocephaly	0.049	0.20
Unicoronal	0.179	0.01
Unilambdoid	0.210	0.23
Frontosphenoidal	-0.171	0.57
Complex	-0.078	0.42
Apert	-0.338	0.05
Muenke	-0.075	0.68
Crouzon-Pfeiffer	-0.171	0.37
Saethre-Chotzen	0.038	0.84
TCF12-related	-0.326	0.26
CFND	-0.265	0.40
IL11RA-related	0.179	0.77
Total Single suture	0.030	0.18
Total Syndromic/Complex	-0.129	0.04
Total Craniosynostosis	0.011	0.60

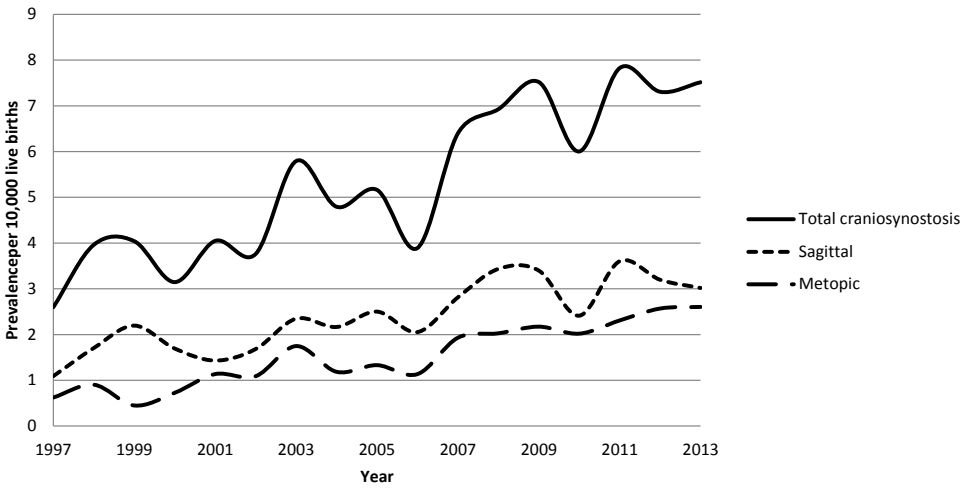

Figure 5 A significant rise of craniosynostosis and more specifically metopic and sagittal suture synostosis was noted (p<0.0001, Poisson regression analysis). Data from 1997 – 2007 are derived from the paper of Kweldam et al. in 2011.[3]

Table 3 Poisson regression analysis for trigonocephaly and scaphocephaly seen from 1997 until 2013. α = 0.017 after Bonferroni correction.

Diagnosis	Beta	P-value	Mean annual effect
Total craniosynostosis	0.051	0.000	+12.5%
Trigonocephaly	0.081	0.000	+20.5%
Scaphocephaly	0.048	0.000	+11.7%

Regional distribution and detection rate

From the treating medical centers we obtained the 4 digit postal code. Postal codes were divided into 6 different regions. Distribution was not significantly different from the estimate (p=0.08), see table 4.

Table 4 Regional spread of craniosynostosis in the Netherlands. [1] Calculated from data provided by the Perinatal Registration of the Netherlands, 2011. (P = 0.08)

Regional code	Study population n (%)	Total Births[1] n (%)
1	125 (16.5)	33278 (18.9)
2	185 (24.3)	43365 (24.6)
3	96 (12.6)	20643 (11.7)
4	127 (16.7)	30681 (17.4)
5	163 (21.5)	31446 (17.9)
6	63 (8.3)	16602 (9.4)
Total	759	176015

DISCUSSION

In this study, we evaluated epidemiological aspects of craniosynostosis in the Netherlands from 2008 to 2013. Compared to data reported in the literature, the present study shows a higher prevalence of 7.2 per 10.000 live births for the total group of craniosynostosis (table 5). [1-5]

Table 5 Prevalence of craniosynostosis reported in the literature.[1] Prevalence per 10.000 live births

Study	Prevalence[1]
French et al, 1990 [2]	3.1
Lajeunie et al, 1995 [4]	4.8
Singer et al, 1999 [5]	5.1
Boulet et al, 2008 [1]	4.3
Kweldam et al, 2011 [3]	6.4

Confirming our expectation based on referral numbers at our unit, Poisson regression showed a significant increase in prevalence from 1997 to 2013. This analysis included data from an earlier publication by Kweldam et al., who performed an epidemiologic study using the same methodology as the present study.[3] This showed a significant rise of prevalence of all three groups, ranging from 11.7% to 20.5% mean annual increase. This confirms recent reports on the increasing prevalence of metopic suture synostosis.[3, 9-11] This rise could be due to two reasons. Firstly, the true prevalence could be on the rise. Secondly, raised awareness among health care providers may have led to a greater detection. Since 2011 a guideline for craniosynostosis care has been implemented in the Netherlands.[15] If this had influenced detection greatly, a sudden change in numbers would be seen after 2011. However, using data from 1997 to 2013 showed this rise to be ongoing for a longer period. This implies that an improved awareness (detection drift) is not the single reason for the rise and that the prevalence may indeed rise. The intriguing question is what factors are at the background.

We were happy to demonstrate about equal detection rates at the national level. Primary care in the Netherlands is organized nationwide, hence we would not expect organization-based differences in referral patterns. Apparently the distance to tertiary centers is not a barrier for referral to tertiary centers (in particular an issue in parts of regions 5, 6, and 7). Also the data suggest universal treatment indications in practice.

Previous literature has shown a birth prevalence of 0.4 per 10.000 live births for syndromic craniosynostosis.[1] More specifically, reported prevalence per syndrome include 0.4 per 10.000 live births for Muenke[6], 0.165 for Crouzon-Pfeiffer [16, 17], 0.2-0.4 for Saethre-Chotzen[18] and 0.1 for Apert syndrome[17]. The present study shows a birth prevalence of 0.5 per 10.000 live births for syndromic craniosynostosis with a confirmed genetic diagnosis. This accounts for approximately 7% of all craniosynostosis cases. However, Wilkie et al. report a proportion of 21% of syndromic craniosynostosis with known genetic diagnoses in a comparable cohort.[6] There are two possible explanations for this difference. Firstly, in our cohort not all patients were genetically tested. In the Netherlands specific genetic testing is offered only, if a genetic alteration is suspected on clinical grounds, such as multiple suture synostosis, familial cases or the presence of additional birth defects. While whole exome sequencing is implemented in our clinical practice, it is only performed if a genetic alteration is suspected on clinical grounds and tests for known genetic alterations are negative. In the case of unicoronal synostosis, genes such as TCF12 and FGFR3 (P250R mutation) are known for their mild phenotype and can thus be missed with this approach.[7, 19] Secondly, metopic suture synostosis is related to several chromosomal abnormalities, such as alterations in chromosome 9p and 11q. In contrast with the paper by Wilkie et al., in this study patients with such alterations are classified as a metopic suture synostosis. Although limited, this negatively influences the proportion of syndromic craniosynostosis. Taken the arguments

together, we expect the 7% found in this study to be a lower bound of the actual proportion of syndromic craniosynostosis.

Wilkie et al. have found that Muenke syndrome is the commonest form of syndromic craniosynostosis, followed by Crouzon-Pfeiffer, Saethre-Chotzen and Apert syndrome. [6] In the present study, Apert syndrome represented the greatest proportion of patients with syndromic craniosynostosis. This can be explained by the clear presentation of Apert's syndrome as opposed to the variable clinical presentation of the other syndromes, such as Muenke and TCF12, which can be mild.[7, 19, 20] Additionally, Crouzon-Pfeiffer syndrome is known for its possible mild presentation and its less abnormal postnatal skull growth than Apert syndrome patients.[21] Previous research showed a prevalence of 0.165 per 10.000 live births, accounting for approximately 4.8% of all craniosynostosis patients.[16] The present study shows a prevalence of 0.095 per 10.000 live births and a proportion of 1.3%. This would indicate that Crouzon-Pfeiffer syndrome is still not fully detected as such in the Netherlands. However, Cohen et al. performed their research based on papers before 1992. Recent literature has shown the changing epidemiology of craniosynostosis, emphasizing the need for recent data on prevalence of the various craniosynostosis syndromes and subforms.

CONCLUSION

The prevalence of craniosynostosis is 7.2 per 10.000 live born children in the Netherlands. Prevalence of total craniosynostosis, sagittal and metopic suture synostosis has risen significantly from 1997 until 2013.

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Chapter 3

Prenatal ultrasound parameters in single-suture craniosynostosis

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ABSTRACT

Introduction Although single-suture craniosynostosis is diagnosed sporadically during pregnancy, timely referral is critical to its treatment. Additionally, craniosynostosis leads to increased maternofetal trauma at birth. In the Netherlands, 95% of pregnant women receive a standard ultrasound at around 20 weeks of gestation, potentially an ideal setting for detecting craniosynostosis prenatally. To enhance prenatal detection of metopic and sagittal suture synostosis, we wished to identify new screening parameters.

Materials and methods

We retrospectively analyzed data of the 20-week anomaly scan in trigonocephaly patients (n=41), scaphocephaly patients (n=41) and matched controls (n=82). We measured six different cranial dimensions, including head circumference, biparietal diameter and occipito-frontal diameter, defining the cephalic index as the ratio between biparietal and occipito-frontal diameter.

Results Prenatal biometric measurements did not differ significantly between trigonocephaly patients and controls. Although significantly lower in scaphocephaly patients (0.76 versus 0.79; p=0.000), the cephalic index by itself is not appropriate for screening at 20 weeks of gestation. Longitudinal analysis suggests a deflection in BPD curve is found in scaphocephaly patients, starting at 20 weeks of gestation.

Conclusions Prenatal biometric measurements do not differ significantly between trigonocephaly patients and controls. The CI is lower in scaphocephaly patients. A deflection in BPD curve should be followed by 3D imaging of the cranial sutures.

INTRODUCTION

During normal development, skull development starts with the formation of bone centers within the membranous anlage, covering the brain. From these, calvarial bones enlarge by ongoing ossification at the edges and cranial suture development starts at the sites where the bones come in close proximity. While open, the cranial sutures are the major sites of calvarial growth.[1] Normally the metopic suture is completely fused at one year of age. The sagittal suture, however, remains open throughout youth and eventually closes at 22-24 years of age.[2] Premature fusion of a suture is known as craniosynostosis and results in an altered head shape and increased risk of elevated intracranial pressure (fig. 1). The process of premature fusion is known to start at 15 weeks of gestation for trigonocephaly and at 18 weeks for scaphocephaly.[1]

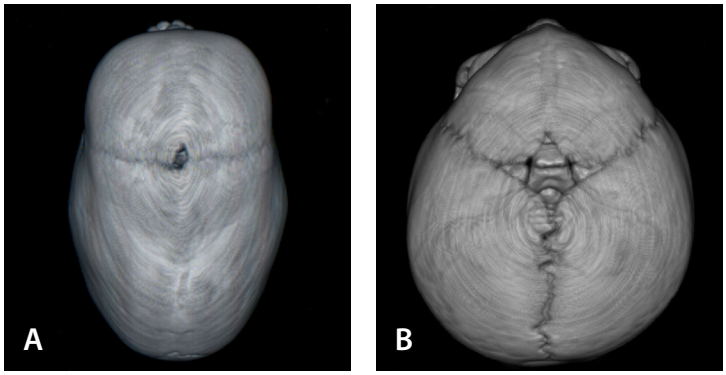

Figure 1 Sagittal and metopic suture synostosis results in different skull shapes shown on a CT-scan before operation. Left: Sagittal suture synostosis, resulting in the typical boat-like shaped skull, scaphocephaly. Right: Metopic suture synostosis, resulting in trigonocephaly.

In 24% of patients, craniosynostosis is accompanied by additional anomalies (syndromic craniosynostosis). In the remaining 76% of patients, craniosynostosis is the only finding, referred to as the isolated form.[3] The two commonest isolated forms are sagittal suture synostosis, called scaphocephaly for its resulting deformity, with an incidence of 1:3,000 live births, and metopic suture synostosis, called trigonocephaly, with an incidence of 1:4,500 live births.[4] Neuropsychological development of children with single suture craniosynostosis is affected.[5] Early surgery (before 6 months of age) may possibly prevent this to some extent.[6] As routine part of free accessible antenatal care in the Netherlands, a 20-week anomaly scan is offered to all pregnant women and 95% chooses to participate.[7] Apart from the syndromic forms, isolated craniosynostosis is detected only sporadically during prenatal ultrasound and, if so, in the third trimester.[8]

An important function of the cranial sutures is to enable molding of the skull when passing through the birth canal.[9] Craniosynostosis may interfere with this natural adaptive process and preclude a normal birth. A higher rate of vaginal breech deliveries and secondary cesarean sections, compared to the general population, has been reported among neonates who were diagnosed with craniosynostosis after birth.[10] Prenatal detection of craniosynostosis could anticipate delivery complications and would enable timely, well-anticipated and on average less invasive treatment and therefore less risk and subsequent complications.

This study aims to identify new ultrasound-based screening methods to enhance prenatal detection of sagittal and metopic suture synostosis. We retrospectively analyzed in a blinded fashion prenatal ultrasound scans performed between 18 and 22 weeks of gestation of 41 scaphocephaly patients, 41 trigonocephaly patients, and their matched controls. To our knowledge this is the first study to investigate prenatal ultrasound detection of the selected types of single-suture craniosynostosis in a large cohort with matched controls.

MATERIALS AND METHODS

The Erasmus University Medical Center's medical ethical board approved this study. (MEC-2013-293)

Patients who were treated for scaphocephaly or trigonocephaly from 2006 to 2013 in the Sophia Children's Hospital in Rotterdam, the Netherlands, were identified. Exclusion criteria were twin pregnancy, a syndromic diagnosis and incomplete follow-up to surgery. Parents of all included patients were asked to provide permission to retrieve ultrasound data and images of the 20-week anomaly scan for the purpose of this study.

Matching

For all patients of whom ultrasound images were available of the 20-week anomaly scan a matched control was obtained. The control population was provided by the *'Foundation Prenatal Screening, south-west region of the Netherlands'* which is responsible for the quality assurance and audit program of 20-week prenatal screening in the South-West region of the Netherlands (approx. 2.5M inhabitants). Exclusion criteria for the control scans were presence of structural anomalies and twin pregnancy. Patients and controls were matched on gestational age (maximum discrepancy of 6 days) and fetal presentation at the 20-week anomaly scan, as breech position may have an effect on BPD.[11] For each case, one control was obtained.

Biometrics

Biometric measurements performed during the 20-week anomaly ultrasound examination included head circumference (HC), biparietal diameter (BPD), occipito-frontal distance (OFD), trans-cerebellar diameter (TCD), inner and outer orbital distance (IOD and OOD) and cephalic index (CI). HC, BPD and OFD were all measured in the standardized axial plane of the cranium.[12] For HC an ellipse was drawn around the outline of the skull, BPD was measured at the outer—outer diameter perpendicular to the midline and OFD was an anteroposterior measurement from outer skull to outer skull. For TCD the distance between the outer lateral edges of the cerebellum was measured in the suboccipito—bregmatic plane.[9, 12-14] The IOD was measured between the inner side of the medial margins of the orbitae and the OOD was measured between the inner sides of the lateral margins of the orbitae. All primary measurements were in absence of any adjuvant information. The CI was calculated as the BPD/OFD ratio.[13] Norm values were derived from Chitty et al.[13] One expert reviewer (I.A.), blinded for the diagnosis, reviewed all original measurements, substituting missing or manifest incorrect values by measurements using the standard *Astraia Software for Women's Health, Obstetric and Gynaecological Database* which allows importation and recalibration of images prior to making measurements.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v21. For the biometric measurements we performed a paired samples t-test, as advocated for case-control studies, matched in a 1:1 fashion, by Niven et al.[15] The intention was an exploratory analysis. Threshold for testing was p=0.05.

Bonferroni's correction was applied to correct for multiple testing. To explore the potential for diagnostic use of the biometric measurements, in particular the cephalic index, we constructed a ROC curve. The yield of the cephalic index was established on various cut-off points; in particular we explored whether above a particular threshold a substantial number of cases were included (screening purpose).

RESULTS

A total of 272 craniosynostosis patients were found eligible and were approached for participation. In total, 74 metopic suture synostosis patients and 130 sagittal suture synostosis patients returned the questionnaire (figure 2). Of the participating patients, median (postnatal) age at referral to our center was significantly higher for trigonocephaly compared to scaphocephaly (5.1 vs 3.2 months, p=0.003, table 1). None of the participating patients was diagnosed prenatally.

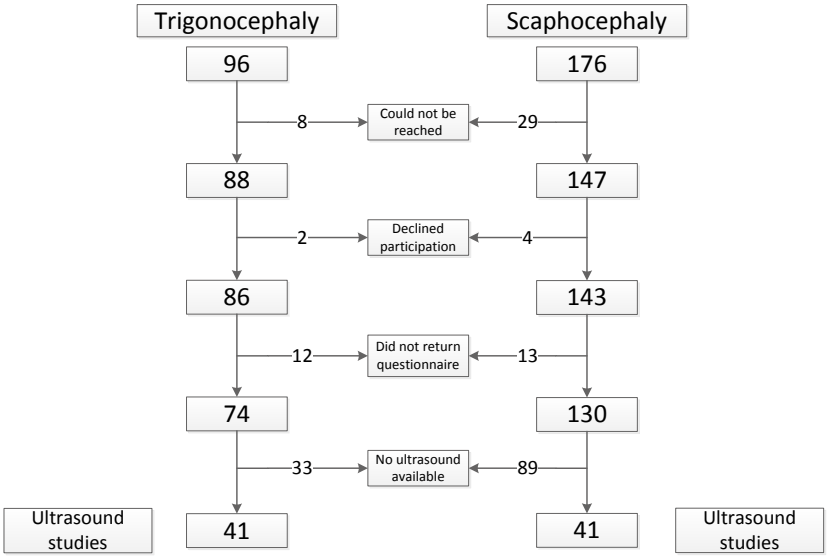

Figure 2 A flowchart of the inclusion of patients.

Table 1 Age at time of referral to our center.

	Trigonocephaly n = 74	Scaphocephaly n = 130
Age at first visit in months	5.1	3.2
(median, interquartile range)	(2.4 – 7.5)	(2.1 – 4.4)
Proportion of patients referred after preferred age for operation	4%	24%

Ultrasound images of the 20-week anomaly scan were digitally available in 41 out of 74 trigonocephaly patients and in 41 out of 130 scaphocephaly patients. Baseline and matching data are shown in table 2. In both patient groups 93% of the pairs were matched with a maximum difference of one day. Maximum difference in gestational age between case and control at time of prenatal ultrasound was six days.

Table 2 Baseline characteristics and matching data.

		Trigonocephaly (n=41)	Trigonocephaly controls (n=41)	Scaphocephaly (n=41)	Scaphocephaly controls (n=41)
Gestational age mismatch in days median (maximum)		0 (3)		0 (6)	
Fetal presentation at anomaly scan	Cephalic	22 (54%)	22 (54%)	24 (59%)	24 (59%)
	Breech	19 (46%)	19 (46%)	17 (41%)	17 (41%)

Biometrics

An example of both a trigonocephaly and scaphocephaly patient's 20-week anomaly scan is shown in figure 3.

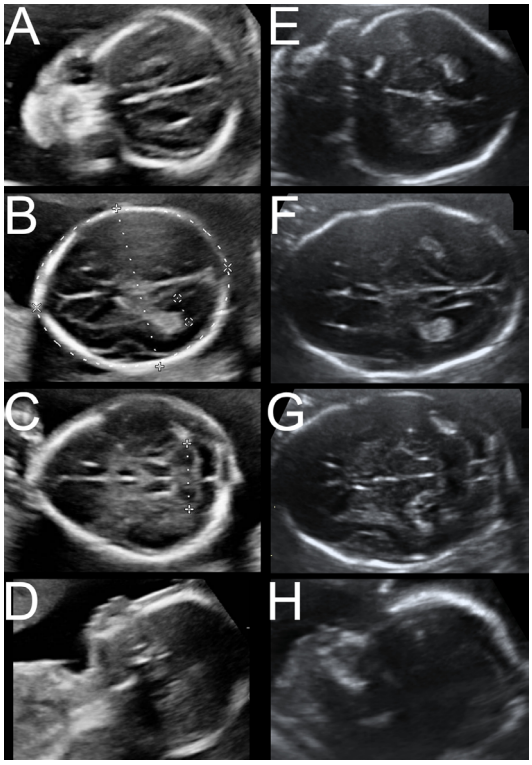

Figure 3 Images of the 20-week anomaly scan of a trigonocephaly and scaphocephaly patient. Images A-D show ultrasound images of a trigonocephaly patient. Images E-H show the ultrasound study of a scaphocephaly patient.

Table 3 shows the outcomes of the paired samples t-test for the biometric data. In the trigonocephaly group, no significant differences were found. In scaphocephaly patients, the cephalic index is significantly lower than in its matched control group (mean 0.76 vs 0.79; $p<0.001$). Bonferroni's correction implied that the threshold for significance was a p-value of .007.

Table 3 Paired samples t-test on biometric data.

	N	Trigonocephaly	Control	P-value	N	Scaphocephaly	Control	P-value
Gestational age (weeks)	41	20.3 ± 0.6	20.4 ± 0.6	-	41	20.4 ± 0.6	20.5 ± 0.7	-
HC (mm)	41	178.12 ± 11.3	175.49 ± 9.7	0.11	41	180.16 ± 9.2	178.87 ± 9.7	0.36
BPD (mm)	41	49.65 ± 3.5	48.65 ± 3.4	0.07	41	49.07 ± 2.1	49.90 ± 3.0	0.10
OFD (mm)	41	63.11 ± 4.6	62.79 ± 3.7	0.64	41	64.99 ± 4.2	63.47 ± 3.7	0.01
TCD (mm)	36	19.93 ± 3.6	20.92 ± 0.9	0.11	37	20.49 ± 1.2	20.99 ± 1.2	0.01
IOD (mm)	13	12.64 ± 1.3	13.04 ± 1.1	0.31	15	13.12 ± 1.0	12.66 ± 1.1	0.24
OOD (mm)	13	33.82 ± 1.9	33.45 ± 2.1	0.66	15	33.50 ± 2.0	33.31 ± 1.37	0.76
CI	41	0.79 ± 0.04	0.78 ± 0.04	0.11	41	0.76 ± 0.04	0.79 ± 0.04	0.00*

* following Bonferroni correction a p-value < 0.007 was considered statistically significant (SD=standard deviation, HC=Head circumference, BPD=biparietal diameter, OFD=occipito-frontal diameter, TCD=transcerebellar diameter, IOD=inner orbital diameter, OOD=outer orbital diameter, CI=cephalic index) Parameters are presented as mean ± SD.

