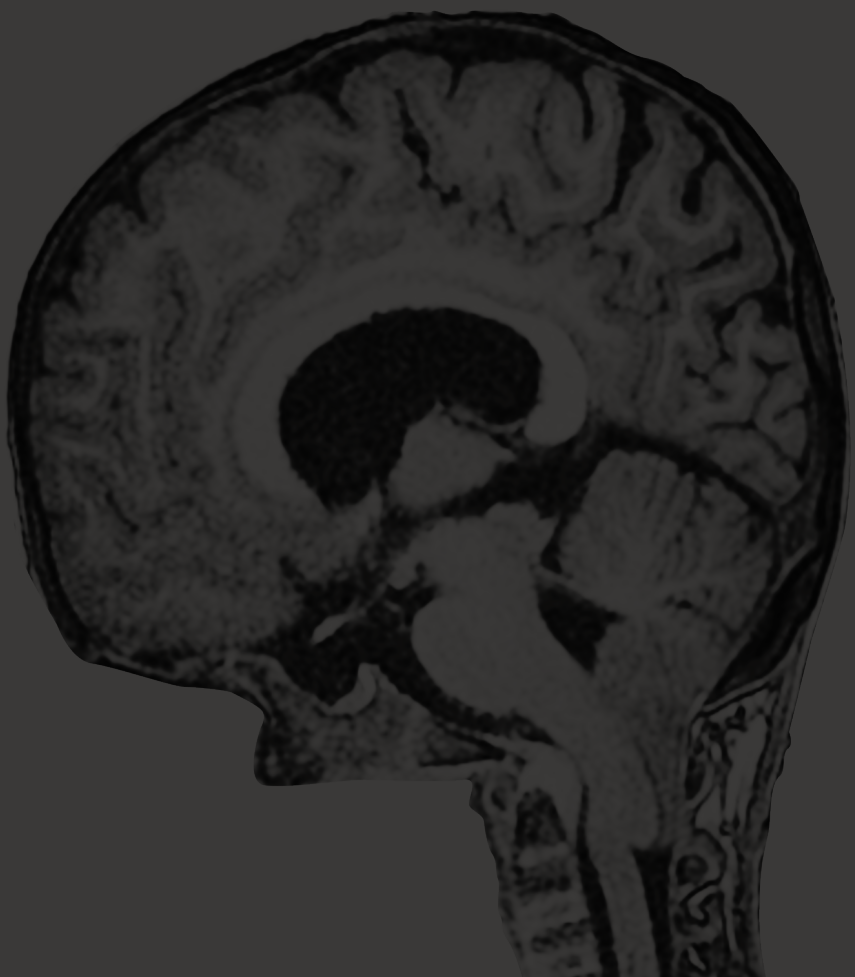
Syndromic and Complex Craniosynostosis:

Skull and brain abnormalities in relation to intracranial hypertension

Bianca F. M. Rijken



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LIST OF ABBREVIATIONS

AD Axial diffusivity
CMI Chiari malformation type 1
CSF Cerebrospinal fluid
FA Fractional Anisotropy
FGF Fibroblast growth factor
FGFR Fibroblast growth factor receptor
FM Foramen magnum
FOA Fronto-orbital advancement
FT Fiber tractography
HU Hounsfield unit
ICH Intracranial hypertension
ICP Intracranial pressure
ICV Intracranial volume
MD Mean diffusivity
OFC Occipito-frontal circumference
OSA Obstructive sleep apnea
PF Posterior fossa
RD Radial diffusivity
TH Tonsillar herniation
VEP Visual evoked potentials

1 General Introduction

INTRODUCTION

This thesis discusses skull and brain abnormalities in children with complex and syndromic craniosynostosis; patients with premature fusion of skull sutures and skull base synchondroses in combination with other congenital abnormalities, including limb deformities. As a consequence of the premature fusion of the sutures and synchondroses, the affected children have an increased risk to develop intracranial hypertension (ICH), which may impair cognitive development, behavior, and cause visual loss by damaging the optic nerves. Understanding the complex pathophysiology of ICH in syndromic and complex craniosynostosis patients, will improve their treatment, and consequently their physical and cognitive outcome.

First, the embryology of the cranial vault and skull base will be described, including the development of the skull sutures, followed by an outline of the most distinct craniosynostosis syndromes and their genetic background. Next, the major disturbances in this unique patient population will be discussed, as well as the most commonly used diagnostic tools and therapies to treat these patients. Lastly, a short introduction of each study will be presented.

Embryology

During the 3rd week of human development, i.e. gastrulation, the embryoblast forms three primary germ layers: ectoderm, mesoderm (including mesenchyme), and endoderm. The ectoderm is the most outer layer and differentiates to form the nervous system, tooth enamel and the epidermis. It also forms the lining of mouth, anus, nostrils, sweat glands, hairs and nails. The mesoderm, the middle layer, gives rise to muscles, blood vessels, lymphatic tissue, and connective tissue including cartilage and bone. The endoderm initiates the development of the inner epithelium, for instance that of pharynx and larynx. Within the 3rd week of gestation, the mesenchyme gives rise to angioblasts and angiogenesis that form the origin of the vascular system. The neural plate, formed out of ectoderm, closes within the 4th week and then becomes the neural tube. At the dorsal limit of the neural tube a group of neural crest cells is located. These cells migrate away from the neural tube, follow specific differentiation pathways, and initiate the growth of a variety of tissues, including neural and non-neural structures such as cartilage and bone, in particular those of skull and face.[1] Within the 5th week, the cranio-caudal axis is established, and the human embryo has developed 5 brain vesicles (including telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon), which will form the two cerebral hemispheres, thalamus and hypothalamus, midbrain, pons and cerebellum, and medulla oblongata, respectively. Meanwhile, several cavities develop within the telencephalon, diencephalon, mesencephalon, myelencephalon, and spinal cord, giving rise to the formation of the lateral ventricles, third ventricle, cerebral aqueduct, fourth ventricle and the central canal, respectively.[2] At week 6, the earliest stage of the skull, also called desmocranium, is formed by a mass of dense mesenchyme. Chondrofication of the desmocranium initiates the development of the chondrocranium, which includes only the skull base. Two weeks later, the first ossification and development of the osteocranium occurs. The human skull is formed by viscerocranium and

neurocranium. The viscerocranium surrounds the oral cavity, pharynx, and upper respiratory passages, while the neurocranium contains the brain. The neurocranium can be subdivided into chondrocranium (cartilaginous) and membranous neurocranium. Bone centers of the membranous neurocranium, which will form the cranial vault, arise around the 10th week,[3, 4] while the chondrocranium forms the skull base via endochondral ossification, between week 11 and 16.[5]

The growth of the cranial vault is mainly formed through the process of intramembranous ossification, i.e. via suture formation. During this process there are no cartilaginous intermediates such as during endochondral ossification. The occipital bone is part of both the skull vault and the skull base and, hence a combined structure: its superior portion is formed by intramembranous ossification, while the inferior portion is formed by endochondral ossification.[2, 6] Normal suture development starts at week 15 for the metopic suture, at week 16 for the coronal and lambdoid sutures, and at week 18 for the sagittal suture.[7]

The bones of the cranial vault are derived from either the neural crest or the mesoderm. The neural crest gives rise to the frontal bones, parietal bones, and meninges. A patch of neural crest cells is located at the anterior part of the further mesoderm-derived parietal bones, and 1 at the central part of the further mesoderm-derived occipital bone.[6] Accordingly, the metopic suture is entirely located in the neural crest domain, while the central part of the lambdoid sutures, and the entire coronal sutures are located at the mesoderm-neural crest boundary. At this boundary different tissues meet, and an interaction occurs between two developmental signaling systems.[8-10] Studies have revealed the importance of numerous genes in the development of skull sutures, including *TWIST1* and fibroblast growth factor receptors (*FGFRs)*.[11] These genes are involved in a complex process/ cascade to keep a balance between cell proliferation and differentiation, and thereby in suture formation. Moreover, studies in mice showed that *fgfr1* and *fgfr2* are involved in a proliferation-differentiation balance during normal coronal suture formation:[12] *fgfr2* regulates osteogenic cell proliferation, while *fgfr1* regulates osteogenic cell differentiation. In addition, *fgfr3* is expressed in both osteogenic and chondrogenic tissue, including a plate of cartilage underlying the coronal sutures, suggesting that it interacts with both tissues during suture development. *Twist1* is expressed by mid-sutural mesenchymal cells,[13] and has its main role in maintaining the boundary between neural crest and cephalic mesoderm at the site of the developing coronal suture.[9] While its expression precedes that of *fgfr* in fetal mouse coronal suture development, *twist1* acts synergistically with transcription factor (*tfc)12*; the amount of *tfc12/twist1* heterodimers is important for normal coronal suture development.[14] An ongoing interplay between multiple genes involved in suture and skull development follows during the further growth.

Postnatal growth of the skull occurs in 3 ways:

1. Sutural growth takes place at the edges of the skull bones, in a perpendicular direction to the suture. Coronal sutures are located between the frontal and parietal bones and allow the skull to grow in anterior-posterior direction. The sagittal suture runs from anterior to posterior and allows the skull to expand in width. Skull sutures have a specific time frame to fuse; the metopic suture

closes first, at about 8 months of age.[15] The sagittal, coronal and lambdoid sutures close during adulthood, at age 22, 24 and 26 years, respectively, while the squamosal suture is the last one to close at age 60 years.[16, 17]

2. Chondral growth is accomplished by cartilage, e.g. the synchondroses located in the skull base. The human skull has an anterior and a posterior skull base, the latter has 8 synchondroses, including Kerckring ossicle, which normally fuses with the supra-occipital bone within the first month of life, the synchondroses of the foramen magnum (FM), including the paired posterior intra-occipital synchondroses (PIOS), which fuse between 3 and 6 years of age, the paired anterior intra-occipital synchondroses (AIOS), which fuse between 6 and 10 years of age, the unpaired spheno-occipital synchondrosis, which fuses around the age of 12 years, the occipito-mastoid suture that closes between 9 and 17 years of age, and the petro-occipital fissure that closes after the age of 18 years.[18]
3. Periosteal or appositional growth within the periosteum involves a balance between apposition of bone on the convex side and resorption of bone on the concave side of the skull. While it has only a small contribution in skull growth, periosteal growth continues into advanced age.[19] Unfortunately, the exact underlying mechanism (trigger, timing and amount) remains unclear, which makes it difficult to determine which role it may play in the case of abnormal skull growth. The driving force for skull growth is expansion of the brain; when the postnatal brain continues to grow, sutures remain open. During this process cells located in the middle of a suture complex remain in an undifferentiated proliferating state, while adjacent cells differentiate into osteoblasts and contribute to the growing bone fronts. Disturbances of this perfectly synchronized process of cell proliferation and cell differentiation might induce premature differentiation of mesenchymal cells in the suture region into osteoblasts, which results in the fusion of adjacent bones.[6, 12] Patients with microcephaly or decreased intracranial pressure (e.g. children with overshunting hydrocephalus) may suffer from premature fusion of the skull sutures because the driving force for the skull to grow and for the sutures to remain open is missing.[20]