To assess the diagnostic value of the cephalic index in scaphocephaly patients a ROC curve was plotted resulting in an area under the curve of 0.70, indicating a fair diagnostic test (fig. 4). Table 4 shows the different test characteristics for various cut-off values. The discriminative power, in terms of the positive likelihood ratio, is maximal (6.4) at CI=0.73.

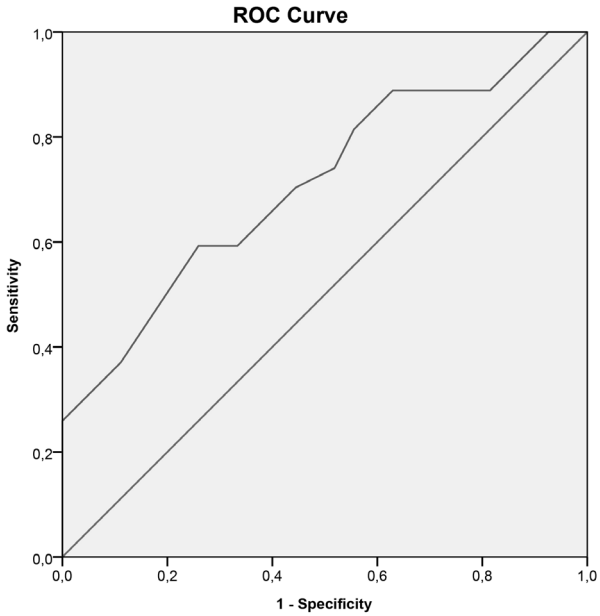

Figure 4 ROC curve to assess the diagnostic value of the cephalic index in scaphocephaly patients. (Area under the curve = 0.702)

Table 4 Test characteristics of the Cephalic Index for Scaphocephaly. Sensitivity, specificity and positive likelihood ratio for different cut-off values of the CI. CI: Cephalic Index

CI Cut off value	Sensitivity	Specificity	Positive Likelihood ratio
0.72	0.27	0.95	5.4
0.73	0.32	0.95	6.4
0.74	0.41	0.88	3.4
0.75	0.51	0.78	2.3

For eight scaphocephaly patients additional ultrasound images at the late second and third trimester were available. HC, BPD, OFC and CI were measured to explore the change of these parameters during fetal development (fig. 5). A notable deflection in the BPD-curve, compared to the norm population, was noted. Two out of the eight patients were in breech position at the time of their last scan.

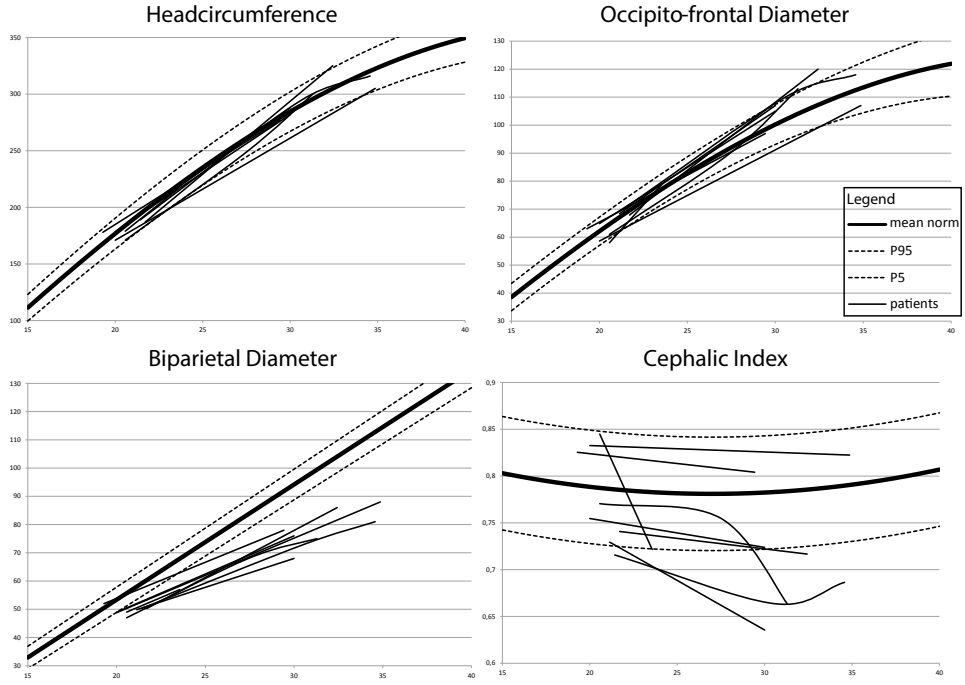

Figure 5 Longitudinal growth curves of the HC, BPD, OFD and CI of 8 scaphocephaly patients in which additional ultrasounds were available. Norm curves are derived from Chitty et al.[13] None of the patients were diagnosed prenatally.

DISCUSSION

Scaphocephaly patients showed a significant lower cephalic index at 20 weeks gestation compared to controls. Theoretically, this morphological parameter can lead to earlier diagnosis of scaphocephaly. At the 20-week anomaly scan, biometric measurements in patients with metopic suture synostosis did not differ from controls, despite the difference in time of onset between metopic and sagittal suture synostosis (15 versus 18 weeks of gestation respectively). Previous studies have shown an increased biparietal diameter in metopic suture synostosis patients before operation. In our data this was not found statistically significant prenatally.[16, 17] We hypothesize the following mechanism to be responsible: the *increase* of BPD in metopic suture synostosis patients is a *secondary*, compensatory, effect after metopic suture synostosis. In contrary to the *decrease* of BPD in scaphocephaly patients, which is a *primary* effect following sagittal suture craniosynostosis. Therefore we would expect the enlarged BPD in trigonocephaly to become visible at a later stage.

Although single-suture craniosynostosis is diagnosed most often in the first year of life, its pathology starts in the early second trimester, with fusion of the sutures, resulting in bone-center displacement.[1, 18] Our study shows the effect of the developing single-suture craniosynostosis on biometric measurements of the skull, particularly the CI, during the second trimester of pregnancy.

The CI was introduced in 1987 to detect fetuses with Down's syndrome who were often more brachycephalic than normal infants.[19] Numerous follow-up studies, however, showed CI to be insufficiently reliable to screen for Down's syndrome prenatally, hence its use in prenatal screening was discarded.[20] However, this study suggests that CI may have a role in prenatal screening for scaphocephaly.

To assess the diagnostic value of the CI in screening for scaphocephaly we constructed a ROC curve. The positive likelihood ratio was maximal (6.4) at CI=0.73. This implies a more than six-fold risk increase for scaphocephaly if CI is less than or equal to 0.73. While a positive likelihood ratio of more than 6 in general terms is a promising figure in screening, the clinical importance in scaphocephaly is mainly decided by the prevalence of the condition (1:1,600 live births).[4] The rarity of the condition implies that even among the selected screen positives, scaphocephaly would be uncommon. A 'watchful waiting' policy after a positive screen would imply a stressful period for the parents. It is clear that the discriminative power of the CI at 20 weeks of gestation is too limited to solely rely on this early single measure.

Several strategies for improvement can be considered. An obvious strategy is to take advantage of the fact that craniosynostosis is an ongoing process. As numerous studies reported a pre-operative cephalic index of scaphocephaly infants of approximately 0.67 at the age of 5-6 months suggesting continued CI decrease over time, we expect a substantial

gain in discrimination with a repeated measurement. [21-23] The repeat scans, executed for growth assessment, in 8 fetuses with postnatally diagnosed scaphocephaly confirm this hypothesized continued decrease of BPD and CI (fig. 4). As only 2 out of 8 fetuses were in breech position at the time of the scan, we assess this has not played a role in these curves.

A second strategy is to combine biometric information with independent other diagnostic information, either scan related or otherwise. Recently, the 'brain shadowing sign' has been suggested as an independent novel marker of craniosynostosis.[24] If truly independent as marker, it could improve discriminatory power if it is added to CI information, like the 1st trimester combination test where the combination of several parameters increases the discriminative power of the test.[25] The presence of the brain shadowing sign can, however, easily be missed in a routine clinical setting, hence field testing must show its additive value.

A third strategy is to add routine measurement of cranial sutures with 3D-ultrasound.[26-28] However, 3D-imaging of the cranial sutures for screening purposes is not feasible as it is time-consuming and highly demanding in terms of expertise. While a defined deflection of BPD or CI justifies further diagnostic imaging, such as 3D imaging of the cranial sutures, this so far does not seem a feasible part of screening.

Third trimester ultrasound is becoming more common to assess fetal growth and provides a chance for the above mentioned strategy concerning repeated measurements. When the third trimester ultrasound shows a deflection in BPD or CI curve it should be followed by 3D-imaging of the cranial sutures.[26] However, before advocating the routine assessment of skull parameters at the third trimester ultrasound in order to detect craniosynostosis, the findings of the present study should first be validated in a larger population.

We finally discuss the potential benefits of early diagnosis. In our view at least there are three. The first was already mentioned: adequate risk management of delivery, as complicated births may be expected.[10] Secondly, prenatal diagnosis enables psychological anticipation. In a recent paper parents, after the first shock, were shown to value the possibility of anticipation and precise treatment planning.[29] Thirdly, scaphocephaly infants are at non-trivial risk for developing increased intracranial pressure and timely treatment is of undisputed benefit. Early referred infants in our center are treated with a spring-assisted cranioplasty between 4.5 and 6 months of age to prevent this complication. At a later age, treatment consists of a total-vault remodeling procedure, which entails a slightly poorer neurodevelopmental outcome, a prolonged hospital stay and greater blood loss.[23] To be able to perform surgery within the preferred period, a referral at a minimum of 6 weeks before maximum age at operation is required. This implies that scaphocephaly patients should be referred before 4.5 months of age. Our results show that 24% of scaphocephaly patients is referred too late to be operated on in time according to our center's treatment protocol. In principle, prenatal detection of single-suture craniosynostosis allows early referral to a craniofacial team and would prevent late surgery.

This study has a number of limitations. Some of these are intrinsic: craniosynostosis is a rare disease and even with national centralization in two centers in the Netherlands, study numbers are limited. Also the retrospective design clearly contributes to further limitation of numbers. Twenty-five percent of patients (68 out of 272) could not be reached, refused to participate or did not return the questionnaire in time. Additionally, although the 20-week anomaly scan was officially introduced in 2007 and required the storage of images, ultrasound images could only be retrieved for 82 out of 204 participating patients. We note that the number of retrievable ultrasound studies was less prior to 2009, as also reported by our audit of the prenatal screening program in our region.[30] The same protocol was followed in both patient groups, therefore we do not have a logical explanation for the difference in number of retrievable ultrasounds between scaphocephaly (41/130) and trigonocephaly (41/74). As all trigonocephaly and scaphocephaly patients were approached for inclusion and all cases were detected postnatally, selection bias most likely did not affect our results.

In conclusion, this study presents a first step towards the prenatal diagnosis of single-suture craniosynostosis. At this stage, the cephalic index is not suitable for screening on scaphocephaly at 20 weeks of gestation. A repeat measurement at a third trimester ultrasound is promising and subject to future research. A deflection of the BPD or CI curve at third trimester ultrasound should be followed by 3D-imaging of the cranial sutures.

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Chapter 4

Perinatal complications in patients with unisutural craniosynostosis: an international multicentre retrospective cohort study

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ABSTRACT

Background Craniosynostosis may lead to hampered fetal head moulding and an increased rate of birth complications. To study the interaction between single suture craniosynostosis and delivery complications an international, multicentre, retrospective cohort study was performed in two national craniofacial centres and national birth registries in the Netherlands and Sweden.

Methods All newborns between 2006 and 2012 with sagittal or metopic suture synostosis were included. All births were included as a reference population. The primary outcome measure was rate of medically assisted labour. The secondary outcomes included method of conception, term of birth, fetal position, birthweight and head circumference.

Results We included 152 trigonocephaly patients, 272 scaphocephaly patients and 1,954,141 controls. A higher rate of assisted reproductive technology (ART) was found in patients with trigonocephaly (13%) and scaphocephaly (7%) compared to controls (3%, $p<0.001$). Scaphocephaly resulted in more post term births (8% vs 4%, $p<0.001$). Trigonocephaly patients showed more preterm births (11% vs 6%, $p<0.001$). Breech position was more frequent (10% vs 4%, $p=0.003$) and labour was more often induced in trigonocephaly patients. Rate of assisted delivery, including cesarean section, was significantly higher in trigonocephaly and scaphocephaly patients. Postnatal head circumference was larger in scaphocephaly patients than in controls (36.2 cm vs 34.9 cm, $p<0.0001$).

Conclusions Scaphocephaly leads to more post term births and an increased rate of cesarean sections. Trigonocephaly is related to ART, additionally higher rates of breech position and cesarean section are found. Prenatal detection of single suture craniosynostosis could improve perinatal care.

INTRODUCTION

Premature fusion of a skull suture is known as craniosynostosis and results in an altered head shape. In 79% craniosynostosis is the only congenital anomaly ('isolated craniosynostosis'). In the remaining 21% craniosynostosis is part of a syndrome and often seen together with extracranial anomalies.[1] The overall prevalence of craniosynostosis is approximately 7.2 per 10.000 live births.[2] The two commonest isolated forms are sagittal suture synostosis, i.e. scaphocephaly, and metopic suture synostosis, i.e. trigonocephaly (fig. 1).

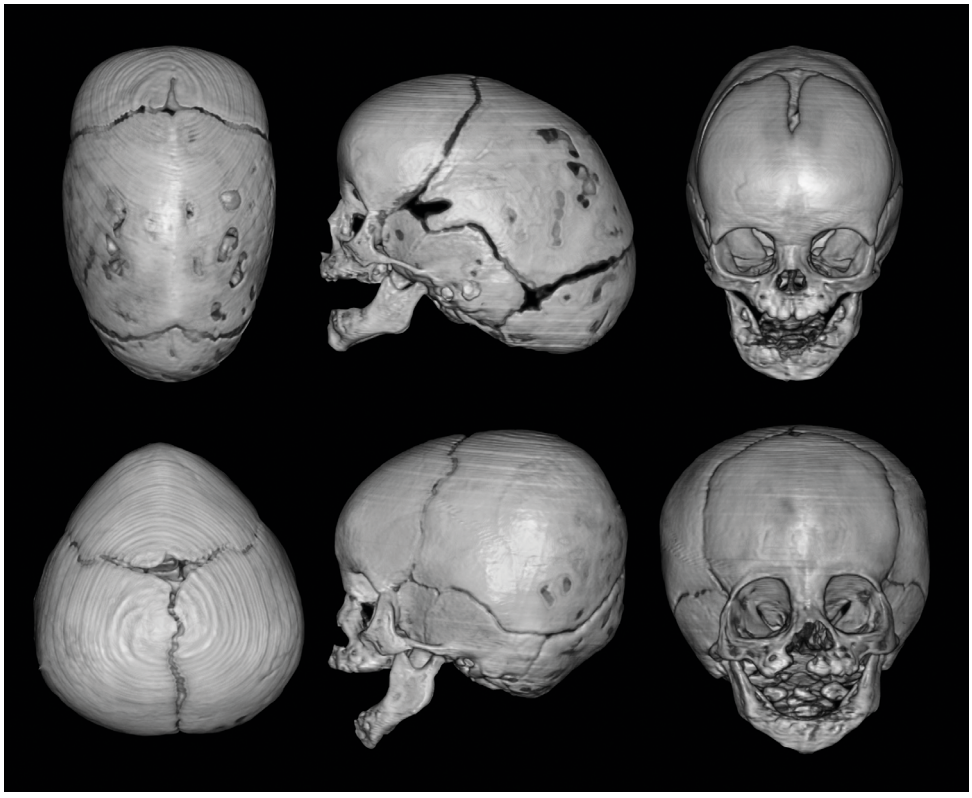

Figure 1 Sagittal suture synostosis (above) and metopic suture synostosis (below) result in altered head shapes

The process of premature fusion is known to start at 15 weeks of gestation for trigonocephaly and at 18 weeks for scaphocephaly.[3, 4] Cranial sutures, while open, are the major sites of calvarial growth, supplying adequate space for the brain to grow.[3-5] Another important function of the cranial sutures is to enable moulding of the skull when passing through the birth canal.[6] Craniosynostosis may complicate this natural adaptive process

and may preclude a normal birth. A higher rate of vaginal breech deliveries and of non-elective cesarean sections in cases with craniosynostosis has been reported.[7] Moreover, a higher rate of subgaleal and subperiosteal perinatal bleeding of the newborn, together with lower APGAR scores, shows the possible impact of hampered fetal head moulding following craniosynostosis.[8] While the etiology is still unclear, recent data suggest that lower gestational age at birth, lower birthweight and more perinatal complications contribute to developmental delay in scaphocephaly.[9] Apart from perinatal problems, premature fusion of one or more cranial sutures increases the risk for elevated intracranial pressure, endangering vision and hampering neuropsychological development.[10]

So far, studies on perinatal complications pooled all single suture craniosynostosis patients. However, as head shape varies greatly among the different subtypes, pregnancy and delivery in particular may be affected in different ways. This study analyzes the perinatal outcomes in a large population of metopic and sagittal suture synostosis patients from two European countries with a national birth registry. To our knowledge this study is the first to test whether different perinatal risk profiles exist for trigonocephaly and scaphocephaly patients, the two commonest forms of craniosynostosis[2]. If indeed such specific risk profiles exist, and if these are similar across countries, we assume the data show a generalizable risk association.

MATERIAL AND METHODS

This study was approved by the institutions' medical ethical committee: the Erasmus Medical Center (id: 2013-293) and the Gothenburg Ethics Committee (id: 333-15).

For this study all patients with metopic or sagittal synostosis born from 2006 to 2012 were included. Patients with syndromic craniosynostosis (i.e. with additional extracranial anomalies), twin pregnancies and children born abroad were excluded.

For the Dutch cohort, a questionnaire on pre- and perinatal data was sent to all parents. Cross-reference with the national perinatal registry of the Netherlands was performed to confirm the reported values in the questionnaire. The Gothenburg Craniofacial Registry covers the majority of patients operated for craniosynostosis in Sweden. Data from that registry was individually linked to the Medical Birth Registry, a registry focused on perinatal parameters covering all deliveries in Sweden and run by the *National Board of Health and Welfare* (*Socialstyrelsen*).[11] Data on maternal age, parity, method of conception, labor, method of delivery, gestational age at birth, birthweight and direct postnatal head circumference were collected.

'Assisted reproductive technology' was noted when conception had taken place after hormonal induction, intra-uterine insemination (IUI), in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Prematurity was noted when birth was before 37.0 weeks of gestation, postmaturity was noted at 42.0 weeks and above.

National reference values were provided for both countries. For the Netherlands the control population was provided by the *Dutch Perinatal Registry*, the registering authority of all births in the Netherlands, with close to complete coverage.[12] For Sweden the control population was derived from the *Medical Birth Registry*. Twin pregnancies were excluded from the norm data of both countries and the participating craniosynostosis patients were excluded from the corresponding national norm population.

The data essentially reflect an observational cohort study design, where the presence of in utero craniosynostosis (determinant, risk factor) is related to perinatal consequences (outcomes). Data collection of both conditions (craniosynostosis, complications) is mutually independent, which allows for a prospective analysis: birth complications already have taken place before the diagnosis craniosynostosis is made, and it is unlikely that the routine and uniform obligatory data collection at birth is influenced by awareness (if any) of the craniosynostosis. In case of the investigation of the association of method of conception to craniosynostosis, the presence of craniosynostosis is the outcome of analysis. In that analysis the mechanics of data collection allow for standard observational analysis as well.
Differences between the Netherlands and Sweden were tested in both patient groups and control populations. If no significant difference was found between countries, we aimed to pool the data of the two countries and then to stratify data into three diagnostic groups: trigonocephaly, scaphocephaly and control persons respectively. If, however, a significant difference between countries was present, we aimed to stratify the data for the Netherlands and Sweden separately.

Continuous data were compared using an independent *t*-test, categorical data were compared using a chi square test. Fisher's exact test was used instead of the chi square test when appropriate. If applicable a Bonferroni correction was performed to correct for multiple testing.

RESULTS

Included patients

For the Netherlands, 96 trigonocephaly patients and 174 scaphocephaly patients were approached for inclusion. Of these, 22 trigonocephaly patients and 44 scaphocephaly patients could not be reached or refused to participate. The resulting Dutch cohort therefore consisted of 74 trigonocephaly patients and 130 scaphocephaly patients (diagnosis specific participation rates of 77% and 75% respectively, table 1). From the available clinical data we could not demonstrate any selective non-participation. The national reference population comprised of a maximum of 1,199,160 controls, depending on the variable in question.

For Sweden, 88 trigonocephaly patients and 156 scaphocephaly patients were approached for inclusion. In total, 10 trigonocephaly patients and 13 scaphocephaly patients could not be reached or did not want to participate. Consequently, the Swedish sample comprised of 78 trigonocephaly patients and 142 scaphocephaly patients (diagnosis specific participation rates of 89% and 91% respectively, table 1). The national reference population comprised of a maximum of 754,981 controls, depending on the variable in question.

For trigonocephaly and scaphocephaly patients, more males then females were affected compared to the distribution of sex in the control population of both countries ($p<0.0001$, chi square test, Table 1). There were no significant differences in sex distribution of trigonocephaly or scaphocephaly patients between the Netherlands and Sweden.

Maternal data

Bonferroni correction was applied to correct for multiple testing with regard to maternal age. This resulted in a significance threshold of $p=0.007$. The control population in the Netherlands had a statistically significant higher maternal age at conception than in Sweden (30.8 vs 29.5, $p<0.0001$, *t*-test). The same (non-significant) trend was found for trigonocephaly ($p=0.10$) and scaphocephaly ($p=0.02$) patients. No significant differences existed with regard to maternal age between the trigonocephaly or scaphocephaly patients and the control population in both countries. There was no significant difference between patient groups and/or countries with regard to parity. The rate of assisted reproductive technology was higher in trigonocephaly patients than in scaphocephaly patients and in the control population ($p<0.001$, chi square test, table 2).

Perinatal data

Mean gestational age at birth was significantly lower for trigonocephaly patients than controls ($p=0.0001$, t-test, table 3); no difference was observed in scaphocephaly patients ($p=0.22$, t-test, table 3). A significantly higher rate of preterm births was found in trigonocephaly patients, while post term births were more frequently seen in scaphocephaly patients ($p<0.001$, chi Square test, table 3). Mean birthweight was lower in trigonocephaly patients ($p=0.01$), and was higher in scaphocephaly patients ($p=0.02$).

The rate of breech position was significantly higher in trigonocephaly patients than in scaphocephaly patients and controls ($p=0.003$, chi Square test, table 3).

The primary analysis showed statistically significant differences between countries with regard to the start of labour and the method of delivery. Bonferroni correction implied that the threshold for significance was a p-value of 0.025.

For the Netherlands, rate of induced labour was higher in trigonocephaly patients ($p<0.0001$, chi Square test, table 4a). For delivery, rate of non-elective CS rate was higher

in trigonocephaly and scaphocephaly, compared to controls (p=0.02, chi Square test, table 4a).

Table 1 Maternal age at conception was higher in the control population of the Netherlands than in the control population of Sweden (p=0.0001, t-test).

	the Netherlands			Sweden		
	Trig.	Scaph.	Pop.	Trig.	Scaph.	Pop.
Number of patients	74	130	1,199,160	78	142	754,981
Maternal age at conception (yrs)	31.6 ± 4.6	31.8 ± 4.8	30.8 ± 5	30.3 ± 5	30.4 ± 5	29.5 ± 5.3
Male:female ratio	3.4:1	4.2:1	1.1:1	5:1	2.9:1	1.1:1
Primiparae	43%	38%	46%	54%	45%	43%

Table 2 A higher rate of assisted reproductive technology was found in trigonocephaly patients (p<0.001, chi square test). Numbers noted as absolute n (%).

Method of conception	**Trigonocephaly** n=152	**Scaphocephaly** n=272	**Population** n=1,783,858
Hormonal ind. / IUI	10 (7)	6 (2)	23,706 (1)
IVF/ICSI	10 (7)	12 (4)	38,553 (2)
Spontaneous	132 (87)	254 (93)	1,721,599 (97)

Table 3 Perinatal parameters. Numbers noted as absolute n (%).

Gestational age at birth	**Trigonocephaly** n=152	**Scaphocephaly** n=272	**Population** n=1,941,336
mean ± SD	38w6d ± 18d	39w3d ± 12d	39w4d ± 13d
<37 weeks	16 (11)	15 (6)	117,100 (6)
> 42 weeks	10 (7)	21 (8)	74,341 (4)
Birth weight (g) (mean ± SD)	3359 ± 662	3560 ± 555	3476 ± 589
Fetal position	**Trigonocephaly** n=145	**Scaphocephaly** n=246	**Population** n=1,917,423
Breech	15 (10)	8 (3)	75,968 (4)
Transverse	2 (1)	2 (1)	25,004 (1)
Vertex	128 (88)	236 (96)	1,816,451 (95)

Table 4 Start of labour and method of delivery in the Netherlands (A) and Sweden (B). Numbers noted as absolute n (%).

	A. the Netherlands			B. Sweden		
	Trigonocephaly	Scaphocephaly	Population	Trigonocephaly	Scaphocephaly	Population
Start of labour	n=74	n=130	n=690,253	n=78	n=129	n=751,272
Induced	24 (32)	31 (24)	139,764 (20)	11 (14)	11 (9)	98,216 (13)
Elective CS	6 (8)	11 (8)	46,144 (7)	13 (17)	19 (15)	68,391 (9)
Spontaneous	44 (60)	88 (68)	504,345 (73)	54 (69)	99 (77)	584,665 (78)
Method of delivery	n=74	n=130	n=1,199,160	n=78	n=139	n=754,981
Vacuum/forceps	7 (10)	18 (14)	115,172 (10)	5 (6)	10 (7)	60,582 (8)
Elective CS	6 (8)	11 (8)	78,715 (7)	13 (17)	19 (14)	68,391 (9)
Non-elective CS	9 (12)	20 (15)	100,362 (8)	17 (22)	25 (18)	63,117 (8)
Uncomplicated	52 (70)	81 (62)	904,911 (75)	43 (55)	85 (61)	562,891 (75)

For Sweden, rate of elective CS was higher in both patient groups compared to the control population with regard to start of labour (p=0.02, chi Square test, table 4b). For delivery, rates of elective and non-elective CS were higher in both patient groups compared to the control population and the rate of uncomplicated delivery was lower in trigonocephaly (55%) and scaphocephaly (61%) compared to the control population (75%) (p<0.001, chi Square test, table 4b).

Head circumference

Direct postnatal head circumference is not routinely measured at birth in the Netherlands, thus only the data from the Swedish cohort were available. Data on the head circumference were present for 76 trigonocephaly patients, 138 scaphocephaly patients and 739,766 controls. Bonferroni correction implied that the threshold for significance was a p-value of 0.017. Head circumference was larger in scaphocephaly patients than in the control population (36.2 vs 34.9, p<0.0001, t-test) and the trigonocephaly patients (36.2 vs 34.5, p<0.0001, t-test). Although smaller, trigonocephaly patients did not show a statistically significant difference compared to controls (34.5 vs 34.9, p=0.04, t-test).

DISCUSSION

The present paper provides detailed pre- and perinatal data on delivery and the postnatal period of mothers and children with isolated sagittal and metopic suture synostosis. The findings in this study clearly suggest two different perinatal outcome profiles in scaphocephaly and trigonocephaly patients.

For scaphocephaly patients no difference in fetal position at onset of delivery is found. We hypothesize that because of a normal position of the fetus, the obstetrician is inclined to wait for the natural start of labour. Normally, the onset of labor is induced by the descent of the fetus into the lower segment of the uterus. Due to the premature closure of the sagittal suture, the head circumference is enlarged. We hypothesize that the altered cranial shape and size found in sagittal suture synostosis patients disturbs the natural fetal descent, causing higher rates of post-term births, inductions of labour, operative vaginal deliveries and cesarean sections. The higher birthweight found in scaphocephaly patients can be directly explained by the increased rate of post term births. The complications of prolonged pregnancy have been studied thoroughly and range from prolonged labor to increased incidence of asphyxia and stillbirth, in particular if other suboptimal features are present.[13-17] For scaphocephaly prenatal and perinatal complications negatively influenced neuropsychological development.[9] This stresses the need for adequate prenatal detection and obstetric planning in these cases.

The mechanism of birth in scaphocephaly patients differs from the one found in trigonocephaly patients. A higher rate of breech position is found in trigonocephaly patients. This indirectly leads to a higher rate of cesarean sections, which is also supported by the literature.[18] Additionally a higher rate of induction of labor is found in the Netherlands in trigonocephaly patients, which suggests a higher rate of abnormal fetal descent. Although cranial dimensions are less affected than in scaphocephaly patients, the biparietal diameter in trigonocephaly patients is significantly larger compared to controls before operation.[19] Taken together with hampered fetal head moulding due to the fused metopic suture, this may result in an abnormal fetal descent, reduced rate of spontaneous labor and obstruction of labor. The lower mean birthweight found in trigonocephaly patients should be regarded as a direct result of the lower mean gestational age at birth and increased rate of preterm births. The reason why metopic suture synostosis patients show more preterm births compared to the normal population remains elusive.

Until now, little is known about the etiology and possible causes of isolated metopic synostosis. One can assume that the higher rate of assisted reproductive technology in trigonocephaly patients implies that there is a higher rate of subfertility (and a longer time-to-pregnancy) in this group. Time-to-pregnancy, rather than induction of pregnancy itself, has been shown to increase the risk of congenital, clinically relevant, abnormalities.[20, 21] This suggests that time-to-pregnancy may play a role in the etiology of trigonocephaly. Future (prospective) research should focus on prenatal factors and (epi)genetics to identify different causes of single suture craniosynostosis, such as a longer time-to-pregnancy.

This multicentre observational study was performed in the Netherlands and Sweden, two European countries with a well-organized perinatal registry with close to complete national coverage. This provides the possibility to acquire large unselected datasets (comparable with previous reported values[22]), permitting to test for possible differences between countries, also of background variables. We noted a statistically significant higher maternal age at conception in the Netherlands for the control population compared to Sweden which is known to demographers. Although non-significant, maternal age was also higher for trigonocephaly and scaphocephaly patients in the Netherlands compared to Sweden which may simply reflect the absence of a relation of maternal age to single suture craniosynostosis.

The results of this study show that the obstetrical factors associated with trigonocephaly and scaphocephaly are the same in both countries (assisted reproductive technology, fetal position and gestational age at birth). However, we do find a difference between countries in the management of these factors. In the Netherlands the induction of labour seems relatively high, whereas in Sweden it seems the obstetrician opts for an elective cesarean section faster in pregnancies where ultimately a child with trigonocephaly or a scaphocephaly is born. The same phenomenon is found when the actual method of delivery is analyzed: in the Netherlands it seems as though operative vaginal delivery is performed more often. Whereas in Sweden it seems the option of operative vaginal delivery is often bypassed, choosing

for an elective or non-elective cesarean section more often. A possible explanation for the increased rate of vaginal delivery in the Netherlands could be that home deliveries are more common than in Sweden.[23, 24] None of the patients were diagnosed prenatally and although differences in obstetric policy are present, it is clear that trigonocephaly and scaphocephaly both result in a higher rate of non-elective cesarean sections in the Netherlands and Sweden. This underlines the importance of improving prenatal detection of these malformations to prevent maternofetal trauma at birth.

The main strength of this study is the multicentre, international design. This enabled the inclusion of a relatively large sample of patients and controls and the possibility to test for inter-country differences with regard to obstetric policy. Although policy did differ between countries, the effect of the condition on obstetric complications is the same in both countries. This strengthens the generalisability and reproducibility of our results. Additionally, this study has some limitations. Craniosynostosis is a rare disease and although this was a multicentre study, involving two of Europe's largest craniofacial centres, numbers remain limited. Also the retrospective design clearly contributes to further limitation of numbers. As with all retrospective studies, we are aware that the associations observed do not prove any causality in the etiology of craniosynostosis. To do so, a prospective study on pre- and perinatal factors should be undertaken.

Craniosynostosis is often regarded as a rare disease which can't be diagnosed prenatally. However, the prevalence of unisutural craniosynostosis (6.3 per 10,000 births) is comparable or even higher than other congenital malformations such as neural tube defects (6.3 per 10,000), abdominal wall defects (4.4 per 10,000) and diaphragmatic hernia (3.5 per 10,000).[2, 25-27] The latter congenital anomalies have yielded many scientific papers on methods to increase prenatal detection and improve perinatal outcome. Moreover, the onset of craniosynostosis takes place at 15-18 weeks of gestation and recent papers have opened possibilities for diagnosing craniosynostosis prenatally.[3, 4, 28] This study shows that with regard to the perinatal situation of unisutural craniosynostosis patients, there is room for improvement in the care for these patients. Taken together, this should encourage the craniofacial surgeon, as chair of the craniofacial team, to involve pre- and perinatal medical professionals in the care for children with unisutural craniosynostosis.

CONCLUSION

For scaphocephaly, disturbed natural fetal descent leads to more post term births and an increased rate of cesarean sections. Trigonocephaly is related to assisted reproductive technology and a higher rate of breech position, which may result in an increased rate of cesarean sections. This implies that prenatal detection could improve perinatal care for single suture craniosynostosis patients and their mothers.

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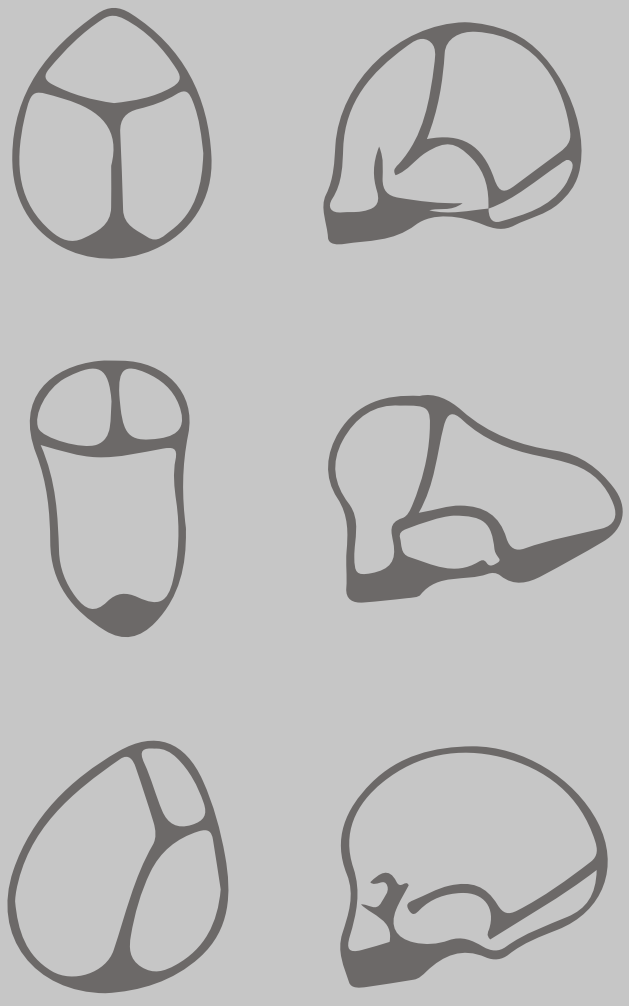

Chapter 5

Pilot Case-Control Study of Cranial Venous Doppler Ultrasound in Craniosynostosis

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ABSTRACT

Introduction Besides craniocerebral disproportion, other factors such as Chiari malformation type 1, obstructive sleep apnea and venous outflow obstruction are considered to play a role in the occurrence of intracranial hypertension in craniosynostosis. This pilot study aims to examine cerebral venous flow velocity data in order to better characterize the complex intracranial venous physiology of craniosynostosis.

Methods Prospective cohort study of craniosynostosis patients referred to a single National (tertiary) craniofacial unit. Control subjects consisted of children referred to the craniofacial unit outpatient clinic that did not have craniosynostosis. Transfontanellar ultrasound scans with Doppler flow velocity were performed at the first outpatient clinic visit and after each surgery, if applicable. Mean venous blood flow velocities of the internal cerebral vein (ICV_v) and the superior sagittal sinus (SSS_v) were recorded and blood flow waveform was scored.

Results Preoperatively, SSS_v was decreased in craniosynostosis patients (n=29) compared to controls (n=26) (7.57 vs 11.31, p=0.009). ICV_v did not differ significantly between patients and controls. Postoperatively, SSS_v increased significantly (7.99 vs 10.66, p=0.023). Blood flow waveform analysis did not show significantly different results between patients and controls.

Conclusions Premature closure of cranial sutures affects SSS_v. This pilot study presents a first step towards better understanding the role of venous outflow obstruction in intracranial hypertension in craniosynostosis.

INTRODUCTION

Craniosynostosis occurs in approximately 1 in 1,500 births and results in abnormal shape of the cranium and increased risk of intracranial hypertension (ICHT).[1] The prevalence of ICHT ranges 1 to 85%, in published series, and is particularly high in the syndromic causes of craniosynostosis.[2-5] Historically, the development of ICHT in craniosynostosis was attributed solely to skull growth restriction (i.e., craniocerebral disproportion).[6] Now, the accumulated evidence suggests that other factors may also be relevant, including [7-11]: cranial vault venous outflow obstruction, ventriculomegaly (or hydrocephalus if progressive), tonsillar herniation or presence of Chiari malformation, type 1, and obstructive sleep apnea (OSA). However, these features are rarely seen in single suture craniosynostosis patients and so we have to conclude that they are unlikely to account for the development of ICHT in such patients. Furthermore, we have recognized a discrepancy in the rate of ICHT by suture involvement that is not readily explained by any of the mechanisms outlined above. For example, in cases of metopic suture synostosis, the rate of ICHT is low (~1 to 2%), irrespective of relatively small intracranial volume after surgery.[5, 12] The opposite is true in sagittal suture synostosis patients; that is, despite a relatively larger intracranial volume, ICHT is found in 6-10% of patients.[13, 14]

In this context there has been a longstanding interest in cerebral venous drainage in craniosynostosis, albeit with few definitive studies. We know that there is an interaction between superior sagittal sinus pressure (P_{SSS}) and intracranial pressure (P_{IC}). For example, as early as 1984, Sainte-Rose et al. suggested that a rise of P_{SSS} due to obstruction resulted in a rise of P_{IC}.[11] We also know that the superior sagittal sinus blood flow velocity using Doppler ultrasound (SSS_v) in single suture cases of craniosynostosis differs from the norm.[15] Last, we know that cranial venous drainage is different in craniosynostosis patients.[8, 10] Taking all of the above stated evidence together we conclude that abnormality in cerebral venous dynamics is an important physiological feature of single suture craniosynostosis. However, understanding the interaction between cerebral venous blood flow, cerebrospinal fluid (CSF) drainage and P_{IC} also requires consideration of anatomy. For example, the superficial venous drainage system, as reflected in the SSS, drains blood from the lateral aspects of the anterior portion of the cerebral hemispheres and collects CSF from the arachnoid granulations. The intracerebral vein (ICV) is a component of the deep venous drainage system, and on each side of the brain it takes blood from the choroid plexus, and thalamic and caudate nuclei. Therefore, in the current pilot investigation we have used Doppler ultrasound to examine cerebral venous flow velocity data from two cerebral venous drainage systems in order to better characterize the complex intracranial venous physiology of craniosynostosis. Comparing both venous drainage systems enables us to evaluate the effect of craniosynostosis on the deep and superficial venous drainage system, to evaluate

the effect of corrective surgery on venous drainage and to identify possible targets to prevent intracranial hypertension more adequately.

METHODS

This study was approved by the institution's medical ethical committee (MEC 2015-044). Informed consent was obtained from all participants. Study subjects were recruited from craniosynostosis patients presenting to the Dutch craniofacial center in 2016. The healthy control group of subjects was also recruited at our center and comprised patients referred for non-synostotic occipital plagiocephaly, metopic ridging or non-syndromic cleft lip.

Patient management

Craniosynostosis patients were treated according to our centers' previously published treatment protocol [16]. Briefly, this meant that fronto-orbital advancement and remodeling (FOAR) was performed between 9 and 12 months of age for the following indications: metopic synostosis, unicoronal synostosis, Saethre-Chotzen syndrome and Muenke syndrome. Sagittal synostosis patients were treated with springs, which were inserted at 5 to 6 months of age, and removed approximately 12 weeks later. Patients with lambdoid synostosis, Apert's syndrome or Crouzon's syndrome were treated with a posterior decompression with the use of springs at around 5 to 6 months of age (removed 12 weeks later).

Doppler ultrasound procedure and analyses

Prospective, transfontanellar ultrasound scans with Doppler studies were performed using an Esaote MyLab Twice ultrasound scanner (Esaote, Genoa, Italy). Scans were carried out at the first outpatient clinic visit and follow-up after each surgery. Control subjects underwent only one ultrasound study at the time of presentation to the outpatient clinic. During the ultrasound procedure, patients were positioned either supine, or with head of the bed up to maximum of 30°. Studies were carried out when a child was quiet and at rest. Data from agitated or crying children were excluded because of the influence of heart rate variability or raised intrathoracic pressure on SSS_v and ICV_v measurements.

ICV_v was measured in the sagittal plane using a convex ultrasound probe at 6.5 MHz (or, at 4.5 MHz in those with larger skull). As position and flow direction was the same in all patients and controls, we did not use any angle correction in the measurements. SSS_v was measured in the coronal plane using a linear probe at 6.5 MHz frequency and an angle of 30° to 45°. The Doppler range gate (2.2 mm) was constant in all measurements.

All ultrasound and Doppler data were obtained by one of the two observers (MC or PD) and digitally stored. (The inter-observer agreement for mean ICV_v and mean SSS_v, as assessed by intraclass correlation coefficient, was >0.95.) The blood flow waveform produced by spectral analysis using image-processing software (Esaote MyLab, Esaote, Genoa, Italy) was scored using a previously described categorization (**Table 1**).[17] Two observers (MA and RdG) scored the waveform independently. In those cases in which both observers scored the waveform differently, the two observers re-evaluated the waveform together and consensus was reached. The evaluators' kappa statistics were 0.89 and 0.73, for the ICV- and SSS-waveforms, respectively.

Table 1 Blood flow waveform categories. Prior described by Ikeda et al.[17]

Grade	Waveform
0	Steady waveform
	Constant perfusion speed
1	Fluctuating waveform
	Minimum speed is never less than half the maximum speed
2	Fluctuating waveform
	Minimum speed is less than half the maximum speed, but never drops to 0 cm/s.
3	Fluctuating waveform
	Minimum speed drops to 0 cm/s

Statistical analyses

Craniosynostosis patients were considered to be in one of two categories according to (syndromic) diagnosis. The sample size for our pilot study was based on previous guidelines [16] and our center's MEC recommendations. The statistical analyses assumed normal distribution for ICV_v and SSS_v data. A multivariate analysis of variance (MANOVA) test was performed to assess the effect of craniosynostosis on SSS_v and ICV_v. The Chi-square test was used for assessment of waveform categorical data. Finally, in the comparisons of pre- to postoperative change, we used the preoperative data along with the data from after the last (or most recent) operation. Post-hoc non-parametric testing (Kruskall-Wallis and Wilcoxon Signed Rank test) was performed when appropriate.

RESULTS

We recruited 34 craniosynostosis patients including 14 patients with sagittal synostosis, 11 with metopic synostosis, 2 with unicoronal synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 3 with Muenke's syndrome and 2 with Crouzon's syndrome. Post-operatively, we were able to obtain ultrasound scans in 22/34 (65%) of these patients

(8 with sagittal suture synostosis, 9 with metopic synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 2 with Muenke's syndrome and 1 with Crouzon's syndrome). The control group comprised 28 patients, with 24 with non-synostotic occipital plagiocephaly or metopic ridging, 2 with cleft lip and 2 unaffected twin siblings of craniosynostosis patients.

None of the patients with craniosynostosis had papilledema at the time of initial assessment. One Muenke patient developed papilledema after the preoperative ultrasound study, and for this reason she underwent posterior cranial vault decompression. Additionally, one Crouzon patient developed papilledema after the first ultrasound. At time of the postoperative ultrasound study the papilledema of both patients was resolving, but had not completely disappeared. None of the other patients had papilledema at the postoperative assessment.