Craniosynostosis refers to the premature closure of skull sutures, which may occur around the 15th-18th week of gestation[7] or develop postnatally.[21] Craniosynostosis occurs in 1:2,100-2,500 of the newborns and is mostly an isolated condition (not associated with other abnormalities). Examples of single suture synostosis include scaphocephaly (sagittal suture synostosis), trigonocephaly (metopic suture synostosis), frontal plagiocephaly (unilateral coronal), and posterior plagiocephaly (lambdoid suture synostosis). In 24% of the cases, craniosynostosis is syndromic and is caused by mutations in various genes.[14] Children with syndromic craniosynostosis usually have more than 1 prematurely closed skull suture, as well as other anomalies, such as limb abnormalities. The most distinct craniosynostosis syndromes are: Apert, Crouzon-Pfeiffer, Muenke and Saethre-Chotzen syndromes.[22]

Craniosynostosis syndromes

The diagnosis of craniosynostosis is made by the clinical presentation of the patient. The skull deformity can easily be distinguished from a deformity with a positional cause. The Dutch guideline for the treatment and care of patients with craniosynostosis recommends to perform X-rays of the skull and/or head CT scans to confirm the diagnosis (**figure 1**).[23]

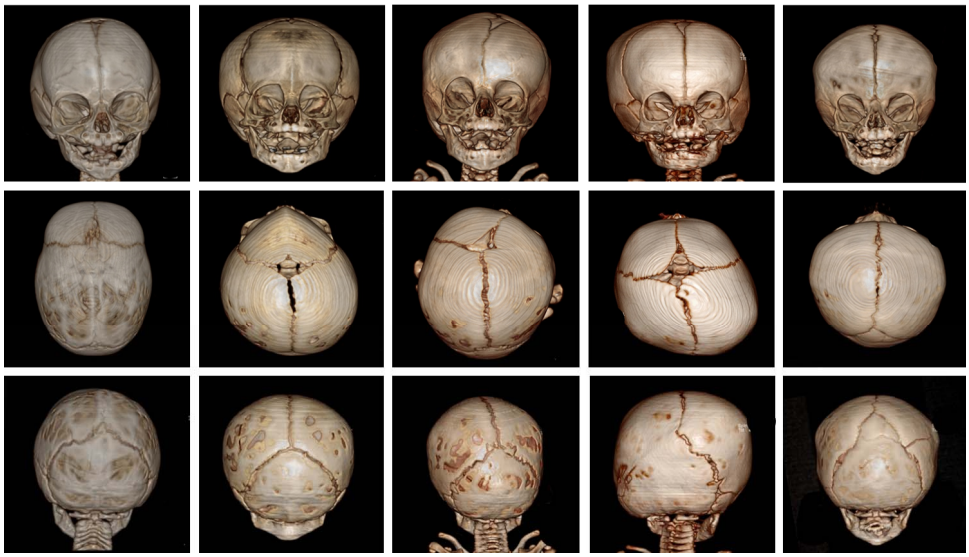

Figure 1: 3D CT scans of different types of craniosynostosis. The upper row shows the frontal view, in the middle row the skull is shown from above, and the lower row shows a posterior view of the skull. From left to right: scaphocephaly, trigonocephaly, right coronal suture synostosis, left lambdoid suture synostosis, bicoronal synostosis.

Patients with syndromic or complex craniosynostosis often have additional abnormalities of teeth, midface, and extremities.

Apert syndrome is an autosomal dominant inherited disorder that occurs in 1:100,0000 newborns. It is most commonly caused by specific de novo missense mutations in *FGFR2*-gene (Ser252Trp and Pro253Arg), or is inherited from the father in whom spermatogonia are mutated during spermatogenesis.[24] Therefore, the prevalence of Apert syndrome increases with increasing paternal age.[25] Apert syndrome is characterized by the premature fusion of both coronal sutures, resulting in a brachycephalic skull shape. In addition, patients present with hypertelorism and midface hypoplasia. In contrast to patients with other craniosynostosis syndromes, patients with Apert syndrome have symmetrical complex syndactyly of both hands and feet. Their intelligence Quotient (IQ) varies between 59 and 94. Intellectual disability (=IQ<84) includes mental retardation (IQ<71) and borderline intellectual disability (IQ 71–84), and is more frequently seen in children with Apert syndrome compared to children with Crouzon-Pfeiffer, Saethre-Chotzen or other complex craniosynostoses.[26]

Crouzon-Pfeiffer syndrome is an autosomal dominant inherited disorder with an incidence of 1:25,000, and is mostly caused by a mutation in *FGFR2*. In rare cases, a mutation in *FGFR1*[27] as well as a mutation in *FGFR3* in combination with acanthosis nigricans may cause Crouzon-Pfeiffer syndrome.[28] Most patients have bilateral coronal suture synostosis, but different skull sutures might be involved, sometimes resulting in pansynostosis. Especially Crouzon patients can develop postnatal pansynostosis: they have a normal skull shape in the early postnatal age that may delay the diagnosis. Exorbitism and midface hypoplasia are almost always present. Although some Crouzon-Pfeiffer patients may have a normal or even high intelligence, the majority has mental retardation (IQ range: 54-133).[26]