Preoperative ICV_v and SSS_v

Table 2 summarizes the initial findings in three categories of study subjects, i.e., non-syndromic and syndromic craniosynostosis, and controls. Age distribution was significantly different between groups (Kruskal-Wallis test, $p<0.001$). Post-hoc testing showed no significant difference with regard to age at ultrasound between syndromic or non-syndromic patients (Mann-Whitney U test, $p=0.24$), but did show a significant difference between the non-syndromic group and controls (Mann-Whitney U test, $p=0.001$). Occipitofrontal head circumference did not show significant differences between groups (ANOVA, $p=0.20$).

Table 2 Preoperative baseline characteristics and mean blood flow velocities in cm/s for both patient groups and controls.

	Non-syndromic craniosynostosis	Syndromic Craniosynostosis	All patients	Controls
Age				
Mean ± SEM (no of measurements)	4.04 ± 0.57 (28)	2.71 ± 0.72 (6)	3.81 ± 0.49 (34)	6.04 ± 0.42 (28)
OFC				
Mean ± SEM (no of measurements)	+0.62 ± 0.24 (28)	-0.32 ± 0.79 (6)	+0.45 ± 0.24 (34)	+0.15 ± 0.25 (22)
SSS_v				
Mean ± SEM (no of measurements)	7.80 ± 0.51 (23)	6.66 ± 0.71 (6)	7.57 ± 0.44 (29)	11.31 ± 1.06 (26)
ICV_v				
Mean ± SEM (no of measurements)	10.00 ± 0.34 (22)	8.57 ± 0.76 (5)	9.74 ± 0.33 (27)	9.68 ± 0.29 (26)

Age in months, OFC in standard deviations compared to the national norm values. OFC Occipitofrontal head circumference, SSS_v Superior sagittal sinus velocity, ICV_v Internal cerebral vein velocity, SEM standard error of the mean.

We performed a MANOVA analysis to test whether there were significant differences with regard to flow velocity between craniosynostosis patients and controls, correcting for age at ultrasound and occipitofrontal head circumference. This analysis showed significantly lower blood flow velocity in the SSS_v in craniosynostosis patients compared to controls (Table 3). Age at ultrasound and occipitofrontal head circumference were not significant contributors to this effect.

Table 3 MANOVA analysis correcting for age at time of ultrasound and occipital frontal head circumference.

	Mean ± SEM		F	df	Sig.
	Craniosynostosis	Controls			
SSS_v	7.37 ± 0.33	11.51 ± 1.13	7.253	1	0.009*
ICV_v	9.74 ± 0.34	9.30 ± 0.30	0.180	1	0.612

Design: Intercept + Age at ultrasound + OFC + Craniosynostosis. Adjusted R^2=0.25.

Blood flow waveform

Preoperative blood flow waveform scores are shown in table 4. Chi square test did not show any significant differences in distribution among the different groups for the 2 measurements.

Table 4 Preoperative blood flow waveform scores for all two groups. No significant differences were found for ICV (p=0.77) or SSS (p=0.62) using Chi Square test.

Blood flow waveform	Non-syndromic craniosynostosis	Syndromic craniosynostosis	Controls
ICV			
0	5	0	5
1	17	5	22
Total	22	5	26
SSS			
0	7	1	5
1	12	4	19
2	4	1	2
Total	23	6	26

ICV Internal cerebral vein, SSS Superior sagittal sinus.

Postoperative blood flow velocity

Pre- and postoperative blood flow velocity of the SSS were available in 15 patients: (4 patients with scaphocephaly, 6 with trigonocephaly, 1 with lambdoid synostosis, 1 with Crouzon's syndrome, 1 with Saethre-Chotzen's syndrome and 2 with Muenke's syndrome). Related-Samples Wilcoxon Signed Rank test showed a significant increase of mean SSS_v postoperatively. (7.99 vs 10.66, p=0.023) The ICV_v remained unchanged (9.73 vs 10.01, p=0.67). Figure 1 shows the patient-specific preoperative to postoperative change of the SSS_v.

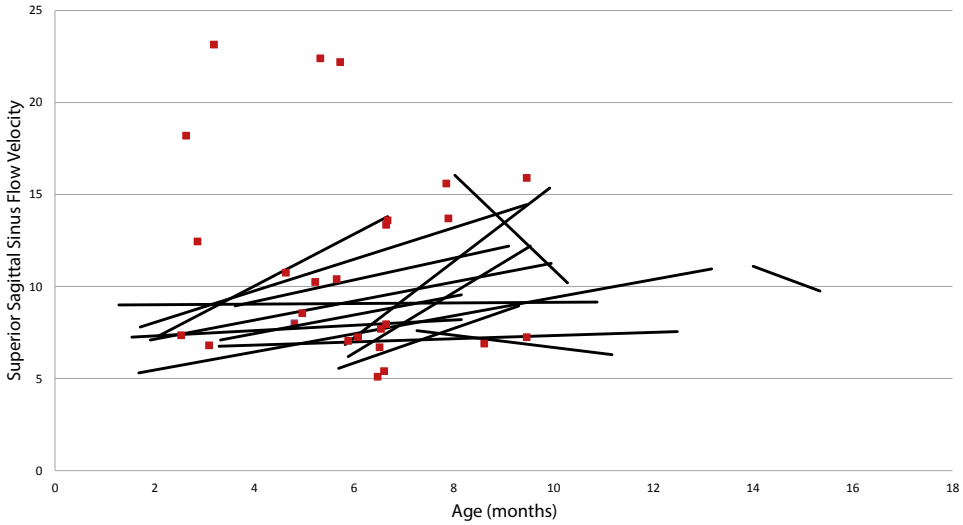

Figure 1 Preoperative to postoperative change of the ICV/SSS ratio of the patients. Each black line represents 1 patient. Red squares represent controls.

DISCUSSION

This study assessed blood flow velocity and blood flow waveform in patients with craniosynostosis and healthy controls using ultrasound. Before surgery, patients with craniosynostosis showed lower blood flow velocity in the superior sagittal sinus compared to healthy controls. Postoperatively, the blood flow velocity in the superior sagittal sinus increased. Blood flow waveform analysis did not show significant differences between cases and controls.

Previous papers have reported on the effect of hydrocephalus and raised intracranial pressure on superior sagittal sinus pressure and hemodynamics in varying patient groups.[11, 15, 18, 19] In a study by Hirabuki et al. in achondroplastic children and healthy controls SSS_v was

assessed with the use of cine phase-contrast MR imaging.[19] In achondroplastic children with hydrocephalus a reduced SSS_v is found. The authors hypothesize that the reduced blood flow is the result of obstruction of venous outflow. The findings of the present paper suggest that, besides the potential effects of ICH on sagittal sinus hemodynamics, premature closure of cranial sutures may in itself be related to a decrease of blood flow velocity in the superior sagittal sinus and thus venous drainage. Contrastingly, a previous paper by Mursch et al. found a higher blood flow velocity of the SSS in craniosynostosis patients.[15] However, these measurements were performed at the point of constriction, whereas the present study assessed SSS_v right before or right after the constriction. Additionally, de Souza et al. have shown that the diameter of the superior sagittal sinus is related to sagittal suture growth.[20] These findings would further strengthen our hypothesis of venous outflow obstruction due to constriction caused by a synostotic suture. Until now, venous hypertension has mainly been attributed to syndromic craniosynostosis.[8, 10] Our data show that a decrease of SSS_v is also found in single suture craniosynostosis patients (table 2). This may play a role in the etiology of intracranial hypertension in these patients, considering the fact that, in general, obstructive sleep apnea, Chiari malformation type 1 and hydrocephalus are not found in this specific patient group. The postoperative increase of SSS_v suggests that surgery may indeed treat the obstruction caused by the synostotic suture and lower the resistance for venous outflow. However, postoperative analysis could only be performed in 15 patients and the present findings should be confirmed in a larger study.

This study also assessed blood flow waveform of the superior sagittal sinus and internal cerebral vein. A previous study by Mursch et al. has shown different pulsatility measurements (pulsatility index and resistance index) of the sagittal sinus in craniosynostosis patients, compared to controls.[15] Contrastingly, blood flow waveform analysis did not show any differences in the present study. Hence pulsatility indices are commonly used to assess arterial pulsatility, normal values for venous cranial structures are lacking, especially in young children, and its values can be easily biased by method and location of measurement. For these reasons we chose to score waveforms instead of measuring absolute values, as previously shown by Ikeda et al.[17] This rough but robust assessment did not show differences with regard to pulsatility waveform in children with craniosynostosis compared to controls. This suggests that although premature suture fusion seems to affect blood flow velocity to some degree, its pulsatility remains unchanged.

This pilot study has confirmed that transfontanellar ultrasound can lead to reliable measurements of intracranial venous blood flow and provide information on the effect of craniosynostosis on blood flow velocity and pulsatility. However, some limitations of this study need to be considered. The cranial venous outflow of patients with craniosynostosis has been a subject of research with growing interest over the past decade. However, only 1 quantitative study has assessed SSS_v until now.[15] The present study was thus designed as

a pilot study to explore potential effects of craniosynostosis on the superficial and deep venous system. In accordance with our institutional's medical ethical board we were only allowed to include a maximum of 15 patients of every diagnostic group. This limited our numbers. Furthermore, postoperative analyses were limited by closure of the anterior fontanelle. A different limitation that should be considered is related to the method of measuring. Ultrasound is a dynamic diagnostic tool and Doppler values can vary according to the angle of insonation. To prevent potential influence of this, patient position and angle of insonation were standardized.

Considering the results of the present study and the aforementioned limitations, we hypothesize that venous outflow may indeed play a role in the etiology of ICH, even in single suture craniosynostosis patients. This should be confirmed in a future study, which should also aim to explore potential differences between different craniosynostosis types. It would be interesting to test whether patients with an affected suture in the midline (metopic or sagittal synostosis) show a more profound effect of suture closure on SSS_v compared to different craniosynostosis subtypes. Additionally, the effect of the operation should be further elucidated. In the present study, this was mainly limited by anterior fontanelle closure. With new ultrasound techniques becoming available transcranial ultrasound is now becoming an option, which would solve this issue to some extent.

Conclusions

This pilot study presents the first step towards better understanding venous outflow patterns in craniosynostosis patients. Premature closure of cranial sutures seems to diminish blood flow velocity in the superior sagittal sinus measured at the anterior fontanelle. Future studies, using transcranial ultrasound, should address the hypotheses generated in the present study.

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Chapter 6

Very low prevalence of intracranial hypertension in trigonocephaly

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ABSTRACT

Background Trigonocephaly is caused by metopic suture synostosis. It is treated by fronto-orbital remodeling, not only to correct the deformity but also to prevent intracranial hypertension, the reported prevalence in trigonocephaly of which ranges from 0 to 33 percent. To support treatment analysis and the design of a treatment protocol for intracranial hypertension in these patients, the authors wished to more accurately quantify the prevalence of pre- and postoperative intracranial hypertension in a large patient cohort.

Methods The authors included all trigonocephaly patients born between 2001 and 2013 who had all been operated on at a single center. During follow up, the presence of intracranial hypertension was evaluated by fundoscopy, and occipitofrontal head circumference was measured. The occipitofrontal head circumference curve was analyzed and its relation to intracranial hypertension assessed.

Results In total, 262 patients with trigonocephaly were included. Before surgery, 1.9 percent of them had intracranial hypertension; after surgery, 1.5 percent did (mean age at last follow-up, 4.9 years). Sixteen of 176 patients (9 percent) had occipitofrontal head circumference curve stagnation, which was significantly related to intracranial hypertension. ($p = 0.001$, Fisher's exact test).

Conclusion Intracranial hypertension occurs only sporadically in patients with metopic suture synostosis. Occipitofrontal head circumference measurement should take a prominent place in the post-operative follow-up of metopic suture synostosis patients; stagnation of the occipitofrontal head circumference requires additional screening for intracranial hypertension.

INTRODUCTION

Trigonocephaly is caused by premature closure of the metopic suture, which restricts growth of the forehead and increases the risk of intracranial hypertension. To prevent intracranial hypertension and to correct the skull deformity, treatment is preferred before 1 year of age.[1-3]

Previous studies have stated widely ranging prevalences (0 to 33 percent) of intracranial hypertension in patients with isolated trigonocephaly[1,4-8] (Table 1). This variance is attributed to a number of factors. First, the method of detecting intracranial hypertension differed between studies, ranging from fundoscopy to epidural or subdural invasive monitoring. Second, not all centers use fundoscopy or invasive intracranial pressure monitoring routinely for post-operative follow-up, thereby limiting the number of observations and reducing the sizes of the patient cohorts. Lastly, most studies on intracranial hypertension in unisutural craniosynostosis to date have pooled all unisutural synostosis patients, possibly due to a lack of numbers. These factors complicate an accurate estimation of the prevalence of intracranial hypertension in trigonocephaly.

Table 1 Overview of studies on intracranial hypertension in trigonocephaly patients

Author	Operative technique	Timing of surgery	Method of monitoring	Threshold raised ICP (mmHg)	Pre-op raised ICP	Post-op raised ICP	Total raised ICP(%)
Renier et al[7]	FOAR	<1 yr	Invasive	>15	0/5	0/2	0
Gault et al[6]	NR	NR	Invasive	>15	NR	0/4	0
Thompson et al[8]	NR	NR	Invasive	>15	3/9	NR	33.3
Renier et al[1]	FOAR	<1 yr	Fundoscopy	n/a	NR	NR	7.7
Florisson et al[5]	FOAR	9-12 mo	Fundoscopy	n/a	3/71	2/71	5.6
Cetas et al[4]	FOAR	NR	Invasive	>15	NR	0/17	0
Present study	FOAR	9-12 mo	Fundoscopy	n/a	5/261	3/196	3.5

ICP, intracranial pressure; FOAR, fronto-orbital advancement and remodeling; NR, not reported; N/A, not applicable

The objective of our study was to use fundoscopy to accurately establish the prevalence of preoperative and postoperative intracranial hypertension in a large cohort of metopic synostosis patients. Such data would make it possible to analyze the efficacy of treatment and show any relationship between intracranial hypertension and skull-growth retardation. It would also enable the authors to design a follow-up protocol specifically for trigonocephaly, with appropriate screening for intracranial hypertension.

METHODS

This study was approved by the institution's medical ethical board (MEC-2015-116).

We retrospectively assessed patients with non-syndromic and syndromic trigonocephaly who had undergone fronto-orbital advancement and remodeling at the Erasmus University Medical Center - Sophia Children's Hospital from January of 2001 to December of 2013. The Indication for surgery was metopic synostosis with an obvious trigonocephalic shape of the forehead with retrusion of the lateral parts of the supraorbital rim and temporal depressions. Syndromic trigonocephaly was defined as having one or more extracranial congenital anomalies, such as a heart defect, tracheal malacia or upper/lower extremity anomaly or the presence of a genetic malformation known to be associated with metopic synostosis, such as 3q, 7p, 9p22-24, 11q23, partial 13q trisomy and 22q11.

Patients who had undergone fronto-orbital remodeling after 2 years of age were excluded.

At our center, treatment of trigonocephaly patients involves fronto-orbital advancement and remodeling, a technique that addresses the frontal bone and supraorbital bar.[9] The supraorbital bar is taken out at the level of the frontozygomatic sutures and reshaped using an open-wedge osteotomy at the midline and insertion of a bone graft at this site, while the lateral curves are created through closed wedge osteotomies. The frontal bone is split at the midline, both bone pieces are turned through 180 degrees, and the resulting bone fragments are adjusted to the best position, with a particular focus on restoring the temporal depressions.

After surgery, follow-up appointments were scheduled according to standard protocol: 3 months after surgery, at ages 2, 4, and 6, and then every 3 years until age 18. These appointments involved occipitofrontal head circumference measurements and fundoscopy, both of which are intended to detect intracranial hypertension.

Fundoscopy

An ophthalmologist performed the fundoscopy by indirect ophthalmoscopy after mydriasis of the pupil with phenylephrine and tropicamide. Patients were examined in the ward or the outpatient clinic. Papilledema is defined as an elevation of the optic disc or blurring of the optic margins. When interpreting the fundoscopy, account was taken of the presence of hypermetropy or optic disc drusen. Results were dichotomized into papilledema or no papilledema. In the event of papilledema, additional fundoscopy was carried out within 4 to 6 weeks for confirmation. Papilledema was taken as a sign of intracranial hypertension.

Occipitofrontal Head Circumference

The occipitofrontal head circumference is a reliable indicator of intracranial volume.[10, 11] A decline in OFC can predict the onset of intracranial hypertension.[12] The occipitofrontal head circumference was measured in centimeters by the plastic surgeon, a method that has been shown to provide reliable measurements in a craniofacial setting.[13, 14] These measurements were compared with control values taken from the Dutch National Standards.

Patients were included for analysis of occipitofrontal head circumference curve if occipitofrontal head circumference measurements were available pre-operatively, <1 year post-operatively, 1-3 years post-operatively and >3 years post-operatively.

Downward deflection of the OFC curve from serial measurements over time was defined as follows: a greater than or equal to 0.5 SD fall from baseline over 2 years, or lack of change in occipitofrontal head circumference growth curve. Patients were subsequently dichotomized into two groups: downward deflection or no downward deflection of the occipitofrontal head circumference curve.

Statistical analysis

Continuous variables are expressed as mean ± SD and were compared using an independent *t* test. Occipitofrontal head circumference curves were constructed, assessed and dichotomized into two categories: downward deflection or no downward deflection. Patients were also dichotomized for the presence of papilledema. Statistical analysis was performed using a Chi-square test, or a Fisher's exact test when appropriate.

RESULTS

In total, we identified 262 patients with metopic synostosis who had been treated at our center, 201 (77 percent) of whom were male and 227 (86 percent) of whom were considered to have non-syndromic trigonocephaly. Mean age at operation was 11 months (SD, 2 mo). In total, 240 patients (92 percent) were operated on within the first year of life. One patient was operated on after 2 years of age and was therefore excluded.

Fundoscopy

Fundoscopy was available before surgery in 261 out of 262 patients, and after surgery in 196 of 262 patients.

Before surgery, 1.9 percent of patients (five of 261) had papilledema (four of 226 non-syndromic versus one of 35 syndromic; p=0.52, Fisher's exact test), which resolved after treatment. After surgery, 1.5% of patients (three of 196) had papilledema (two of 167 non syndromic versus one of 29 syndromic, p=0.38, Fisher's exact test). One patient had

papilledema both before and 4 years after the primary surgery, for which a second operation was performed. The development of papilledema in the patients with papilledema is shown in table 2.

Table 2 Development of papilledema (N/A, not applicable.)

Patient	Syndromic	Pre-op papilledema	Age at 1st operation	Post-op papilledema	Age at onset of post-op papilledema	Age at 2nd operation
1	-	+	6 mo	-	n/a	n/a
2	-	+	8 mo	-	n/a	n/a
3	-	+	14 mo	-	n/a	n/a
4	+	+	8 mo	-	n/a	n/a
5	-	+	9 mo	+	4yr11mo	5yrs
6	-	-	13 mo	+	6 yr1mo	6yr6mo
7	+	-	11 mo	+	3yr7mo	n/a

Occipitofrontal head circumference

Complete preoperative and postoperative occipitofrontal head circumference measurements were available for 150 patients. Figure 1 shows the occipitofrontal head circumference expressed in SD during the preoperative and postoperative course. Preoperatively, mean occipitofrontal head circumference was -0.53 SD, which increased to a mean occipitofrontal head circumference of 0.14 SD after surgery. In the postoperative course this declined to -0.11 SD at T3 (between 1 and 3 years after surgery). At last follow-up, the mean OFC was -0.07 SD (>3 years postoperatively).

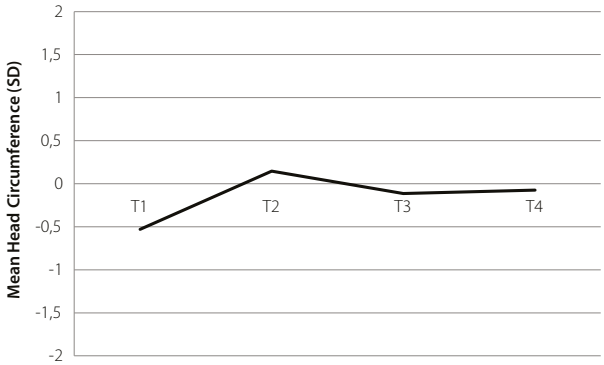

Figure 1 Mean occipitofrontal head circumference at different time points. T1, preoperatively; T2, less than 1 year postoperatively; T3, between 1 and 3 years postoperatively; T4, more than 3 years postoperatively. Only patients with occipitofrontal head circumference measurements at all time points were included (n = 150).

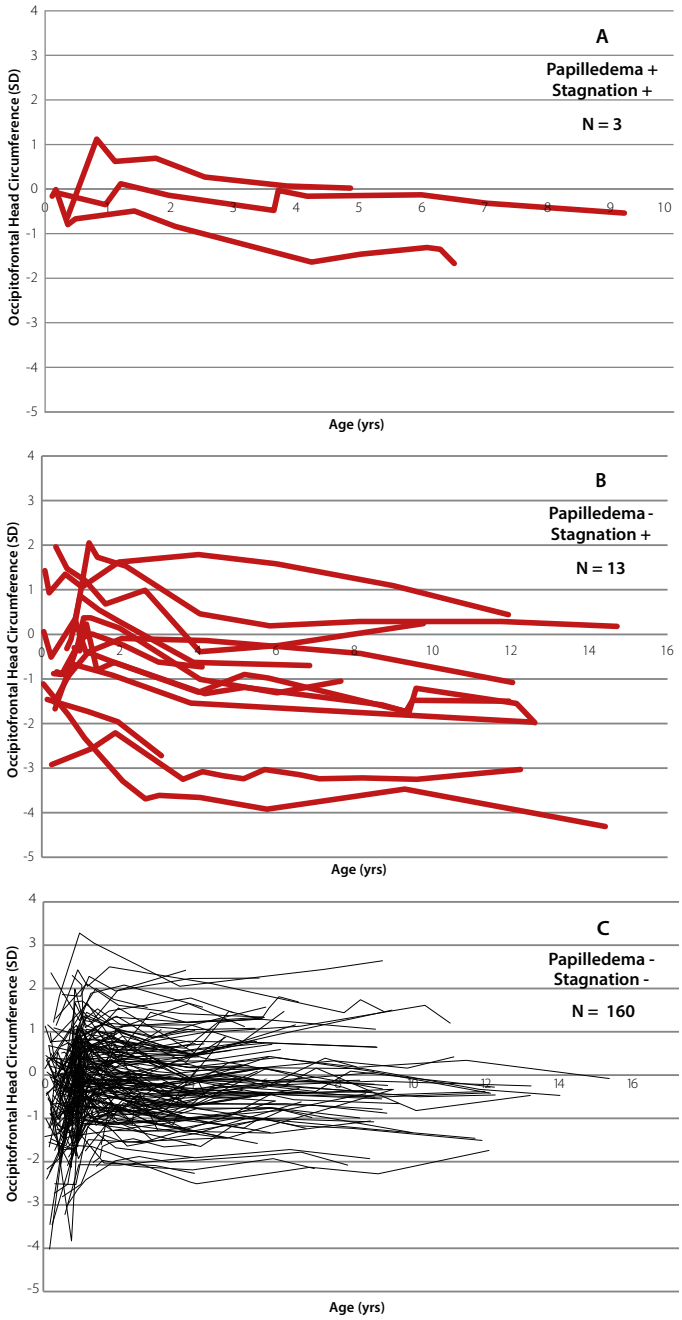

Figure 2 Occipitofrontal head circumference curve trajectories for patients with papilledema and occipitofrontal head circumference stagnation (*A*), with stagnation but without papilledema (*B*), and without stagnation or papilledema (*C*).

Preoperatively, we found a nonsignificant difference in mean occipitofrontal head circumference of 0.5 SD between patients with papilledema (-1.08 SD) and those without (-0.57 SD; p=0.25). Complete postoperative follow-up was available in 176 patients. Three or more postoperative occipitofrontal head circumference measurements were unavailable for 30 patients, and 56 patients had not undergone postoperative fundoscopy. Postoperative occipitofrontal head circumference curve stagnation was found in 16 of the 176 patients (9 percent), three of whom had papilledema at fundoscopy. The remaining 13 patients with stagnation had shown no papilledema at repeated fundoscopy. One of these 13 patients had reported headaches, 7 of whom showed a beaten-copper pattern on their skull radiographs. In two of them, an additional computed tomographic scan had shown no signs of intracranial hypertension. None of the patients without occipitofrontal head circumference curve stagnation had had papilledema. Figure 2 shows the occipitofrontal head circumference curve trajectories for patients with and without postoperative papilledema.

A statistically significant relationship was noted between occipitofrontal head circumference curve stagnation and the prevalence of papilledema (p = 0.001, Fisher's exact test, table 3).

Table 3 Crosstable of incidence of papilledema and OFC curve stagnation*

	Stagnation	No stagnation	Total
Papilledema	3	0	3
No papilledema	13	160	173
Total	16	160	176

*p = 0.001, Fisher's exact test

Occipitofrontal head circumference curve stagnation was more common in syndromic patients than in non-syndromic patients (p = 0.022, Fisher's exact test, table 4).

Table 4 Crosstable of syndromic diagnosis and OFC curve stagnation*

	Stagnation	No stagnation	Total
Syndromic	6	22	28
Non-syndromic	10	141	151
Total	16	163	179

*p = 0,022, Fisher's exact test

Re-operation because of intracranial hypertension was performed in 0.8 percent of patients (two of 262). The first patient of these patients was non-syndromic and had had a positive

fundoscopy before the primary operation at 9 months. Although the papilledema had resolved post-operatively, a recurrence was noted approximately 4 years after surgery, and was confirmed by repeated fundoscopy 6 weeks later. This was the indication for the second cranial vault surgery, after which the papilledema resolved.

The second of these patients underwent invasive ICP monitoring after repeated positive fundoscopy. This showed a mean intracranial pressure of 14.9 mmHg with multiple peak pressures of 30 to 35 mmHg. The patient had had his initial operation a slightly later age than in our protocol (1 year and 1 month). After the positive invasive ICP monitoring, a second operation was performed at 6 years and 6 months. After this, the papilledema disappeared.

A third patient, who had syndromic trigonocephaly and post-operative papilledema, did not undergo a second operation. Although fundoscopy showed papilledema 3 years 7 months after the initial operation, a computed tomographic scan showed no signs of intracranial hypertension; a visual evoked potential test also showed no disturbances. The papilledema resolved after 2 months. Six years after the initial operation, a second episode of papilledema was noted. Again, a computed tomographic scan showed no signs of intracranial hypertension, and again the papilledema resolved (after 3 months). No second operation was performed.

For these 3 patients the median time between first operation and onset of papilledema was 3 years 11 months (range 2.7 – 5 years).

DISCUSSION

This study assessed the prevalence of papilledema in a large cohort of patients with metopic synostosis. Before surgery, which was performed at a mean age of 11 months, 1.9 percent of patients had papilledema. After surgery, the prevalence declined to 1.5 percent, showing that intracranial hypertension following craniofacial correction is relatively uncommon in metopic synostosis.

Because the occipitofrontal head circumference is a reliable indicator for intracranial volume, this too, was analyzed, as a decline in occipitofrontal head circumference can precede intracranial hypertension. Indeed, we found a clear relationship between stagnation of the occipitofrontal head circumference curve and the incidence of papilledema.

The earlier literature on raised intracranial pressure in metopic synostosis showed a great variance in prevalence (table 1). Thompson et al. found intracranial hypertension preoperatively through invasive subdural pressure monitoring in 33 percent of the cases. Two factors explain this high prevalence. First, the ICP recordings in question were performed in patients who ranged in age from 1 month to 14 years. However, the authors

did not specify how old the patients were at the time of ICP monitoring, which may greatly have affected the prevalence. Second, their metopic synostosis group consists of only 9 patients Statistical analyses in such small patient groups can be greatly influenced by bias and should be interpreted with care. In contrast, our own study analyzed intracranial hypertension in 261 patients, which is, to our knowledge, the largest cohort to date. This resulted in a prevalence of papilledema of 1.5 percent after surgery, and shows that the pre- and postoperative prevalence of papilledema in trigonocephaly is very low.

The question therefore arises of whether the operation is indicated to prevent intracranial hypertension, or is performed solely for esthetic reasons. The answer depends on a factor that is largely unknown: the natural course of intracranial hypertension in untreated trigonocephaly patients. An earlier study showed that intracranial pressure in non-operated craniosynostosis patients increased until approximately 6 years of age, when the intracranial pressure reaches its maximum.[7] Although there are no definitive data on untreated trigonocephaly patients and the prevalence of intracranial hypertension, Renier et al. state that the frequency of intracranial hypertension in trigonocephaly doubles after 1 year of age.[1] Together, these data, the low postoperative prevalence of papilledema found in our study and the stable occipitofrontal head circumference result during follow-up, all suggest that the timing of surgery at approximately 9 to 12 months of age is appropriate and may also successfully prevent the development of intracranial hypertension in a proportion of patients.

Our findings for trigonocephaly contrast with earlier findings in scaphocephaly patients, in whom the prevalence of intracranial hypertension was approximately 10 percent before operation at 11 months and 9 percent at post-operative follow-up.[15, 16] Similarly, significantly different occipitofrontal head circumference growth curves have been shown for scaphocephaly, showing that the different types of unisutural craniosynostosis should be seen as different entities with respect to treatment and follow up.[16]

Recent research on neurocognitive outcome for children with unisutural craniosynostosis has shown that neurocognitive outcome is highly variable and suture dependent. For instance, language, learning and memory have been shown to be poorer in children with single suture synostosis; however, attention and executive function did not differ significantly compared with healthy controls.[17-19] Although studies reporting on differences within the unisutural craniosynostosis population are contradictory and subject to various recent papers within the craniofacial community,[17-23] account should be taken of the influence of intelligent quotient, which seems to partly explain the neurocognitive vulnerability of patients with metopic synostosis.[24]

Historically, it was thought that intracranial hypertension had prime responsibility for the neurocognitive deficit in unisutural craniosynostosis. Although this hypothesis may be accurate for scaphocephaly, as neurocognitive outcome seems to benefit from early surgery

(before the onset of intracranial hypertension),[20, 21] research suggests that the prevalence of neurocognitive and behavioral problems is higher in patients with metopic suture synostosis. However, this is not consistent with the prevalence of intracranial hypertension, as patients with sagittal suture synostosis have a much higher prevalence of intracranial hypertension before and after surgery than those with metopic suture synostosis.[5, 15, 16]

This strengthens the hypothesis that neurocognitive problems are not secondary due to intracranial hypertension in patients with metopic suture synostosis, but are a primary phenomenon in the pathophysiology of this specific type of craniosynostosis. Since 2013, referral to our child psychiatry department is regularly offered based on suspicion of behavioral or cognitive problems at the follow-up appointment. Preliminary analyses of the data resulting from these referrals suggest that the prevalence of behavioral and cognitive problems in our metopic synostosis patient population is relatively high, corresponding with the expectation we based on the aforementioned literature.

At our center, the findings we present above have led to a change of protocol for metopic synostosis patients. On the basis of a 1.5 percent prevalence of papilledema after surgery, postoperative fundoscopy is no longer performed regularly. There are two possible indications for fundoscopy: stagnation of the occipitofrontal head circumference growth curve, or when raised intracranial pressure is assumed, based on clinical signs or symptoms, such as headaches in the morning or frequent awakenings during the night. If intracranial hypertension is suspected but repeated fundoscopy does not show papilledema, optical coherence tomography or invasive intracranial pressure monitoring should be considered. However, one should bear in mind that an optical coherence tomographic scan can be performed accurately only in patients aged approximately 3 years or older.

This study has three limitations that need to be considered. Firstly, we used papilledema as an indicator for raised ICP, and a decline in occipitofrontal head circumference to mark impaired skull growth. At our center, fundoscopy is part of the standard follow-up protocol, as it is a practical, clinically relevant tool for screening craniosynostosis patients for intracranial hypertension. However, given its low sensitivity in young children, there may in theory be patients with raised intracranial pressure without papilledema.[25] In that case, patients at risk would be those with occipitofrontal head circumference curve stagnation. During this study, the 16 patients in that category received repeated fundoscopies, and were watched closely for other signs of intracranial hypertension, such as headaches in the morning. To rule out any intracranial signs of intracranial hypertension, two underwent computed tomographic scanning. With optical coherence tomography becoming more available and reliable, we recommend that these patients are analyzed with optical coherence tomography and fundoscopy. A second limitation is that although occipitofrontal head circumference stagnation has high sensitivity (100%) and specificity (92%), the positive predictive value is low (19%). This may be explained by the small number of patients with a

positive fundoscopy (3).

With this in mind, we recommend that occipitofrontal head circumference measurements become an important factor in these patients' follow-up. However, the decision-making process for revision surgery should also weigh factors such as radiologic findings and frequent headaches in the early morning.

Lastly, this study was performed retrospectively in our complete cohort of patients with metopic synostosis, in whom surgery was scheduled at 9 to 12 months and regular fundoscopic examinations were conducted. As with all studies, the study population and the protocol applied should be taken into account when the results are interpreted and extrapolated to other patients.

Conclusions

Intracranial hypertension in patients with metopic suture synostosis is only sporadic. Occipitofrontal head circumference measurement should be given a prominent place in the postoperative follow-up of metopic suture synostosis patients. Any stagnation of the occipitofrontal head circumference requires additional screening for intracranial hypertension.

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Chapter 7

Reply: Letter to the Editor: Re: Very Low prevalence of intracranial hypertension in trigonocephaly

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Journal of Plastic and Reconstructive Surgery, June 2017.

Dear Sir,

We read with interest the reply of Professor Rogers on our paper on the prevalence of intracranial hypertension in trigonocephaly.[1] This paper describes the occurrence of intracranial hypertension, assessed through fundoscopy, and its relation with the occipito-frontal head circumference curve. This study, in 262 metopic synostosis patients, shows that not only intracranial hypertension (a positive fundoscopy) is rare pre- and post-operatively, but also that it is related to stagnation of the occipito-frontal head circumference curve, as also shown in a previous paper in syndromic craniosynostosis patients.[2]

Professor Rogers raises two concerns with the methodology of the study, on which we are glad to comment. Firstly, the accuracy of fundoscopy in the detection of intracranial hypertension is questioned. As Tuite et al. have shown the sensitivity of fundoscopy in young children may be low.[3] This may have resulted in an underestimation of prevalence of intracranial hypertension in our series, if the patients were assessed by fundoscopy alone. As stated in the discussion section of the paper, we would consider patients with a deflection of the OFC curve, but with a negative fundoscopy, the ones most at risk for a false-negative result of the fundoscopy. These patients underwent repeated fundoscopies and were watched closely for other signs of intracranial hypertension, such as headaches in the morning. We feel that this approach adequately deals with the possible shortcomings of fundoscopy in the screening for intracranial hypertension.

The second issue raised by Prof. Rogers is the diagnostic criteria used to diagnose trigonocephaly, or metopic synostosis. The metopic suture is the first cranial suture to close, mostly within the first year of life. A physiologic closure can indeed occur in the first months of life, without a necessity to operate. We agree with prof. Rogers that a closed metopic suture on itself is not a reason to operate. In our center, the indication for surgery is based on the following assessments: a radiographically confirmed closure of the metopic suture, retrusion of the lateral orbital rim and obvious hypotelorism. The potential bias prof. Rogers is suggesting is based on two assumptions:

1. Within the patients that were included there is a large group of mild trigonocephaly patients.
2. A mild trigonocephaly results in a lower risk of intracranial hypertension.

In our eyes, these assumptions may not be accurate. Prof. Rogers advocates the use of radiographically-based cranial measurements to standardize the diagnosis and suggests that the use of clinical parameters as mentioned above would lead to wide diagnostic and

treatment variability. However, in a paper by Anolik et al., it has been shown that these specific measurements relate closely to the expert decision whether to operate or not.[4] In other words, our clinical judgement would not differ greatly from the computer-based decision whether to operate or not.

Additionally, the prevalence of intracranial hypertension has not been linked to severity of trigonocephaly to date. As previously shown, the intracranial volume of trigonocephaly patients is smaller than controls post-operatively.[5] In contrast, scaphocephaly patients usually have a normal or larger intracranial volume.[6] Nevertheless, sagittal synostosis patients show a higher prevalence of intracranial hypertension, both pre- and post-operatively.[7] This illustrates that intracranial hypertension is not just a surrogate of cranial shape or 'severity', but is the result of a complex interplay between several parameters, which we may not fully understand to date.

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Chapter 8

Unilateral versus bilateral correction of unicoronal synostosis; an analysis of long-term results

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ABSTRACT

Introduction Hollowing of the temporal region is a common problem after cranioplasty for unicoronal synostosis. In this study the development of temporal hollowing pre- and postoperatively is evaluated. Secondly, the origin of temporal hollowing is investigated by comparing two operative techniques. Ultimately, the relation between timing of surgery and the development of hollowing is investigated.

Methods From 1979 to 2010 194 patients with unicoronal synostosis were operated at our center. Patients were treated with a unilateral or bilateral correction of the supraorbital rim. Forty-eight patients qualified for the present study. Mean age at follow-up was 7.5 years. Cephalic landmarks were identified on radiographs prior to and after surgery to determine the growth of the forehead. For visual analysis, two independent observers evaluated normal photographs for the presence and severity of temporal hollowing.

Results Preoperative osseous asymmetry improved significantly after surgery. Twenty-one patients show an increase of temporal hollowing on photographs after surgery (46%). In 35 out of 48 patients postoperative temporal hollowing was noted (73%). Bilaterally treated patients showed more severe temporal hollowing compared to unilaterally treated patients, however not significantly (23% vs 6%, p=0.229). Timing of surgery (before or after the age of one year) did not influence the occurrence of severe temporal hollowing.

Conclusions Fronto-supraorbital advancement was unable to achieve normal growth in the temporal region in a large proportion of patients, although more symmetry was achieved. The operative technique itself did not seem to influence the occurrence of temporal hollowing, nor did the timing of surgery.

INTRODUCTION

Premature ossification of one of the coronal sutures results in frontal plagiocephaly. Clinical features include retrusion of the supraorbital rim and the frontal bone, and hollowing of the temporal region on the affected side, combined with bossing of the frontal bone on the contralateral side, with orbital dystopia and with a slight concavity of the face towards the affected side.

The incidence of frontal plagiocephaly or unicoronal synostosis currently resides in Europe at approximately 1 in 11.000 live births (1, 2). This type of craniosynostosis accounts for approximately 30 percent of all cases of single-suture craniosynostosis treated in our center.

The treatment of choice for unicoronal synostosis is a fronto-supraorbital advancement and remodelation (FOAR). The surgery aims to correct both the frontal volumetric restrictions as well as the asymmetry of the frontal bone and supraorbital bar, and is thought to be indicated before the age of 12 months in order to prevent raised intracranial pressure (3, 4). Considering the asymmetry of the malformation, some have advocated an unilateral correction of the supraorbital rim, while others prefer a bilateral approach, considering that on average both sides of the forehead are affected (5).

(Bi)temporal hollowing is the most common feature after cranioplasty (6-13). The hollowing is usually located just lateral and slightly cranial to the lateral apex of the eyebrow. While the preoperative findings are believed to be due to restricted growth, the etiology of the postoperative hollowing still remains unknown.

This study was set up to investigate whether there was a relation between the severity of the initial malformation and the occurrence of postoperative temporal hollowing in our population with unicoronal craniosynostosis. Secondly, the influence of the operative technique used (unilateral approach *vs* bilateral approach) was evaluated in an attempt to clarify its etiology. Ultimately, the relation of timing of surgery and the development of hollowing is investigated.

PATIENTS AND METHODS

In order to evaluate post-operative growth photographs and radiographs before and after surgery were evaluated for the presence and severity of temporal hollowing (photographs) and the width of the forehead and supraorbital bar (radiographs).

This study was conducted according to the principles of the Declaration of Helsinki (version January 5th, 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Records of patients with unicoronal synostosis who were treated surgically at our department over a period of 31 years (between 1979 and 2010) were reviewed.

The following inclusion criteria were used:

1. Complete treatment including follow-up was done at the Sophia Children's Hospital,
2. Surgery was performed before the age of two years
3. Complete and detailed record of the treatment was present:
   a. Pre- and/or postoperative photograph and radiograph,
   b. Postoperative photograph and radiograph were taken at least two years postoperatively,
   c. The postoperative photograph and radiograph were taken not more than a week apart from each other (to prevent interference by growth) (14-17),

Operative technique

Unicoronal synostosis can be treated in either a unilateral or bilateral fashion. In both cases, access to the anterior cranial vault is gained via a bicoronal incision. The frontal bone is removed in one piece, after which, when performing a bilateral correction, the complete supraorbital bar is mobilised. This segment is then reshaped by advancement of the synostotic side together with an adequate adjustment of the shape of the contralateral side. The forehead is split in the midline and the resulting bone fragments are adjusted and replaced in the most optimal position on top of the supraorbital bar, where they are fixed with metal wires (before the year 1997) or absorbable sutures (Vicryl®) (Fig. 1).

When using the unilateral method, only the ipsilateral half of the supraorbital bar is mobilised and subsequently adjusted.

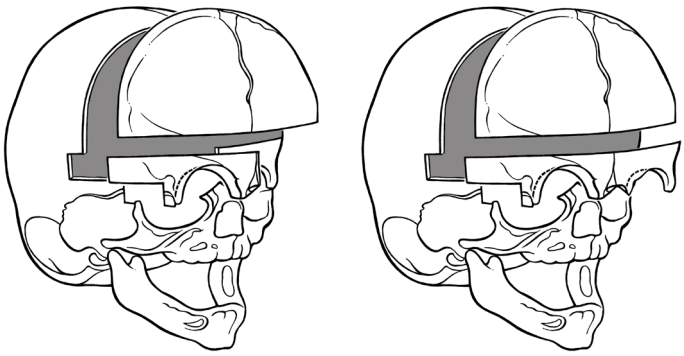

Figure 1 Fronto-orbital advancement and remodellation. The osteotomies placed near the temporal bone could result into the lack of lateral expansion. The left drawing shows the unilateral technique, the right shows the bilateral technique.

Photographic assessment

The pre- and postoperative photographs were checked for the presence and severity of temporal hollowing by two panel members (the senior author and a medical PhD student). A score of 0 (normal), 1 (moderate deformity) or 2 (severe deformity) was assigned to each side of every patient (Fig. 3A). Each observer scored the photographs at two independent occasions. A third score was given in case the second score was different from the first score, resulting in one conclusive score for each side of each patient per observer. An interrater reliability analysis using the Kappa statistic was performed to determine consistency among raters. In those cases where both observers scored a photograph differently, the two observers together evaluated the photograph and consensus was reached. This resulted in one conclusive score for each side of each patient.

Radiographic assessment: cephalograms

Older, non-digital radiographs were digitalized with a Diagnostic PRO plus Film scanner running at 300 dots per inch (DPI). Two validated landmarks for determining orbital growth (15, 18-27), were subsequently marked on each side with the use of the computer program Image J (Wayne Rasband, National institute of health, USA): the most medial point of the medial orbital wall (Mo) and the junction of lateral orbital wall and sphenoid wing (LoSp). The Medial orbital wall on the left and right side of the patient were used to establish the midline (Mi). Because LoSp is located on the anterior border of the area most associated with the hollowing, the distance between LoSP and Mi was taken to be the indicator of the skeletal widening of the temporal region (fig. 2). Figure 3B shows an example of the post-operative radiographic assessment performed on a patient.

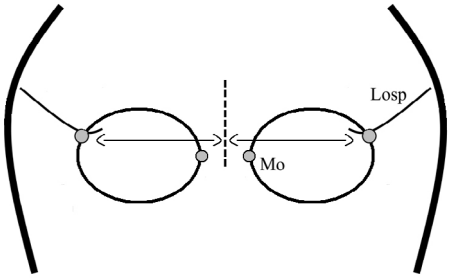

Figure 2 Mo and LoSp, here shown on a schematic drawing, were identified on radiographs.

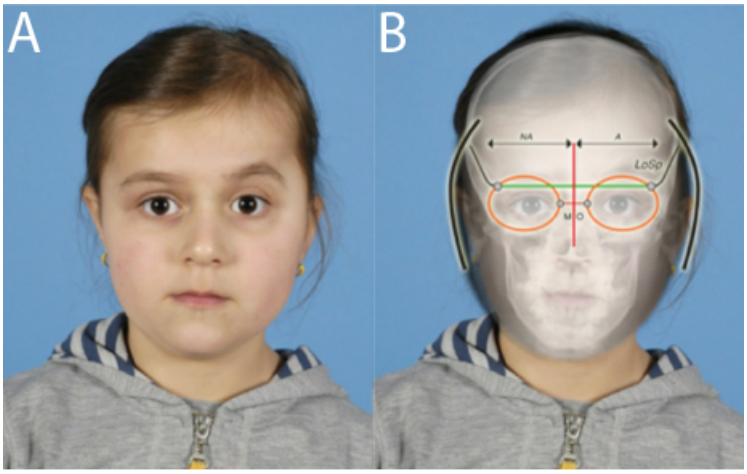

Figure 3 (A) An example of the photographic and radiographic assessment. This patient's photographic score was noted as 1—0, the left side being the affected side. (B) The distances measured on this specific radiograph resulted in a growth ratio of 0.84, indicating more lateral bone growth of the non-affected side.