Muenke syndrome is diagnosed by its clinical findings, and its diagnosis is confirmed by the presence of the *FGFR3* pathogenic variant (Pro250Arg), which is inherited with an autosomal dominant pattern and has an incomplete penetrance and variable expressivity.[29-31] Muenke syndrome can result in unilateral or bilateral coronal suture synostosis. In the case of unilateral coronal suture synostosis patients have facial asymmetry, including ipsilateral flattened forehead, elevated superior orbital rim and eyebrow, and deviation of the nasal root. On the contralateral side, there is frontal bossing. When both coronal sutures are involved, patients have a flattened forehead with temporal bossing.[29] However, patients with Muenke syndrome may present with macrocephaly without craniosynostosis, or they may not have any skull deformity.[32] Other findings such as sensorineural hearing loss,[33-36] high arched palate,[37] and brachydactyly can also be present. The cognitive functions of patients with Muenke syndrome range between borderline intellectual disability and normal intelligence (IQ of 73-124). Behavioral problems such as social problems and attention problems, as well as hyperactivity/ impulsivity are more frequently found in Muenke patients compared to children with other craniosynostosis syndromes. This is independent on IQ and therefore suggests a direct relationship with the gene mutation.[26]

Saethre-Chotzen syndrome results from a loss-of-function mutation or haplo-insufficiency of *TWIST1*, which leads to unicoronal or bicoronal suture synostosis. Abnormalities of the extremities, such as broad, laterally deviated first finger and/ or toe, brachydactyly and cutaneous syndactyly, ptosis of the upper eyelid, and small ears with horizontal crura can be also seen.[22] Patients with Saethre-Chotzen syndrome have variable cognitive functions with the IQ ranging between 52 and 141.[26]

Complex craniosynostosis includes patients with premature fusion of two or more sutures, but an unknown genotype. Therefore, this is a heterogeneous group including patients with different types of craniosynostosis. The number of patients included in this group is progressively decreasing because an increasing number of genes such as *MSX2*,[38] *IL11RA*,[39] *ERF*[40], *TCF12*[14] has been associated with craniosynostosis.

Functional disabilities

Patients with complex and syndromic craniosynostosis often have behavioral problems, visual difficulties, and hearing problems. In addition, some patients (particularly children with Apert syndrome) have functional problems due to limb anomalies, which may result in a lower quality of life.

De Jong et al. (*unpublished data*) studied the long-term outcome of craniosynostosis patients (mean age around 10 years of age). They found that most patients with Crouzon-Pfeiffer and Saethre-Chotzen have a long-term intellectual outcome within the normal limits, while patients with Apert syndrome have typically an IQ below the norm. In addition, a large group of patients within all 3 syndromes has an IQ that is 2SD or more below the normal limits. This means that a large proportion of patients cannot work and live independently.

Mild to moderate hearing loss is found in a large number of patients with craniosynostosis syndromes; 44% in Apert, 28.5% in Crouzon-Pfeiffer, 62.1% in Muenke, 28.6% in Saethre-Chotzen, and only 6.7% in complex craniosynostosis patients. Moreover, Muenke patients are the only ones with sensorineural hearing loss instead of conductive hearing loss caused by recurrent otitis media. An early diagnosis of hearing loss is important because of its treatment possibilities and its involvement in speech and language development.

The most frequent ocular problems seen in craniosynostosis patients are strabismus and refractive errors. Strabismus has been detected in 61.4% of the patients, and is present most commonly in Apert patients. Refractive errors including myopic and hyperopic errors are seen in 52% of the craniosynostosis patients, whereas astigmatism and anisometropia are less common.[41]

Craniosynostosis patients have a high risk for developing ICH, possibly due to the premature fusion of skull sutures and skull base synchondroses leading to a disproportion between brain and skull vault. Other possible causes are venous hypertension due to impaired venous outflow at the skull base, cerebrospinal fluid (CSF) excess, and obstructive sleep apnea (OSA). Prolonged ICH may lead to disturbances in the development of cognition and behavior. In addition, the pressure on the optic nerves can cause visual loss, ultimately leading to blindness. A higher understanding of the pathophysiology of ICH in patients with craniosynostosis is needed and it will improve the treatment and long-term outcome of the affected patients. Therefore, this thesis focuses on the pathophysiology of ICH and the presence of additional brain and skull abnormalities in patients with craniosynostosis syndromes.

Intracranial hypertension

Definition and prevalence

The development of increased intracranial pressure (ICP) is the main concern in patients with craniosynostosis syndromes; it can contribute to developmental, behavioral and learning problems, visual loss and even blindness.[42, 43] Treatment is initially targeted to the prevention of ICH, which may require a cranial vault expansion in the first year of life. During follow-up patients are regularly screened for symptoms and signs of ICH to increase early recognition and improve treatment. Clinical symptoms such as headache, vomiting, visual deficits, and behavioral changes, as well as impressiones digitatae on skull X-rays may suggest elevated ICP, but are inconclusive.[44] Prior to vault expansion, patients with syndromic craniosynostosis have a high risk for developing increased ICP, with different prevalence for the individual syndromes. In general, raised ICP can be reduced by 1) increasing the intracranial volume (ICV) with a vault expansion, 2) treating venous hypertension, or 3)

a combination of both. However, even after surgical treatment ICH has been observed in 9% to 43% craniosynostosis patients. For an overview of the pre- and postoperative occurrence of ICH for the various craniosynostosis syndromes see **table 1**.

Table 1: Preoperative and postoperative prevalence of intracranial hypertension.