Due to the lack of standardized radiographs corrected for the age of the patient, ratios were used instead of absolute distances. The temporal hollowing ratio was defined as:

$$\frac{\text{Mi-LoSp on the affected side}}{\text{Mi-LoSp on the contralateral side}}$$

Statistical analysis

The interobserver variability in the evaluation of the radiographs was tested using an intraclass correlation coefficient (ICC). To determine consistency among raters for the evaluation of the photographs an interrater reliability analysis using the Kappa statistic was performed. Correlations of photographic scores of the affected and non-affected sides and the pre- and postoperative photographic scores were determined using Fisher's exact test. X-ray ratios of the pre- and postoperative assessment were compared using a paired T-test. The effect of the operation technique and the timing of operation were evaluated using crosstables. A chi square test was performed for every single variable. Fisher's exact test was used when the chi square test was not eligible because of too much cells with an expected count of less than 5. A Mann-Whitney test was used to assess the residual growth after surgery. All statistical procedures were performed using SPSS (SPSS version 20; SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 192 patients were identified of which 144 patients did not meet the given in- and exclusion criteria; of 108 patients no complete record of the operation or follow-up could be identified (75%) and 36 patients were operated upon after their 2nd year of age (25%). This resulted in 48 patients to be included in this study.

In 2 of the 48 patients (4%) there was no preoperative photograph available and in 9 of the 48 patients (19%) there was no pre-operative radiograph available. These patients were only included in post-operative photographic or radiographic analysis.

Demographic data derived from the present study population is shown in table 1.

Table 1 Table showing demographic data from the present study.

	Avg. Age (years)	**SD**
Pre-operative photographic evaluation	0.65	0.39
Pre-operative radiographic evaluation	0.72	0.39
Operation	1.1	0.3
Follow-up	7.5	2.6
	No. of patients	**Proportion**
Treated unilaterally	18	38%
Treated bilaterally	30	62%
Left-sided UCS	20	42%
Right-sided UCS	28	58%

Level of agreement between observers

Agreement between observers of the pre-operative photographic scores was determined by the use of the kappa statistic and resulted in 0.68 for the right side and 0.51 for the left side. The kappa statistics for the postoperative photographic score of the left and right side of the patient were 0.59 and 0.58 respectively. According to Landis and Koch (28) this constitutes for moderate to good agreement among observers.

Analysis of the reliability of measurements of the Mi-LoSp distance on the preoperative radiographs showed ICC's of 0.97 (left side) and 0.95 (right side).

The ICC's for the Mi-LoSp distance measured on the postoperative radiographs were 0.95 and 0.94 for the left and right side respectively, which all indicate nearly identical measurements between the two different observers.

Photographic assessment

Where pre-operatively all patients presented with (a varying) degree of temporal hollowing, post-operatively this was reduced to 73% (table 2).

Analysis of changes of pre-operative to postoperative photographic scores highlighted a marked decrease in 20 patients (43%, fig. 4), indicating a decrease of temporal hollowing after surgery. While five patients remained stable (11%), twenty-one patients showed an increase of temporal hollowing after surgery (21/46, 46%).

However, compared to pre-operative results, patients showed more symmetry after the operation (p=0.002, table 3).

Table 2 Results of the photographic assessment, pre- and postoperative.

Pre-operative	**No. of patients**	**Proportion**
No Hollowing	0/46	0%
Mild Hollowing	32/46	70%
Severe Hollowing	14/46	30%
Post-operative	**No. of patients**	**Proportion**
No Hollowing	13/48	27%
Mild Hollowing	27/48	56%
Severe Hollowing	8/48	17%

Table 3 Crosstable of pre- (3A) and postoperative (3B) photographic scores of the affected and non-affected sides. Although statistically not significant more hollowing was observed in the affected sides preoperatively (98% vs 15%, p=0.15). A significant positive correlation between affected and non-affected sides is noted postoperatively (p=0.002).

A.		**Non-affected side**			**Total**
Pre-operative		0	1	2	
Affected Side	0	0	1	0	1
	1	29	2	1	32
	2	10	3	0	13
Total		39	6	1	46

B.		**Non-affected side**			**Total**
Post-operative		0	1	2	
Affected Side	0	13	7	0	20
	1	5	15	0	20
	2	2	4	2	8
Total		20	26	2	48

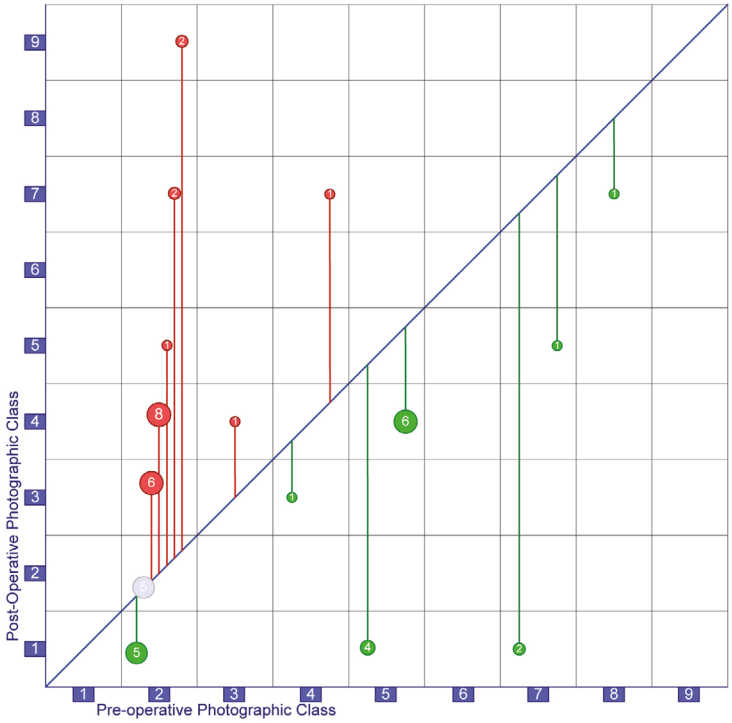

Figure 4 Figure showing the migration of patients from their pre-operative photographic class to their post-operative photographic class.

Radiographic assessment

Pre-operatively the mean X-ray ratio of the total study population was 0.89 (SD 0.08). After surgery the mean X-ray ratio of the total study population was 0.96 (SD 0.07), indicating an increase in bony symmetry (paired-samples T-test, $p<0.001$).

The postoperative X-ray ratio however was still significantly lower than '1' (which would represent symmetry of both sides of the forehead), indicating less postoperative growth on the side of the suture synostosis compared to the other, unaffected side of the forehead ($p<0.001$). This was regardless of what operative technique was used. The mean x-ray ratio for unilaterally and bilaterally treated patients was 0.96 (SD 0.07 and 0.06 respectively)

Due to a lack of numbers no significant correlation was found between photographic and radiographic scores.

Effect of treatment technique on temporal hollowing

Thirty patients were treated bilaterally and 18 patients unilaterally. Seven out of 30 (23%) bilaterally treated patients showed severe temporal hollowing at follow-up but only one out

of eighteen (6%) unilaterally treated patients showed severe temporal hollowing (table 4). However, this marked difference was not statistically significant (Fisher's exact test p=0.226).

Table 4 Crosstable of patients treated unilaterally and bilaterally and the occurrence of severe temporal hollowing. This may suggest that bilaterally treated patients show more severe temporal hollowing.

Post-operative	Treatment Technique		Total
	Unilateral	Bilateral	
No or non-severe hollowing	17	23	40
Severe hollowing	1	7	8
Total	18	30	48

Fisher's exact test, p=0.229

Effect of age at operation on temporal hollowing

This part of the study focused on the occurrence of severe hollowing in relation to the timing of surgery. The timing of treatment is generally considered to be optimal before the patient reaches 1 year of age (3, 4). In the present study no difference was found in post-operative temporal hollowing when patients are operated before or after one year of age (Fisher's exact test, p=0.6).

Residual growth after operation

No correlation was found between occurrence of severe hollowing and an increasing length of follow-up (Mann-Whitney test, p=0.761). This suggests that there was no or only very limited growth in the temporal area following the operation.

DISCUSSION

Bitemporal hollowing is the most frequently seen feature after surgical correction of unicoronal synostosis. Theories on the etiology of this temporal hollowing have focussed on either bone or soft tissue. In trigonocephaly for instance, the occurrence of temporal hollowing was shown to be linked to an impaired lateral bone growth following corrective cranioplasty. (9, 10) The osteotomies placed in the temporal region in order to mobilise the supraorbital bar, could very well be of influence on the lack of lateral bony expansion (Fig. 1). The mobilization of soft tissues like the temporal muscle and the temporal superficial fat pad during the operation, damaging their vascularity in the process, has also been suggested to be contributing to the hollowing. (7-9, 13, 29-31) Our operative approach however is purely subperiosteally and does therefore preserve the vascularisation and innervation of these soft tissue layers.(32, 33) Malpositioning of the muscle is also considered a contributing

factor. Prior research showed however that the muscle is routinely fixed to the temporal crest and its position remained stable over time. It is thus unlikely that this factor plays a significant role in the pathogenesis of temporal hollowing in our study group.

Photographic score outcome

Photoanalysis showed an increase of temporal hollowing after surgery in twenty-one patients (46%). This makes clear that our treatment was unable to achieve normal growth in the temporal region in a large proportion of patients.

We did however note a significant postoperative correlation between the photographic score at the affected and non-affected sides. Although the treatment did not manage to minimise temporal hollowing, it did achieve more symmetry.

Unilateral vs bilateral correction

Several publications described a superior cosmetic result when using the bilateral approach. (4, 5, 34-36) This finding could not be supported by our study, as there were more severe temporal depressions occurring in patients treated with a bilateral correction (23% *vs* only 6% in the unilateral group). This was however statistically not significant (Fisher's exact test, p=0.229).

Timing of the operation

It is widely advocated that correction of craniosynostosis should be performed before the patient reaches the age of one year.(3, 4) Patients are treated early to prevent the development of increased intracranial pressure. Our results show that age at time of operation had no influence on the occurrence of (severe) temporal hollowing after the procedure.

Indication bias

One could argue that more severe cases would automatically qualify for a more extensive bilateral correction, whereas relatively less severe cases would be treated unilaterally. The choice of technique in our center however, was surgeon dependant. One single surgeon operated all but three of the patients that were treated unilaterally and did not perform any bilateral surgeries. Analysis of pre-operative photographs showed no difference in severity between the cases that were operated in a uni- or bilateral way (Chi square test, p=0.436).

Therefore a possible indication bias in the present study should not have affected the results.

Limitations of the study

Radiographs could not be standardised due to the young age of these patients. As in our previous metopic synostosis analysis we reverted to the use of growth ratios instead of absolute values. In our trigonocephaly group this proved not to be of influence on the outcome.(9, 10)

Following our strict in- and exclusion criteria, the number of patients eligible for this study was limited to 48 patients (participation rate 25%). The patients were all analysed and categorised. This resulted in even smaller subgroups, which made statistical analysis more difficult. This study found no correlation between photographic score and X-Ray ratio. This is most likely due to the fact that some of the subgroups are underpowered. A multicenter study with an increased number of patients would be needed to resolve such a question.

CONCLUSIONS

Fronto-supraorbital advancement was unable to restore normal contour in the temporal region in a large proportion of patients, although more symmetry was achieved. This trend is present regardless of the choice of operative technique, which does not seem to play a significant role in the occurrence of severe temporal hollowing.

Age at time of operation also did not influence the occurrence of severe temporal hollowing in the long term.

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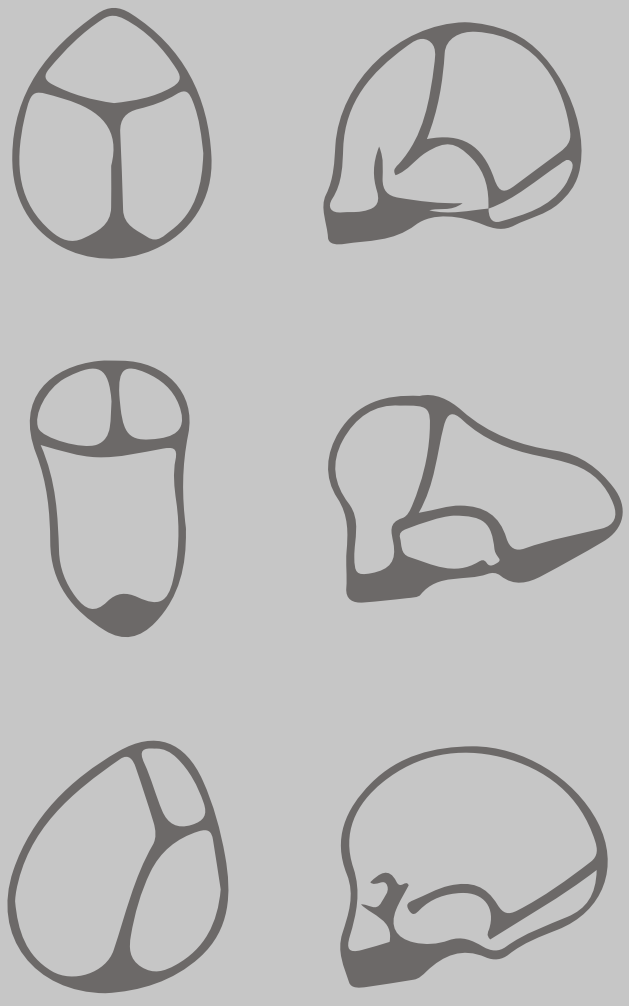

Chapter 9

General discussion

Within the craniofacial community, unisutural craniosynostosis is also known as 'simple' craniosynostosis. Mostly because it's usually compared to its more complex counterpart, syndromic craniosynostosis. The clinical features of syndromic craniosynostosis lie outside the aim of this thesis, but, in general, a high prevalence of intracranial hypertension, breathing disorders, ophthalmic problems and possible mental delay make syndromic craniosynostosis a very complex condition. These problems are less frequently seen in unisutural craniosynostosis, partly explaining the *nickname* 'simple' craniosynostosis. However, both entities are completely different with regard to treatment and follow-up and a comparison between both seems illogical. Hence, to answer the question posed on the cover of this thesis – Unisutural craniosynostosis: simple or complex? – this thesis focused on three specific areas for unisutural craniosynostosis:

- Epidemiology
- Prenatal detection and perinatal complications
- Intracranial hypertension and long term surgical follow-up

Taken together, this thesis provides a complete overview of the factors important for the care for unisutural craniosynostosis patients and trigonocephaly and scaphocephaly patients in particular.

This thesis has shown that with regard to prevalence of the condition, perinatal problems, prevalence of intracranial hypertension and postoperative follow-up there are differences between the subforms of unisutural craniosynostosis. These findings, combined with previous reported data[1, 2], illustrate the necessity to study and report on these individual diagnoses, instead of clustering all unisutural craniosynostosis into one group.

Up until 2012 craniosynostosis patients were treated in 5 different university medical centers in the Netherlands. Because craniosynostosis is a rare condition, centralization of care for these patients was implemented in the Netherlands in 2012.[1] Eventually this resulted in the remainder of 2 craniofacial centers equipped to provide care for patients with unisutural craniosynostosis and one for syndromic craniosynostosis.[1]

IMPLICATIONS OF RESULTS

Recently, various papers have reported on the rising prevalence of craniosynostosis and trigonocephaly in particular.[3-5] The first question this thesis aimed to answer was what the prevalence of craniosynostosis is in the Netherlands. This question is answered through an accurate description of the prevalence of each type of (non-)syndromic craniosynostosis, exploring regional variation and change over time. The overall prevalence of craniosynostosis was found to be 1 in 1400 births, resulting in an average of approximately 120 patients per year in the Netherlands. The previous reported rise of prevalence of metopic suture synostosis is confirmed.[3-5] Additionally, the prevalence of sagittal suture synostosis seems

to be rising as well. Prevalences for the various forms of unisutural craniosynostosis were as stated in table 1.

Table 1 The prevalence of the various subforms of unisutural craniosynostosis in the Netherlands from 2008 – 2013.

Fused suture	Prevalence
Sagittal	1 in 3.000
Metopic	1 in 4.500
Unicoronal	1 in 14.500
Unilambdoid	1 in 88.000
Frontosphenoidal	1 in 250.000

Although still a rare condition, this study showed that there is a clear rise of prevalence of craniosynostosis (+12.5%, annually from 1997 to 2013), which can mostly be explained by the rise in prevalence of metopic synostosis. The metopic suture is known to close at around 6-8 months of life and racial variation with regard to timing of suture closure is present.[6] Metopic suture closure in the first months of life may result in a so-called *metopic ridge*, a palpable ridge over the metopic suture, but without the wedge-shaped forehead, biparietal widening and hypotelorism found in true metopic synostosis patients developing at 15 week of gestation. The threshold between metopic ridge and metopic synostosis depends on the timing of suture closure and is based on the aforementioned, subjective, clinical features. With an increased detection and referral to a craniofacial center in the past years, this may partly be responsible for the rise in prevalence of metopic synostosis and possibly overdiagnosis and overtreatment. The low prevalence of intracranial hypertension found in metopic synostosis, suggests that extensive craniofacial surgery may not be required in all cases. Possibly, screening for intracranial hypertension through fundoscopy doesn't do justice to the pathology and alternative methods such as Arterial Spin Labelling or transcranial Doppler studies may shed new light on the changed physiology in trigonocephaly, with new insight into treatment indications. These new insights may result in a decreasing number of metopic synostosis patients that need surgery in the future. Care providers should be open to adapting their treatment strategy if future research shows that there are no functional benefits from surgery, including the esthetic outcomes.

As craniosynostosis is such a rare disease, there is little to no knowledge about the condition within the primary care community (of which the ultrasonographers performing the 20-week anomaly scan are a part). This may partly explain that unisutural craniosynostosis is only sporadically diagnosed prenatally. The importance of prenatal detection of unisutural craniosynostosis has long been neglected in international research. However, with the rise of early (spring-assisted) surgery at 4-6 months for scaphocephaly at our center, an early

diagnosis has become more important to ensure timely referral. Additionally, since other craniofacial centers advocate a suturectomy combined with a moulding helmet for sagittal, metopic and unicoronal synostosis, an early diagnosis and referral may be as important for all unisutural craniosynostosis patients.[7, 8]

Recent papers show that the opinion on the importance of prenatal detection of craniosynostosis is changing and the first stages of the development of prenatal detection tools are described.[9, 10] Haratz et al advocate the use of the 'brain shadowing sign', a hypodense area positioned under the fused suture. However, this can be subtle and thus easily missed in a primary care (screening) setting. Moreover, it would mean another addition to the set of quantitative and qualitative parameters measured at the 20-week screening ultrasound. For these reasons, we set out to find discriminative measurements within the existing set of measurements already performed at the 20-week ultrasound. We found that the cephalic index, the ratio between biparietal diameter and occipitofrontal diameter, is significantly lower in scaphocephaly patients. However, at 20-weeks its discriminative power is too limited to incorporate it into the screening ultrasound. With increasing gestational age, the biparietal diameter seems to deviate further, making a prenatal diagnosis possible. For trigonocephaly patients no significant differences in cephalic measurements were found compared to controls at 20 weeks of gestation. Currently, a deviation of head circumference or biparietal diameter sporadically leads to a referral to a specialized center. However, our results show that when sagittal synostosis is suspected on the basis of the BPD or CI value at the 20 week anomaly scan a follow-up ultrasound in the third trimester is indicated, preferably in combination with 3D-imaging of the cranial sutures.

As stated before, prenatal diagnosis is desired to ensure timely referral for early treatment. Another benefit of early diagnosis is the possibility to prepare for possible perinatal complications. Previous studies have shown a higher rate of caesarean sections, an increased rate of maternofetal trauma and lower APGAR scores in the neonate.[11, 12] These studies have pooled all unisutural craniosynostosis patients together. However, head shape varies greatly among the different subtypes, possibly affecting pregnancy and birth in different ways and magnitudes. We analyzed perinatal complications in a large population of metopic and sagittal suture synostosis patients in two European countries with an accurate birth registry. By combining data from Sweden and the Netherlands we were able to show that the antenatal background of the condition (assisted reproductive technology, fetal position and gestational age at birth) is different from normal, suture specific and not influenced by the country. Although differences with regard to the policy to deal with this altered biology were found between countries, the overall rate of medically assisted deliveries (operative vaginal deliveries or caesarean sections) was higher in both countries. The higher rate of medically assisted deliveries may be caused by hampered fetal head moulding, resulting in obstruction of labor and the need to perform operative

vaginal delivery or a caesarean section. Additionally, the increased rate of breech position resulted to higher caesarean section rates. Prenatal diagnosis would enable the obstetrician to prepare for possible perinatal complications and may prevent maternofetal trauma.

Historically, clomiphene stimulation and IVF/ICSI have been associated with a higher rate of birth defects.[13, 14] However, the studies seemed unable to separate the potential effect of the underlying subfertility from the treatment effects.[15] A longer time-to-pregnancy has been shown to result in higher rates of congenital abnormalities and neurodevelopmental and behavioral disturbances in children.[16, 17] In our study we found an increased rate of assisted reproductive technology (ART) in trigonocephaly patients. This may be a marker of subfertility in the parents of the affected child, with a corresponding longer time-to-pregnancy. This suggests that ART and/or time-to-pregnancy may play a role in the etiology of trigonocephaly and the cognitive and behavioral development disorders found in these patients. Causative mechanisms in rare diseases are often hard to display, mainly limited by the sample size of the average cohort studies performed within the craniofacial community. Two recent initiatives may be able to solve this problem. Firstly, as already stated above, large population cohort studies, such as the *Generation R*-study, may be able to display these causative mechanisms. Secondly, in 2016 the European Reference Network on craniofacial abnormalities was founded. This network consists of the largest European craniofacial centers and enables fast and efficient communication between the several centres. Moreover, with this initiative, the European commission aims to stimulate trans-European research. This would result in larger patient cohorts, a higher quality of research and better generalizability. This evolution could help in displaying the complex, multi-factorial, mechanisms responsible for causing craniosynostosis.