	Apert	Crouzon-Pfeiffer	Muenke	Saethre-Chotzen	Complex	Combined group
Before surgery						
-Renier et al. 1982 [45]	50%	100%				
-Thompson et al. 1995 [46]	38%	64%		43%		
-Renier et al. 1996 [47]	45%					
-Renier et al. 2000 [48]					47%	
-Kress et al. 2006 [49]	35%		None	51%		
-Marucci et al. 2007 [50]	83%					
-Spruijt et al. 2015 [51]	10%	36%	11%	33%	19%	
After surgery						
-Renier et al. 1982 [45]						47%[1]
-Bannink et al 2008. [44]	18%					35-43%[2]
-Kress et al. 2006 [49]	35%					
-Marucci et al. 2007 [50]						
-Spruijt et al. 2015 [51][a]	10%	9%	11%	0%	8%	
-Spruijt et al. 2015 [51][b]	50%	36%	0%	17%	12%	

Prevalence of intracranial hypertension per craniosynostosis syndrome.
[1] Included: oxycephaly, scaphocepahly, plagiocephaly, brachiocephaly, trigonocephaly, Apert and Crouzon patient.
[2] Included: Apert, Crouzon-Pfeiffer, and Saethre-Chotzen patients.
[a] Results within one year after surgery.
[b] Results after one year after surgery.

The gold standard test for the diagnosis of ICH is an invasive ICP measurement. Unfortunately, normal values of ICP in children are lacking, because true ICP measurements can only be assessed invasively, and are mainly performed in older patients having hydrocephalus, craniosynostosis, or after having trauma. ICP can be measured with different invasive techniques, including lumbar puncture, which gives a several minutes lasting ICP measurement. Moreover, it can be measured within the ventricles or at the brain surface (subarachnoid and subdural) for a longer period of time, and within the brain parenchyma for an even prolonged recording. ICP levels may differ between subdural and epidural measurements, which may underestimate ICP.[46, 52-57] In addition, ICP may vary between awake and asleep (including REM and nonREM) state. Therefore, interpretation and comparison of different studies is challenging. In general, the following classification is used for the mean baseline ICP: normal <10mmHg, borderline 10-15mmHg, and increased >15mmHg. In addition to baseline ICP, there may be plateau waves of raised ICP that occur particularly during REM sleep. Three types of waves can be distinguished. A waves, which represent steep rises in ICP up to 50 mmHg or more, lasting for 5–20 minutes and then quickly fall down. A waves may occur in patients with traumatic brain injury, but not in craniosynostosis patients. B waves are rhythmic oscillations developing every 1–2 minutes, and reach levels of 20–30 mmHg higher than baseline. They are thought to be related to changes

in cerebrovascular tone and cerebral blood volume. Moreover, they seem to be indicative of failing intracranial compensation, and can be seen in craniosynostosis patients. C waves are oscillations that occur less often and with smaller amplitude than B waves and, hence, have less pathological importance.[58, 59] Within craniosynostosis patients it may be difficult to diagnose ICH, because craniosynostosis patients often have a variable ICP ranging between normal ICP and borderline ICP. Moreover, B waves are considered to be subjective and therefore not harmful in case of a normal baseline pressure.[60, 61] Nowadays, increased ICP can be defined as: baseline ICP >15 mmHg (for at least 12 hours, during sleep) and/ or at least 3 plateau waves of ICP >35 mmHg (at least 20 minutes).[50, 55, 62, 63] Although invasive ICP measurement is the gold standard, it is an invasive procedure that requires admission to a hospital and is associated with potential complications. Therefore, it is not used as a routine screenings method and true ICP levels in children are not available.

Screening methods

Since the optic nerve is an extension of the central nervous system, and has direct contact with the subarachnoid space of the brain, increased ICP is transmitted via the optic nerve. Swelling of the optic nerve or edema of the optic disc can be seen as an indirect sign of increased ICP,[21, 44, 55, 62] and assessed via the eyes. Therefore, non-invasive techniques such as fundoscopy, optical coherence tomography (OCT), and visual evoked potential (VEP) are useful in the assessment of increased ICP.

Within patients with different types of craniosynostosis, including isolated and syndromic forms, papilledema is a very specific indicator of increased ICP, and fundoscopy is most often used as a screening tool for ICH. Papilledema is defined as elevation of the optic disc or marginal blurring, which is caused by swelling of the optic nerve in the presence of raised ICP. It is assumed that papilledema develops after ICP rises above 15 mmHg, and occurs within 7 to 14 days in patients with moderately and chronically elevated ICP. However, it is uncertain whether this applies in children with syndromic and complex craniosynostosis, when ICP levels rise shortly during the night. The optimal screening tool for detecting ICH is still controversial. The sensitivity of fundoscopy varies depending on the age of the patient; Tuite et al. found a sensitivity of 100% in children older than 8 years, but only 22% under the age of 8 years.[54] They advise to use fundoscopy with caution in children under the age of 8 years, though the reason for the low sensitivity is not explained. Driessen et al. found that measuring the optic nerve sheath with the use of ultrasound might be helpful in detecting ICH; they found that the optic nerve sheath is greater in children with papilledema, and that there is a real time relationship between nocturnal sonography of the diameter of the optical nerve sheath and the presence of ICH measured by invasive intra-parenchymal ICP measurements.

VEP may be useful to assess visual pathway function and indirectly raised ICP. The interpretation of the results, however, may be difficult and high experience is required. VEP reflects activity of the visual pathway representing the central visual field, i.e. macula, and is clinically characterized by amplitude, latency, and waveform. In chronic papilledema, all three characteristics may be affected: amplitudes are reduced, latencies increased, and waveforms degraded.[64]

Ocular coherence tomography (OCT) is a promising screening tool and is increasingly used; it makes use of broad-band near infra-red light sources, and penetrates the tissue up to 3mm. Therefore, it

can detect microstructural abnormalities of 1 µm. Hence, OCT is believed to detect retina abnormalities earlier than fundoscopy, which makes it a useful tool in detecting increased ICP in an early stage.[65] In addition, retina thickness is a quantitative, objective measure that is observer independent and therefore easy to use for follow up. However, it is important to have a cooperative patient to obtain a reliable measure. This makes the application of OCT very difficult in children younger than the age of 4 years.

At our clinic, fundoscopy is performed by the ophthalmologist to screen for increased ICP at the time of the first visit at the outpatient clinic, 1 day before skull vault surgery, 3 months after surgery, every 6 months between the ages 1-4 years, and then annually till the age of 6 years. After the age of 6 years, patients underwent fundoscopy only in the presence of signs of increased ICP, such as a stagnating growth curve of head circumference, disturbed sleeping or behavioral changes. When papilledema is detected, fundoscopy should be repeated within 4 to 6 weeks, to confirm the finding.[23, 63] Nevertheless, papilledema may be absent even when ICP is elevated. Therefore, when papilledema is absent, but other signs of increased ICP are present an OCT or invasive ICP measurement should be considered to diagnose raised ICP.

Causes of intracranial hypertension

The Monro-Kellie hypothesis is known as the pressure-volume relationship between ICP and the volume of CSF, blood, and brain tissue. It states that the cranial compartment is incompressible, i.e. ICV is a fixed volume and body responses are aimed to a state of volume equilibrium. Any increase in volume of one of the intracranial components will be compensated by a decrease in volume of another. CSF and to a lesser extent blood volume are the main buffers for increased volumes.[66] In craniosynostosis patients, additional factors such as tonsillar herniation and OSA may interact as well, which makes it a very complex condition.

Craniocerebral disproportion

In general, growth of the cranial vault, skull base and brain takes mainly place within the first 2 years of life, but it continues until age 18.[67] When a mismatch occurs between brain and skull vault growth rate, and the brain grows faster than the skull, a craniocerebral disproportion follows. One single study showed dynamic changes of the ICV in craniosynostosis patients compared to controls: the ICV is smaller from birth until the age of 6 months, but then it normalizes. The patients in this study are more likely to have involvement of multiple sutures, but the exact syndromes are not specified. Most likely, a compensatory growth of the skull occurred in these patients, although it is not totally clear whether a skull vault expansion has been performed in this group of patients.[68]

Other studies showed that ICV in craniosynostosis patients is not reduced compared to controls, but it may be larger compared to healthy controls, (for an overview see **table 2**).[69] Later in life, ICV depends on the diagnosis; ICV is normal in patients with unicoronal suture synostosis,[70] normal or slightly enlarged in sagittal synostosis,[71-73] and enlarged in patients with Apert and Crouzon-Pfeiffer syndromes,[69] suggesting that skull growth is not impaired and sufficient for the development of the brain. However, ICV alone does not predict the presence of elevated ICP in craniosynostosis.[52, 74] A single study analyzed the brain volume in Crouzon-Pfeiffer syndrome and found it is equal to controls.

This cross-sectional study was performed in non-operated Crouzon patients.[75] A recent longitudinal study has focused on ICH in relation to the presence of OSA and skull growth by measuring the occipito-frontal circumference (OFC) over time. This study showed that in 92% (12 out of 13) of the craniosynostosis patients growth arrest of the OFC, which was defined as a downward deflection in OFC ≥0.5 standard deviation from baseline over 2 years, or lack of change in OFC, was related to ICH.[51]

Tonsillar herniation

Tonsillar herniation is defined as a herniation of the cerebellar tonsils through the foramen magnum (FM). When the herniation is less than 5mm below the FM it is called a tonsillar herniation (TH), when it is more than 5mm below the FM it is called Chiari I malformation (CMI; classic definition).[76-79] Many studies argue that a smaller posterior fossa (PF), due to underdevelopment of the occipital bones, causes CMI.[80-82] Nevertheless, none of these studies was performed in craniosynostosis patients. In 1972, Saldino et al. were the first to report on the association between craniosynostosis and CMI.[83] More recent studies showed that TH may also be associated with ventriculomegaly, either as a consequence or as a cause to it.[84] Different hypotheses about this relation are discussed; the most simple hypothesis suggests that a primary obstruction of the CSF flow as example at the outlet of the 4th ventricle causes enlargement of the ventricular system and increased ICP that results in TH and CMI.[85] Although CMI and ventriculomegaly are present in a high number of patients with craniosynostosis syndromes,[78, 86] not all patients with CMI and craniosynostosis do have ventriculomegaly.[87] Hence, a more complex underlying pathomechanism is likely, including an interaction between venous outflow obstruction, impaired CSF circulation at the level of the FM, and overcrowding of the PF due to a mismatch between the volume of the infratentorial brain structures and the volume of the PF. The combination of a smaller PF and an obstruction at the level of the FM may impair the CSF flow, resulting in increased intraventriculair CSF pressure.[84] This may lead to a craniocerebral disproportion within the PF, resulting in TH or CMI.