Treatment of unisutural craniosynostosis is aimed at treating or preventing intracranial hypertension. In trigonocephaly, this thesis shows that the pre- and postoperative prevalence of papilledema in trigonocephaly is very low. The question therefore arises whether the operation is indicated to prevent intracranial hypertension or is performed solely for esthetic reasons. The answer depends on a factor that is largely unknown: the natural course of intracranial hypertension in untreated trigonocephaly patients. An earlier study showed that ICP in non-operated craniosynostosis patients, syndromic and non-syndromic, increased until approximately 6 years of age, when the ICP reaches its maximum.[18] Although there are no definitive data on untreated trigonocephaly patients and the prevalence of intracranial hypertension, Renier et al. state that the frequency of intracranial hypertension, measured extradurally, in trigonocephaly is approximately 8% and doubles after 1 year of age.[19]

The detection of intracranial hypertension remains a much debated subject to date. Throughout the literature the methods for detecting raised intracranial pressure range from clinical findings such as cracked-pot percussion note of the skull, marked irritability and

decline of skull circumference, to fundoscopy and invasive intracranial pressure monitoring.[2, 20, 21] All methods have their specific drawbacks and advantages. Invasive monitoring remains the golden standard, providing the clinician with an absolute value of intracranial pressure. However, invasive monitoring means another surgery with risk of complications and the values derived from the monitoring are not always conclusive.[22] Fundoscopy has been shown to be a highly specific method of detecting raised intracranial pressure. However, a lower sensitivity was found in young children in a single study, which is yet to be confirmed in different studies.[23] We have shown that decline of the skull circumference is closely related to papilledema, illustrating the importance of skull circumference measurement during follow-up.[24] These differences imply that the prevalence of intracranial hypertension reported by a study should be evaluated with the specific method of detection of ICH in mind. In the future, the different methods of detecting intracranial hypertension should be compared within the same patients to find a definitive answer.

Our findings for trigonocephaly patients contrast with earlier findings in scaphocephaly patients, in whom the prevalence of intracranial hypertension was approximately 10% before operation at 11 months and 9% at long-term post-operative follow-up.[25, 26] Similarly, significantly different occipito-frontal head circumference growth curves have been shown for scaphocephaly, showing that the different types of unisutural craniosynostosis should be seen as different entities with respect to treatment and follow up.[26]

The same is true for neurocognitive outcome in unisutural craniosynostosis. Recent literature on cognition and behavior has shown that, although attention and executive function did not differ from healthy controls, language, learning and memory seem to be poorer in children with single suture craniosynostosis.[27-29] To what extent is highly variable and seems to be suture dependent. In a large study by Starr et al. it was shown that patients with sagittal synostosis perform better compared to metopic and unicoronal synostosis patients in neurodevelopmental tests and language at 3 years of age.[30] In a different study, executive function and attention did not differ between different forms of single suture craniosynostosis.[27] The influence of IQ must not be underestimated and seems to partly explain the behavioral vulnerability of patients with metopic synostosis in particular.[31] Neurocognitive outcome has been a 'hot' subject for craniofacial research the past years. Neurocognitive development is a process influenced by a large range of factors, which can potentially cause bias in the studies presented. Most studies adjust for known confounders such as socioeconomic status, IQ of the parents, race and age. Nevertheless, contradictory results are described, illustrating the complexity of neurodevelopmental testing at a young age, especially in such a rare and heterogeneous condition as single suture craniosynostosis.[29, 30, 32-36] A different factor that should be considered is the fact that neurocognitive testing can only be done reliably at around an age of 4-6 years and older. This implies that practically all children have been operated on before the neurocognitive

tests are performed. Consequently, the results that these tests show may also be influenced by type and timing of correction and the effect of anesthetic agents on a young developing brain, which are suggested not to be trivial by recent reports.[37] Additionally, in most craniofacial centers genetic testing is not routinely offered in unicoronal synostosis patients, possibly misdiagnosing syndromic patients as non-syndromic unicoronal synostosis patients, which would lead to an overestimation of the neurodevelopmental deficits in this group. This is mostly the case for children with Muenke syndrome, which are often misdiagnosed as isolated unicoronal synostosis and have been shown to have a slightly lower than normal IQ.[38] Accounting for the above, one can conclude that unisutural craniosynostosis patients show more neurocognitive deficits compared to healthy controls. Behavioral disturbances are more often seen in metopic suture synostosis patients, whereas sagittal suture synostosis patients seem to perform closer to normal values. Detection and adequate treatment of neurocognitive deficits remains an important part of the care for unisutural craniosynostosis patients and should be on the agenda of all caregivers involved in the care for these patients.

Historically, it was thought that intracranial hypertension had prime responsibility for the neurocognitive deficit in unisutural craniosynostosis. Although this hypothesis may be accurate to some degree for scaphocephaly, as neurocognitive outcome seems to benefit from early surgery[33, 35] (before the onset of intracranial hypertension), research suggests that the prevalence of neurocognitive and behavioral problems is higher in patients with metopic suture synostosis. However, this is not consistent with the prevalence of intracranial hypertension, as patients with sagittal suture synostosis have a higher prevalence of intracranial hypertension before and after surgery than those with metopic suture synostosis.[2, 25, 26] We hypothesize this difference can be explained by the embryologic basis behind the different forms of single suture craniosynostosis. As described in the introduction of this thesis the embryologic background of metopic synostosis differs from the other forms of single suture craniosynostosis. The metopic suture is the only suture that derives from neural crest cells, which are also involved in the development of the brain and its meninges. We hypothesize that neurocognitive problems are not secondary due to intracranial hypertension in patients with metopic suture synostosis, but are a primary phenomenon in the pathophysiology of this specific type of craniosynostosis and find their origin in the same aberration in the neural crest cells causing metopic suture synostosis. This is further supported by clinical findings from our child psychiatry department, often describing visual function impairment (unpublished data), apart from the abnormal ocular movements that are known in metopic suture synostosis patients.[39] The interplay between embryology, prevalence of intracranial hypertension and neurocognitive deficit remains one of the important issues for craniofacial research. Analysis of white matter structure (DTI) and intracranial blood flow (ASL) may clarify this matter in the coming years.

It was long thought that intracranial hypertension in unisutural craniosynostosis patients is solely caused by craniocerebral disproportion. However, the low prevalence of intracranial hypertension found in this thesis, combined with recent volumetric studies[40], suggests that in unisutural craniosynostosis craniocerebral disproportion is not an important factor to influence intracranial pressure. Other risk factors for ICH are: venous outflow obstruction, ventriculomegaly and obstructive sleep apnea.

Ventriculomegaly and obstructive sleep apnea rarely occur in unisutural craniosynostosis, implying that, besides craniocerebral disproportion, venous outflow obstruction may be a significant contributor in the prevalence of intracranial hypertension in unisutural craniosynostosis patients.[41-43]

In this thesis we studied the role of venous outflow obstruction through transfontanellar Doppler ultrasound of the superficial (superior sagittal sinus) and the deep venous drainage system (internal cerebral vein). This showed a significantly different blood flow velocity ratio between the superficial and deep system in children with metopic and sagittal synostosis compared to healthy controls, possibly indicating obstructed outflow of the superior sagittal sinus due to closure of the overlying suture. These findings are supported by previous studies on intracranial venous outflow. Hirabuki et al showed a similar blood flow velocity in the superior sagittal sinus for achondroplastic children with hydrocephalus.[44] In contrast to our study, Mursch et al measured superior sagittal sinus blood flow velocity at the point of constriction, whereas we measured blood flow velocity right before or after the point of constriction.[45] The results of Mursch et al strengthen our hypothesis that premature closure of the overlying suture results in a constriction of the venous outflow, resulting in a diminished blood flow before or after the constriction (our findings) and a relative increase at the site of constriction (Mursch et al.). The results of this pilot study suggest that although the deep intracranial venous system seems to remain unharmed, the blood flow in the superficial venous system is diminished in children with single suture craniosynostosis. Future research focusing on differences between different types of craniosynostosis should clarify its role in the occurrence of intracranial hypertension further. For these studies, an additional measurement at the occipital fontanelle should be considered to measure the full effect of a synostotic sagittal suture on superior sagittal sinus blood flow. By adding this measurement to the ultrasound protocol one would be able to clearly identify the difference between metopic and sagittal suture synostosis patients.

Although the indication for surgery in trigonocephaly is subject to change, unisutural craniosynostosis is generally treated with a cranioplasty within the first year of life. Regular follow-up during the first 18 years of life implies frequent hospital visits. One of the most frequently seen sequelae after fronto-orbital advancement and remodellation (FOAR) is temporal hollowing. Essentially, temporal hollowing is the example that our surgery is not actually treating the underlying mechanism, but is merely a way to prevent intracranial

hypertension. After surgery, the biology of the craniosynostosis is continuing, providing too little lateral growth at the temporal area resulting in temporal hollowing. This postoperative regression to the initial deformity is also seen in sagittal synostosis patients, illustrated by a decrease of cephalic index in the years following surgery.[25] This may be an effect of a diminished growth stimulus of the brain, not stimulating the skull to expand laterally at the forehead (metopic synostosis) or the parietal bones (sagittal synostosis). This strengthens our hypothesis that craniosynostosis is not solely an issue of the cranial suture, but also affecting the brain primarily.

In total, 73% had some degree of postoperative temporal hollowing after FOAR in our unicoronal synostosis patient population. In some cases, secondary surgery at a later age is warranted, particularly aimed at improving cosmetic outcome. This illustrates the impact that unisutural craniosynostosis has on normal life for these children and its possible effect on quality of life.[46] Moreover, this should motivate the craniofacial surgeon to strive for the best possible cosmetic result in the first go, as it has been shown that a good result of the first operation will lower the chances of needing secondary surgery for cosmetic reasons.[47]

LIMITATIONS

As with all studies, the results of this thesis should be interpreted with the limitations of the presented studies in mind. Overall, this thesis has two main limitations. Firstly, the cross-sectional design used in some of the studies. The development of craniosynostosis and its effect on cranial growth, occurrence of increased intracranial pressure and long term surgical outcome are a complex and lengthy process. These aspects are all influenced by different factors as time goes by and are less appreciated in a cross-sectional study than in a longitudinal (preferably prospective) designed study. Secondly, among the craniofacial community there are large differences with regard to treatment, timing of surgery and frequency and content of follow-up appointments. The study population and the protocol applied in the specific study should be taken into account when the results are interpreted and extrapolated to other patients. Recently, attempts to create consensus on parameters to evaluate outcome in craniosynostosis patients have started within the international craniofacial community. Up until now, every craniofacial center has their own treatment and follow-up protocol. This limits the generalizability of our results. Ideally, a comparison between two centers with different treatment protocols, but identical follow-up protocols, would provide us with generalizable results on the effects of different treatment protocols. Ultimately, this would optimize treatment and outcome.

CONCLUSION

This thesis focused on unisutural craniosynostosis and ranged from epidemiology and prenatal diagnosis to long term surgical follow-up. The prevalence of unisutural craniosynostosis is rising, which cannot be attributed to raised awareness alone. Prenatal detection of metopic and sagittal synostosis seems possible in selected cases, but large scale screening using existing cephalic measurements at the 20-week ultrasound is not feasible at this moment. With increasing data of prenatal ultrasounds of patients screening may become possible in the future. Prenatal diagnosis is important for unisutural craniosynostosis patients as feto-maternal trauma may be prevented and early referral would lead to an earlier, less invasive, operation.

Intracranial hypertension is only sporadically found in metopic suture synostosis patients, unlike sagittal suture synostosis patients. Hence, these conditions should be seen as different entities with regard to treatment, follow-up and in clinical research.

The superficial venous drainage system of children with sagittal or metopic synostosis is diminished, in contrast to the unaffected deep venous system. Venous outflow obstruction may play an important role in the occurrence of intracranial hypertension in children with sagittal craniosynostosis.

With regard to long term follow-up: although surgery restores symmetry, temporal hollowing is still frequently seen post-operatively in trigonocephaly and unicoronal synostosis. The craniofacial surgeon should pay attention to this at the initial operation, possibly preventing the need for secondary surgery.

Considering the evidence presented in this thesis, unisutural craniosynostosis should not be regarded as a uniform and simple condition. Hence, the answer to the question posed on the cover of this thesis *'Unisutural Craniosynostosis: Simple or Complex'* really is simple: complex. Its treatment requires a highly specialized environment and the follow-up should be structured, based on scientific grounds and tailored to affected suture and individual needs. Perhaps, it should be seen as a game of football: the surgeon or team should be well prepared and highly trained. A precise planning should be made before the game starts, thinking a few moves ahead, but ready to divert from the plan should it be necessary for the individual patient.

FUTURE PERSPECTIVES

Technological innovation is rapidly changing all industries, including healthcare. For instance, the price to sequence a full genome came down from $100 Million when it was first done in 2001, to just over $1000 in 2017.[48] The ability to observe, store and analyze big data files has changed medical research globally.[49] For unisutural craniosynostosis

specifically, a GWAS study to identify loci for non-syndromic sagittal synostosis has already provided the craniofacial community with target genes for further studies.[50]

The relation between intracranial hypertension and the premature closure of skull sutures has been a subject of study for decades. The occurrence of intracranial hypertension is a process which is influenced by numerous factors, many of them known, some of them perhaps still unknown. The rarity of the condition, combined with the longitudinal aspect, make this a hard subject for causative studies. With 'big data' systems becoming available, researchers focused on craniosynostosis can in the near future incorporate all the different bits of (longitudinal) data. Combining all the different pieces of the puzzle may indeed lead to a clearer image of how craniosynostosis and intracranial hypertension are related and influenced. Ideally, a future study should incorporate the following data:

- Prenatal skull biometry and shape
- Affected suture
- Affected gene (if applicable)
- Type and timing of operation
- Data on intracranial hypertension
- Visual tests
- Skull shape
- Intracranial volume (occipitofrontal head circumference)
- Esthetics
- Neurocognitive outcome
- Patient reported outcome measures

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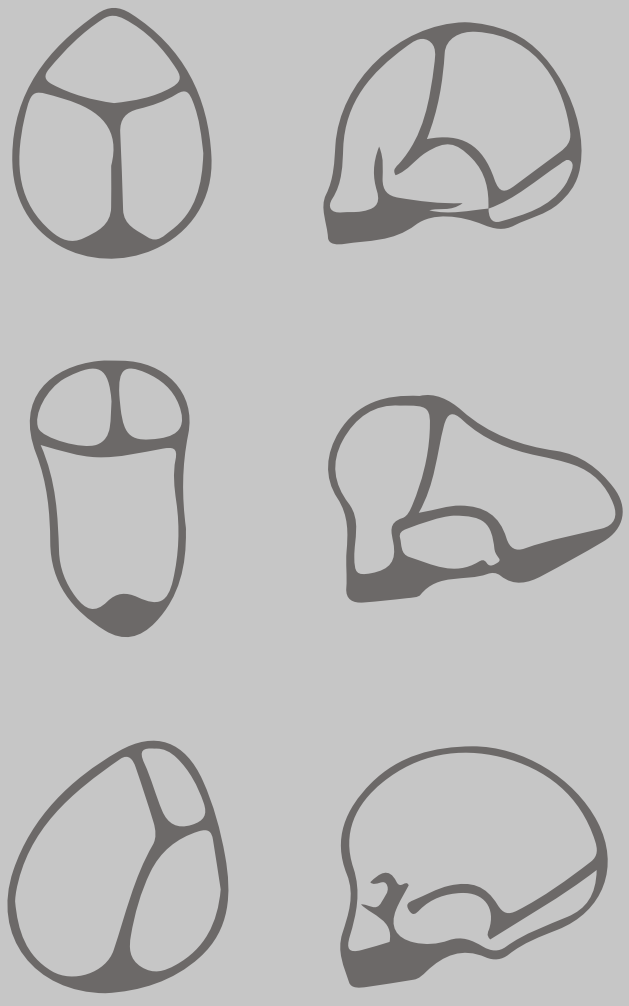


Chapter 10

Summary

The premature fusion of skull sutures, craniosynostosis, occurs in approximately 1 in 1500 births and results in an altered skull shape and increased risk of intracranial hypertension. This thesis focused on several aspects of unisutural craniosynostosis, in which only 1 suture is affected and closed prematurely. This chapter will summarize the most important findings and the clinical implications following from this thesis.

In **chapter 2** we describe our study on the epidemiology of craniosynostosis in the Netherlands. Through the use of the accurate registration of the Dutch Association for Cleft Palate and Craniofacial Anomalies, combined with data from all of the participating hospitals, we found a rise of prevalence of craniosynostosis from 1997 until 2013 in the Netherlands. Furthermore, the prevalence is shown to be notably higher than the values reported in previous literature. The rise cannot solely be explained by raised detection, as we have found that the rise of prevalence has been ongoing for 15 years and is not greatly influenced by implementation of the national guideline on craniosynostosis in 2011. For now, we have shown that craniosynostosis is not as rare as commonly thought. Future studies focusing on etiology of craniosynostosis should clarify the background of this rise further.

In **chapter 3** we explored the possibilities of detecting single suture craniosynostosis prenatally through the regular prenatal screening program. This study showed that with the use of existing ultrasound parameters metopic suture synostosis is not suitable to detect in a screening setting. For sagittal suture synostosis the cephalic index is significantly different prenatally. However, its discriminative power is too limited for screening at the 20-week anomaly scan. Sagittal suture synostosis seems to lead to a deflection of biparietal diameter during the late 2nd and 3rd trimester. When such a deflection is noted, 3D analysis of the sagittal suture is indicated to assess suture patency.

Chapter 4 describes the pre- and perinatal problems found in patients with metopic or sagittal suture synostosis. Trigonocephaly seems related to higher rates of assisted reproductive technology, a higher rate of breech position and caesarean sections. For scaphocephaly, disturbed natural fetal descent leads to more post term births and an increased rate of caesarean sections. These findings illustrate the importance of prenatal diagnosis of craniosynostosis: timely diagnosis and referral may prevent non-elective caesarean section and thus possible maternofetal birth trauma.

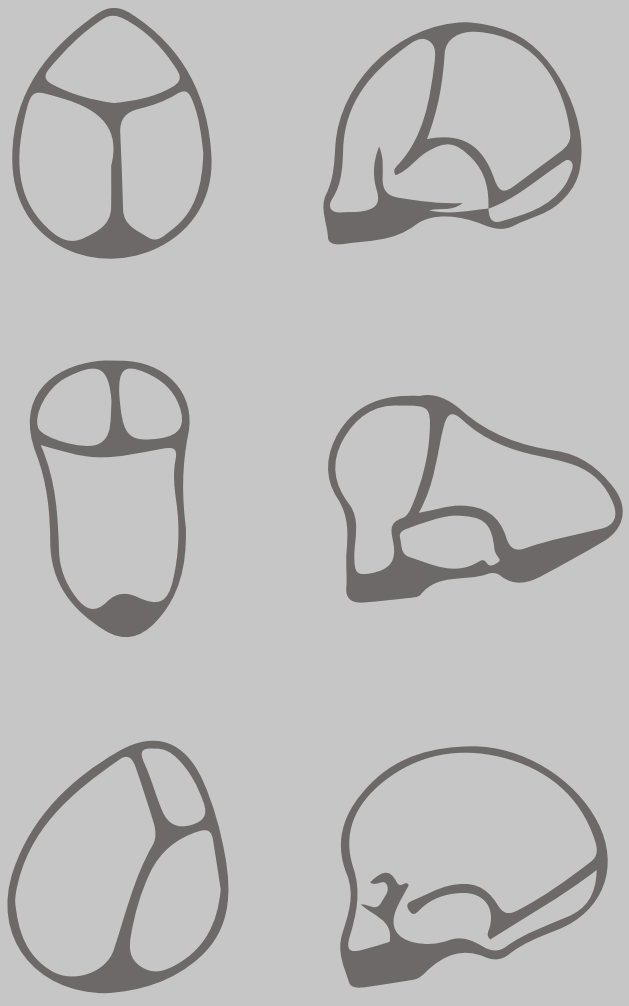
After birth, the biggest concern for patients with craniosynostosis is the occurrence of intracranial hypertension, which occurs in up to 10 percent of patients with unisutural craniosynostosis. In sagittal suture synostosis the prevalence of intracranial hypertension is markedly higher than in patients with trigonocephaly (approximately 8 percent vs 2 percent). This difference does not correspond with the difference in postoperative intracranial volume between these two subforms. This implies that besides craniocerebral disproportion, there must be other factors influencing the onset of intracranial hypertension. In **chapter 5** we performed the first step to explore the role of venous outflow obstruction in the onset

of intracranial hypertension. This pilot study showed, through transfontanellar Doppler ultrasound, that the venous outflow of the superficial system is diminished in patients with midline craniosynostosis. This is in contrast to the deep venous system, which seems to remain unaffected. The role of this phenomenon in the onset of intracranial hypertension should be clarified further in future studies.

As stated before, the prevalence of intracranial hypertension varies throughout the different forms of unisutural craniosynostosis. In **Chapter 6** we studied the prevalence of intracranial hypertension in metopic suture synostosis specifically. Additionally, we studied the relation between intracranial hypertension and stagnation of skull growth, expressed as the occipito-frontal head circumference. This study showed a very low prevalence of intracranial hypertension in metopic suture synostosis patients, which was 1.9 percent before surgery and 1.5 percent during the post-operative course. In comparison, in a previous study the preoperative prevalence of intracranial pressure in sagittal suture synostosis at 11 months was 10 percent and 9 percent postoperatively. Stagnation of the head circumference was significantly related to intracranial hypertension. Following these results, the standard postoperative follow-up in our center was changed and regular fundoscopy for metopic synostosis is no longer performed postoperatively. Fundoscopies are now only made when intracranial hypertension is suspected. Moreover, occipito-frontal head circumference stagnation seems to be an important factor to incorporate in the postoperative follow-up and we advise other craniofacial centers to give head circumference measurements a prominent place in the postoperative follow-up of metopic suture synostosis patients.