Within craniosynostosis syndromes, patients with Crouzon-Pfeiffer syndrome have the highest incidence of CMI (up to 73%).[87] Most likely the high prevalence of CMI depends on the inclusion criteria that have been used for the study: Cinalli et al. included CT and MR scans that have been performed in patients with clinical signs of ICH. In addition, the presence of TH was evaluated based on the aspect of the FM on axial CT images, instead of measuring the TH in relation to the basion-opisthion line on sagittal images. A distinction was made between a normal aspect of the foramen magnum (absence of tonsillar herniation based on clear visualization of the cisterna magna) and a full foramen magnum (excess of soft tissue present at the level of the FM). An MRI was performed if the CT images could not be evaluated. Moreover, herniation of the cerebellar tonsils >2mm below the basion-opisthion line was considered as chronic tonsillar herniation (CTH), without any distinction between a classic CMI (tonsillar herniation >5mm) and TH (<5mm).[88]

Ventriculomegaly and hydrocephalus

CSF is produced by the choroid plexus, mainly in the lateral ventricles, and to a lesser extent in the 3rd and 4th ventricle. Its function is to protect the brain and spinal cord from external pressure, to

transport nutrients and to export waste products. CSF flows from the lateral ventricles through the foramen of Monro to the 3rd ventricle and via the Sylvian aqueduct to the 4th ventricle. From here, the CSF flows through the foramina of Luschka and Magendie, via the subarachnoid spaces, and is absorbed by the sinuses, mainly the sagittal sinus. Enlargement of the ventricular system occurs when there is overproduction or reduced absorption of CSF. A stable enlargement of the ventricular system is called ventriculomegaly, while a progressively increasing size of the ventricular system is called hydrocephalus. Craniosynostosis patients develop hydrocephalus in rare cases,[89] while the occurrence of ventriculomegaly is common, particularly in patients with Apert and Crouzon-Pfeiffer syndromes (40-90% and 30-70% respectively).[89-92] The high prevalence in these syndromes is most likely related to the underlying gene mutation. *Fgfr* genes are expressed in the choroid plexus during early development. *Fgfr1* and *fgfr4* are expressed only during early development, until around the 6th week of gestation, while *fgfr2* is expressed throughout the entire development of the choroid plexus. Therefore, mutations in *fgfr2* contribute most likely to an increased production of CSF.[93]

Venous outflow obstruction

Dural venous sinuses including the superior and inferior sagittal sinus, the transverse sinus, the sigmoid sinus, and the cavernous are responsible for the intracranial blood outflow and drain into the jugular veins. Therefore, the jugular veins are responsible for the vast majority of the intracranial venous outflow. Additional drainage occurs though emissary veins, which connect the extracranial venous system and the intracranial venous sinuses. In case of an obstruction along this venous tract, venous pressure rises, and may result in venous hypertension. Three hypotheses have been suggested to explain the development of venous hypertension:

1. Constriction theory. Venous obstruction can be secondary to growth disturbances of cranial vault and skull base. Disturbance of bone development may include a disturbed development of foramina. Normally, foramina allow blood vessels to pass through the skull, however in case of developmental disturbances they may be narrowed or absent. This can result in partial or total obstruction of veins that pass through the foramina. The constriction theory is supported by the narrowing or absence of the jugular/ sigmoid complex in syndromic craniosynostosis patients, [94-96], that is more closely located to the adjacent bones (in comparison with the sagittal and transverse sinuses).[94, 97]
2. Primarily due to the *FGFR* mutation. During head development, *fgfr1* and *fgfr2* are present in head mesenchyme, and are involved in the development of the cranial vault and dura mater. Moreover, their presence has also been proven in endothelia.[98, 99] It is therefore possible that mutations in these genes may lead to vascular abnormalities, such as agenesis or hypoplasia of the jugular vein, or the development of occipital-mastoid collaterals.[100]
3. Persistence of the fetal pattern of intracranial venous drainage. This theory is based on the failure of the normal development of venous drainage in the PF and may result in narrowing or absence of the sigmoid/ jugular complex, and maintenance of mastoid emissary venous collaterals.

Since the angiogenesis precedes the formation of the skull it is unlikely that venous obstruction is secondary to growth disturbances of the skull and skull base. It is more likely that disturbances in the vascular origin, possibly caused by the genetic mutation, are already present before bony parts of the skull develop. However, the continuous interaction between the developing vascular system and the bony parts of the skull vault and skull base does not exclude the influence of a disturbed skull and skull base development in obstructing the venous outflow.

Obstructive sleep apnea

In addition to the intracranial components, syndromic craniosynostosis can be associated with several upper airway abnormalities, including midface hypoplasia, palatal abnormalities, hypertrophic adenoids and tonsils, mandibular hypoplasia, and tracheal rings. Therefore, these patients have a high risk for developing obstructive sleep apnea (OSA).[101-104] Driessen et al. showed an overall prevalence of OSA in syndromic craniosynostosis patients of 68%, of which 26% has moderate-severe OSA. OSA can result in a decreased oxygen level and increased carbon dioxide level, i.e. hypoxia and hypercapnia respectively. Hypercapnia may cause cerebral vasodilatation, and consequently increases the ICP. The increase in ICP is followed by a reduced cerebral perfusion pressure, which causes a compensatory vasodilation to preserve the cerebral blood flow.[99] Moderate-severe OSA was shown to be a significant contributor to the development of increased ICP.[51]