The last study of this thesis, **chapter 8**, studied the long term results after fronto-orbital advancement and remodeling in patients with unicoronal synostosis. Treatment for unicoronal synostosis varies between surgeons; some prefer to correct the supraorbital bar bilaterally, while others feel that only the affected side of the supraorbital bar needs to be corrected. This study compared both techniques with regard to temporal hollowing and found some degree of postoperative temporal hollowing in 73 percent of patients. Operative technique was not significantly related to severity of temporal hollowing. Although the operation prevents intracranial hypertension in a proportion of patients, the high proportion of temporal hollowing shows that the operation does not treat the underlying condition, as is illustrated by the regression of the skull shape to the original malformation. To prevent secondary surgery to correct temporal hollowing, the surgeon should take extra care in correcting the temporal region at the first operation.

In conclusion, this thesis has travelled from prenatal detection to long-term postoperative follow-up. Considering the above, the answer to the question posed on the cover of this thesis *'Unisutural Craniosynostosis: Simple or Complex'* really is simple: complex. The full range of clinical care that is warranted in the care for patients with unisutural craniosynostosis demands a highly specialized center, with high standards of patient care, research and education.



Chapter 11

Nederlandse Samenvatting

Vroegtijdige sluiting van schedelnaden, craniosynostose genaamd, treedt in ongeveer 1 op de 1500 geboorten op en resulteert in een afwijkende schedelvorm en een verhoogd risico op intracraniële hypertensie. Dit proefschrift richtte zich op verschillende aspecten van unisuturale craniosynostose, waarbij 1 schedelnaad is aangedaan en te vroeg gesloten. Dit hoofdstuk zal de belangrijkste bevindingen en daaruit volgende klinische consequenties samenvatten.

In **hoofdstuk 2** beschrijven wij onze studie naar de epidemiologie van craniosynostose in Nederland. Door gebruik te maken van de registratie van de *Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen*, in combinatie met de data van alle participerende ziekenhuizen, hebben wij een duidelijke stijging in het voorkomen van craniosynostose gevonden tussen 1997 en 2013. De gevonden prevalentie ligt hoger dan eerdere onderzoeken laten zien. Omdat deze stijging de afgelopen 15 jaar aan de gang lijkt te zijn en niet direct lijkt te zijn beïnvloed door de implementatie van de nationale richtlijn 'Behandeling en Zorg voor Craniosynostose' is het aannemelijk dat de stijging niet alleen door een verhoogde detectie wordt veroorzaakt. In conclusie laat deze studie zien dat de prevalentie aanmerkelijk hoger ligt dan de huidige literatuur doet vermoeden. Welke factoren nog meer bijdragen aan die stijgende prevalentie zal moeten worden onderzocht in toekomstige studies gericht op de etiologie van craniosynostose.

In **hoofdstuk 3** hebben we gezocht naar methoden om craniosynostose prenataal te diagnosticeren binnen het bestaande prenatale screening programma (de 20-weken echo). In deze studie vinden we dat de bestaande echografische parameters niet geschikt zijn om trigonocephalie prenataal te herkennen. Ondanks het feit dat in patiënten met scaphocephalie de *cephalic index* significant lager is in vergelijking met gezonde controles, is deze bepaling niet sensitief genoeg om als screeningparameter te gebruiken op 20-weken. De biparïetale diameter laat een afbuiging zien gedurende het 2^{e} en 3^{e} trimester. Wanneer een dergelijke afbuiging wordt gezien, lijkt 3D analyse van de sagittaal naad geïndiceerd om craniosynostose van de sagittaal naad aan te tonen.

In **hoofdstuk 4** beschrijven we de pre- en perinatale problemen die voorkomen bij patiënten met scaphocephalie en trigonocephalie. Bij patiënten met trigonocephalie blijkt de conceptie vaker medisch geïnduceerd en worden er meer stuitliggingen en keizersneden gezien bij geboorte. Voor kinderen met scaphocephalie lijkt een gestoorde indaling in het geboortekanaal te leiden tot een langere zwangerschapsduur en meer keizersneden. Deze bevindingen onderstrepen nog maar eens de potentiele impact van het prenataal diagnosticeren van craniosynostose: tijdige diagnose en verwijzing kan mogelijk maternofoetale problemen rondom de geboorte voorkomen.

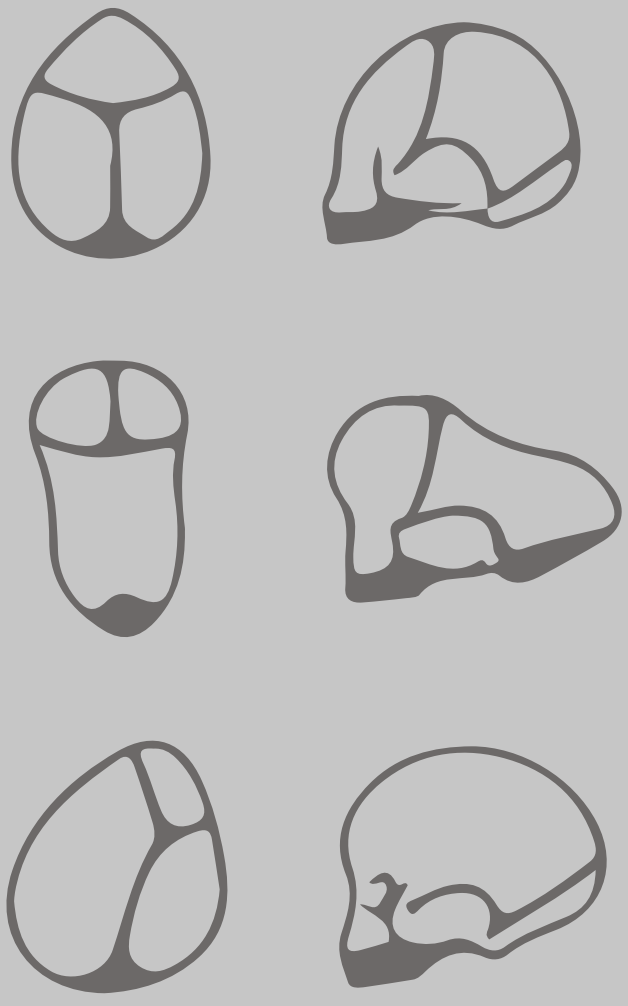
Na de geboorte lopen patiënten met craniosynostose een verhoogd risico op intracraniële hypertensie, wat in 0-10% van de patiënten met unisuturale craniosynostose kan voorkomen. In scaphocephalie patiënten(8 procent) is dit risico duidelijk hoger dan in kinderen met trigonocephalie (2 procent). Dit verschil strookt niet met het verschil in

hoofdomtrek tussen beide vormen. Dit impliceert dat buiten craniocerebrale disproportie er nog andere factoren van invloed zijn op het ontwikkelen van intracraniële hypertensie. In **hoofdstuk 5** hebben we een eerste stap ondernomen om het effect van obstructie van craniële veneuze afvloed op de ontwikkeling van intracraniële hypertensie te onderzoeken. Deze pilotstudie liet middels transfontanellaire Doppler echografie zien dat de veneuze afvloed van het oppervlakkige systeem is verminderd in patiënten met een prematuur gesloten schedelnaad in de midline. In tegenstelling tot het diepe systeem, waarbij geen effect werd gezien van de te vroeg gesloten schedelnaad op de stroomsnelheid van het bloed. Een voortzetting van deze studie in de toekomst zal het effect van veneuze afvloedbelemmering op intracraniële hypertensie nog verder moeten verduidelijken.

Zoals eerder benoemd varieert de prevalentie van intracraniële hypertensie tussen de verschillende vormen van unisuturale craniosynostose. In **hoofdstuk 6** onderzochten we de prevalentie van intracraniële hypertensie voor trigonocephalie patiënten in het bijzonder. Daarnaast onderzochten we of er een relatie bestaat tussen het optreden van intracraniële hypertensie en stagnatie van de schedelgroei. Preoperatief vonden we een prevalentie van 1,9 procent, welke na de operatie verminderde tot 1,5 procent. Ter vergelijking, in een andere studie van ons centrum werd bij kinderen met scaphocephalie een prevalentie van intracraniële hypertensie van 10 procent preoperatief (bij een leeftijd van 11 maanden) en 9 procent postoperatief. Daarnaast werd er in de huidige studie een duidelijk verband gevonden tussen stagnatie van de schedelgroei en optreden van intracraniële hypertensie. Volgend op de resultaten van deze studie is het postoperatieve beleid voor patiënten met trigonocephalie aangepast. Fundoscopieen worden niet langer routinematig postoperatief gemaakt, maar alleen wanneer er een duidelijk verdenking op intracraniële hypertensie is. Schedelgroei blijkt een belangrijke voorspeller van intracraniale hypertensie en we adviseren andere centra dan ook deze meting op te nemen in hun postoperatieve follow-up, welke gericht is op het opsporen van verhoogde hersendruk.

In het laatste hoofdstuk van dit proefschrift, **hoofdstuk 8**, bestudeerden we de lange termijn resultaten na chirurgische correctie van unicoronale synostose. De behandeling van deze specifieke vorm verschilt per chirurg: sommigen kiezen voor een unilaterale benadering, waar anderen een bilaterale benadering prefereren. Deze studie vergeleek beide operatietechnieken met het oog op het optreden van temporale deuken, welke in 73% van de patiënten voorkwamen. Uit deze studie bleek dat operatietechniek niet significant is gerelateerd aan het optreden van (ernstige) temporale deuken. Alhoewel de operatie intracraniële hypertensie in een deel van de patiënten lijkt te voorkomen, laat de regressie van de schedel naar de originele vorm (het optreden van temporale deuken) zien dat de operatie de onderliggende ziekte niet behandeld. Om secundaire chirurgie, gericht op de correctie van temporale deuken, te voorkomen, zullen chirurgen bij de primaire operatie extra aandacht moeten besteden aan de temporale regio.

Concluderend behandelt dit proefschrift het volledige klinische traject van unisuturale craniosynostose, van prenatale detectie tot aan lange termijn follow-up. Al het bovengenoemde in ogenschouw nemend, is het antwoord op de vraag '*Unisuturale craniosynostose: simpel of complex?*' heel simpel: complex. Het brede scala aan klinische zorg dat nodig is bij kinderen met unisuturale craniosynostose vraagt om een zeer gespecialiseerd behandelcentrum met hoge standaarden van patiëntenzorg, wetenschappelijk onderzoek en onderwijs.



Appendices

List of publications
PhD Portfolio
Dankwoord
Curriculum Vitae

LIST OF PUBLICATIONS

Unilateral versus bilateral correction of unicoronal synostosis: an analysis of long-term results.
Cornelissen MJ, van der Vlugt JJ, Willemsen JC, van Adrichem LN, Mathijssen IM, van der Meulen JJ
J Plast Reconstr Aesthet Surg. 2013 May; 66(5):704-11

Increase of prevalence of craniosynostosis
Cornelissen M, den Ottelander B, Rizopoulos D, van der Hulst R, Mink van der Molen A, van der Horst C, Delye H, van Veelen ML, Bonsel G, Mathijssen I
J Craniomaxillofac Surg. 2016 Sep;44(9):1273-9.

Very Low Prevalence of Intracranial Hypertension in Trigonocephaly.
Cornelissen MJ, Loudon SE, van Doorn FE, Muller RP, van Veelen MC, Mathijssen IM
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Cornelissen MJ, Apon I, van der Meulen JJ, Groenenberg IA, Kraan-van der Est MN, Mathijssen IM, Bonsel GJ, Cohen-Overbeek TE.
J Matern Fetal Neonatal Med. 2017 May 28:1-21.

Reply: Letter to the editor: RE: "Very low prevalence of intracranial hypertension in trigonocephaly'
Cornelissen MJ, Mathijssen IMJ
Plast Reconstr Surg. 2017 Jun 5: Epub ahead of print.

Perinatal complications in patients with unisutural craniosynostosis: an international multicentre retrospective cohort study.
Cornelissen MJ, Söfteland M, Apon I, Ladfors L, Mathijssen IMJ, Cohen-Overbeek TE, Bonsel GJ, Kölby L.
J Craniomaxillofac Surg. 2017 Jul; Accepted for publication

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Martijn J. Cornelissen
Erasmus MC, University Medical Center
Department: Plastic and Reconstructive Surgery and Hand Surgery
PhD Period: 2014 – 2017
Promotor: Prof. Dr. IMJ Mathijssen

1. PhD Training

General Courses	Year	ECTS
Research Integrity	2014	0.3
BROK course	2014	1
English Biomedical Writing and Communication Course	2014	3
Specific Courses		
Basic Human Genetics Course: Genetics for Dummies	2011	0.7
Principles of research in medicine and epidemiology	2014	0.7
Introduction to data analysis	2014	1
Methods of clinical research	2014	0.7
Case-control studies	2014	0.7
Microsurgery	2014 - 2017	300 hrs
Seminars and workshops		
Methodology of patient related research and preparation of grant applications.	2012	0.3
23rd Esser Course *'On your nerves'*	2014	0.3
Annual meeting of the Dutch Society for Cleft Palate and Craniofacial Anomalies (NVSCA) *Rotterdam, The Netherlands*	2014	0.3
Tendon Reconstruction Course *Rotterdam, The Netherlands*	2014 - 2016	0.7
Nerve Reconstruction Course *Rotterdam, The Netherlands*	2015 - 2017	0.7

Oral presentations

Analysis of temporal hollowing after fronto-supraorbital cranioplasty. Presentation at the annual meeting of the Dutch Society for Cleft Palate and Craniofacial Anomalies (NVSCA) Amsterdam, The Netherlands	2011	1
Unilateral Versus Bilateral Correction of Unicoronal Synostosis; An Analysis of Long-Term Results. Presentation at the biannual meeting of the International Society of Craniofacial Surgery (ISCFS) Jackson Hole, Wyoming, USA	2013	1.5
Teamwork in prenatal detection of unisutural craniosynostosis. Presentation at the annual meeting of the Dutch Society for Plastic Surgery (NVPC) Maastricht, The Netherlands	2015	1
Prenatal ultrasound screening for unisutural craniosynostosis. Presentation at the biannual meeting of the International Society of Craniofacial Surgery (ISCFS) Tokyo, Japan	2015	1.5
Perinatal complications in patients with unisutural craniosynostosis: an international retrospective study. Presentation at the biannual meeting of the European Society of Craniofacial Surgery (ESCFS) Birmingham, United Kingdom	2016	1.5
Prevalence of intracranial hypertension is very low in trigonocephaly. Presentation at the biannual meeting of the European Society of Craniofacial Surgery (ESCFS) Birmingham, United Kingdom	2016	1.5
Increase of prevalence of craniosynostosis in the Netherlands. Presentation at the annual meeting of the Dutch Society for Cleft Palate and Craniofacial Anomalies (NVSCA) Utrecht, The Netherlands	2016	1

Diagnosis and treatment of craniosynostosis. Presentation at the annual meeting of the Regional Prenatal Screening Foundation (SPSZN) Rotterdam, the Netherlands	2016	0.5

Grants

'*Prenataal echoscopisch onderzoek bij craniosynostose*' Fonds NutsOhra, €136.000	2014	2

2. Teaching activities

Lecturing

2nd year medical school: musculoskeletal elective	2015-2016	1
3rd year medical school: dysmorphology	2015-2017	3

Skills

Microsurgery coach (Skillslab, ErasmusMC)	2016	0.7
Wound debridement (WCS)	2016	0.5

Supervising master thesis

Inge Apon	2014	3
Rogier Muller	2015	3
Renée van Seeters	2017	3

3. Organizing activities

Symposiums and seminars

Organizing the 24th Esser Course 'Ins and outs of nose surgery'	2014	4
Organizing the 25th Esser Course 'Oncoplastic Breast Surgery'	2016 - 2017	4
Organizing 'Hoofdschaak'	2016 - 2017	2

DANKWOORD

Beste Prof. dr. IMJ Mathijssen, Lieve Irene, na het afscheid van Jacques uit het Sophia nam jij de directe begeleiding van mijn promotie over. Vele papers, congressen, etentjes, borrels en poli's later kan ik hier alleen maar heel erg dankbaar voor zijn. De drive die jij hebt om op gebied van patiëntenzorg en onderzoek tot de top van de wereld te behoren is bewonderenswaardig en werkt aanstekelijk. Het is bijzonder om te zien hoe '*the rotterdam-group*' op elk internationaal congres de meest vernieuwende ideeën presenteert met de grootste patiënten aantallen. Jaren geleden heb jij hiervoor de basis gelegd en daarvan mogen wij promovendi nu de vruchten plukken. Inmiddels ben je ook 'nog even' afdelingshoofd geworden, een job die je moeiteloos lijkt te hebben opgepakt en ingepast in je toch al overvolle agenda. Ik kijk er naar uit om over 2 jaar terug te keren en mijn opleiding tot plastisch chirurg onder jouw leiding voort te zetten.

Beste Titia, jouw streven de prenatale zorg in Rotterdam en Nederland naar een hoger plan te tillen is bewonderenswaardig. Daar waar de gynaecologen het nut er niet zo van inzagen, was jij altijd vol overtuiging over de waarde en haalbaarheid van het herkennen van 'een cranio' op een prenatale echo. Daarnaast vond jij zelfs na 5 keer submitten weer de energie om samen met mij door het stuk heen te ploegen. Het was mooi om samen te pionieren. Heel veel dank daarvoor.

Dear prof. Hayward, dear Richard, your papers on intracranial pressure in craniosynostosis have been the cornerstone of the treatment of craniosynostosis and many PhD projects, including this one. It's an honor that you're part of my PhD committee and I look forward to discussing our findings with you.

Beste Prof. dr. Vingerling, Prof. dr. Steegers, Prof. dr. Oosterlaan en Dr. Joosten, hartelijk dank dat u zitting wilt nemen in de promotiecommissie. Het multidisciplinaire karakter van de zorg rondom craniosynostose wordt onderstreept door uw aanwezigheid.

Beste Jacques, ik weet nog goed dat ik voor de eerste keer met je meeliep bij een cranio-OK. Alhoewel jij het handonderzoek nog aanprees, was ik direct verkocht. Na mijn keuzeonderwijs en keuzeonderzoek bij je begon ik als promovendus en heb ik ongelooflijk veel van je mogen leren, zowel op klinisch als persoonlijk vlak. Het was bijzonder om samen met Anne-Sophie in Wenen bij jullie huwelijk te zijn en erg mooi dat je nu in mijn promotiecommissie zit. Jouw lijfspreuk '*Live the life you want to remember*' zal ik nooit vergeten. Dank.

Lieve Sarah, mijn on-officiële co-promotor! Heel veel dank voor de gezelligheid en je goede adviezen. Alhoewel je bij geen enkel artikel van dit proefschrift als co-auteur staat, ben je er toch altijd bij betrokken geweest. In Mexico dan ons eerste stuk samen. Hopelijk volgen

er nog velen. Inmiddels is het echt tijd voor een Wenen-reünie, wellicht kunnen we Louie Austen verleiden tot een bezoekje.

Lieve Hansje, de surrogaatmoeder van alle craniokinderen, maar ook van de cranio-promovendi! Wat is het een luxe dat jij in het Sophia rondloopt, altijd op de hoogte van de patiënten en nooit te beroerd om ouders en kinderen te motiveren om mee te doen voor weer een volgende studie. Dank voor de gezellige praatjes en dropjes(!) als ik weer eens genoeg had van mijn beeldscherm. De gezelligheid tijdens alle internationale congressen zal ik nooit vergeten. Misschien moeten we in Mexico maar weer gaan raften...

Beste Prof. dr. Hovius, hartelijk dank voor het vertrouwen dat u me gaf en de mogelijkheden die u bood bij de start van dit project. De besprekingen bij opzet van dit promotietraject zijn van grote waarde geweest.

Beste Gouke, als epidemioloog verbeterde je onze fondsaanvraag dusdanig dat hij geaccepteerd werd en we groen licht kregen voor ons onderzoek. Daarna bestelde je bij een van onze eerste afspraken direct de 'bijbel van de medische statistiek' (Altman) voor me, hij staat nog altijd binnen reikwijdte. In de jaren daarna heb ik veel van je mogen leren over methodologie, terminologie en statistiek. Jouw scherpe blik heeft onze artikelen altijd verbeterd en voegde iets toe wat wij misten. Heel veel dank.

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Beste Marie-Lise, Léon, Jeroen, Paul en Maarten, hartelijk dank voor jullie adviezen en medewerking. Het is mooi om te zien dat we met de combinatie van alle verschillende specialisaties de zorg en het onderzoek rond craniosynostose naar een hoger plan tillen.

Dear Lars and Madiha, it was great being able to join forces and to profit from our countries' urge to register literally everything. It was a great pleasure working with you and I'm looking forward to continue doing so.

Ineke, Manja en Esther, wat was het een luxe om elke woensdagochtend bij jullie aan te mogen schuiven. Dank voor alle uren training en welkome afleiding van het computer scherm, maar ook voor de vrijheid om nieuwe dingen te proberen.

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Inge, ooit als master-student begonnen, nu co-auteur van 2 artikelen. Veel dank voor al je hulp. Met jouw kwaliteiten ben ik er van overtuigd dat je in de toekomst daar komt waar je wilt zijn, met of zonder promotietraject van de plastische!

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Maatschap Algemene Heelkunde van het Ikazia Ziekenhuis, dank voor de mogelijkheid terug te keren op het oude nest.

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CURRICULUM VITAE

Martijn Johannes Cornelissen was born on July 8th 1989 in Utrecht, the Netherlands. Fourteen years after moving to Rotterdam he graduated from the Erasmiaans Gymnasium in 2007. Shortly after, he started medical school at the Erasmus University in Rotterdam. During his third year he first came in contact with the department of Plastic and Reconstructive Surgery during an elective and made his first steps into research under the guidance of Dr. JJNM van der Meulen. During his medical internships Martijn spent one elective at the department of Plastic and Reconstructive Surgery at Isala Klinieken Zwolle (Dr. M. Tellier). His senior internship took place at the department of Plastic and Reconstructive Surgery of the Erasmus MC (Prof. dr. SER Hovius), after which he graduated cum laude from the Erasmus University Rotterdam.

He then started working on his PhD-project on unisutural craniosynostosis (Prof. dr. IMJ Mathijssen). From May 2015 until November 2015 Martijn worked as a resident (ANIOS) at the department of Plastic and Reconstructive Surgery of the Erasmus MC, after which he got accepted for the plastic surgery residency program in Rotterdam. The following years Martijn spent working on his PhD full time.

After working in the ER-department for 3 years during his studies (*Les Forgerons*, Dr. R Boelhouwer), Martijn returned to the Ikazia Ziekenhuis in August 2017 and started his residency in general surgery (Dr. T den Hoed). He will return to the department of plastic and reconstructive surgery at the Erasmus University Medical Center for 4 years of plastic surgery residency starting from May 2019.