Skull vault surgery

Initial surgical treatment of patients with craniosynostosis syndromes has two goals; to prevent/ treat increased ICP, and to correct the skull deformity and normalize the patient's appearance. In our institution, patients are surgically treated within their first year of life;[48, 105, 106] in patients with Apert, Crouzon-Pfeiffer and Saethre-Chotzen syndromes, the vault expansion is performed between the age of 6 to 9 months within our clinical protocol, or earlier in case of increased ICP. For Muenke patients, skull vault surgery is performed between 9 to 12 months of age, because these children have a lower risk to develop increased ICP, and early surgery may have poor results in terms of the shape of the forehead. In Apert and Crouzon-Pfeiffer syndromes, the treatment of first choice is the occipital vault expansion that allows to increase the ICV, preserve the facial profile, and hence facilitate a monobloc, facial bipartition or Le Fort III procedure in a later stage. Nowadays, this kind of occipital expansion is a minimally invasive procedure that needs the use of springs.[107] For patients with Muenke and Saethre-Chotzen syndromes, a fronto-orbital advancement is the surgical approach of first choice, because it corrects facial appearance at the same time, and additional procedures in these groups are uncommon. However, occasionally Saethre-Chotzen patients need an additional vault expansion such as an occipital expansion or biparietal widening. In patients with complex craniosynostosis, the choice of the procedure depends on the sutures that are involved. If coronal sutures have closed prematurely, a fronto-orbital advancement is the procedure of first choice, while in patients with involvement of lambdoid sutures, an occipital vault expansion is typically performed. Nevertheless, in case of severe exorbitism, visual loss and/ or severe OSA, a monobloc-advancement with distraction should be performed as first procedure.[108, 109]

Aim of this thesis

The aim of this thesis is to better understand the pathophysiology of increased intracranial pressure (ICP) in relation to additional abnormalities of skull and brain in patients with syndromic and complex craniosynostosis. Increased knowledge of these processes will favor the development of a more sophisticated and individualized management of patients with craniosynostosis syndromes, and potentially improve the functional and neurodevelopmental outcome.

Chapter 2 will describe volumetric measurements of the brain and ventricles, which are studied in 3D MR scans. This study is designed to investigate whether brain and ventricular volume in craniosynostosis patients are equal to the normal population. In addition, the incidence of tonsillar herniation and CMI will be studied; this information can improve our understanding about the involvement of brain and ventricle volumes in the development of increased ICP.

Chapter 3 will study one of the hypotheses postulated in literature, namely that TH is the result of an overcrowded PF. Volumes of both PF and cerebellum will be assessed in 3D T1-weighted MR images, and the ratio of both volumes will be calculated. Volumes and ratio of patients will be compared to those of healthy controls. This study should explain whether TH and CMI are caused by an overcrowded PF.

Besides the premature fusion of skull sutures and skull base synchondroses, pathogenic gene mutations causing craniosynostosis might also be responsible for disturbances in brain white matter integrity. It still remains unclear whether abnormalities are secondary to the bone disease or primarily caused by the genetic mutation. Recent studies suggest that white matter disturbances may be a primary disorder.[110, 111] Diffusion tensor imaging (DTI) fiber tractography (FT) allows the study of white matter integrity. In **chapter 4** we first evaluate whether DTI-FT is a reliable tool in patients with a deformed skull and brain. Secondly, we compare the diffusion parameters of multiple white matter tracts between craniosynostosis patients and controls.

The human skull is caudally bordered by the FM, which forms the output for CSF to flow from brain to spinal sac. FM size might therefore be important in CSF outflow and be involved in the development of ICH, by either being smaller or enlarged compared to controls. Therefore, in **chapters 5a, b**, we will study the size of the FM and the closure of its intra-occipital synchondroses, the cartilage structures that enable its expansion. Furthermore, in chapter 5a the relation between TH and FM size will be established in Crouzon-Pfeiffer patients, while chapter 5b focuses on FM size and closure of the intraoccipital synchondroses within the different syndromic diagnoses.

Chapter 6 will describe the relation between the ICV and the OFC. The OFC is measured at every visit at the outpatient clinic to follow-up skull growth; however it has never been related to the ICV in syndromic craniosynostosis patients. Therefore, it is unclear whether OFC is a reliable marker of ICV and skull growth, and consequently whether patients are developing craniocerebral disproportion.
Finally, as described earlier in our institution a cranial vault expansion is performed within the first year of life. Until 2005, the first choice of treatment for different craniosynostosis syndromes was a fronto-orbital advancement. Since 2005, the protocol for Apert and Crouzon-Pfeiffer patients includes an occipital expansion as the first operation. An occipital expansion was expected to be more effective

Table 2: Intracranial volume in craniosynostosis patients based on CT measurements: overview of the literature.

Author	Diagnosis	Age	Number of patients	Methods	Limitation	Conclusion
Gault, 1992[112]	Nonsyndromic, syndromic	6m-14y (mean: 29m)	66 Complex 5 Oxycephaly 4 Crouzon 3 Brachy 2 Apert 1 Trigono 4 Plagio 3 Scapho 44	Slice thickness: 5mm Planimeter Compared to normal population.	No distinction between the different groups The majority of the group had simple craniosynostosis No control group: normal population based on Lichtenberg 1960 (radiographs)	No relation between intracranial volume and intracranial hypertension. The conclusion cannot be applied for syndromic craniosynostosis patients. In addition, the incidence of increased ICP is much lower in simple craniosynostosis, a relation with intracranial volume is therefore hard to find.*
Fok, 1992[74]	Nonsyndromic, syndromic	1.5m-10y (mean: 27m)	41 Unicoronal 7 Bicoronal 7 Sagittal 6 Metopic 2 Lambdoid 2 Multiple 3 Crouzon 7 Apert 5 Saethre-Chotzen 2	Slice thickness 5mm Planimeter Compared to normal population.	No clear distinction between the different groups The majority of the group had simple craniosynostosis No control group: normal population based on Lichtenberg 1960 (radiographs)	-70.7% normal volume. -19,5% increased volume. -9,8% reduced volume. *idem
Gosain, 1995[113]	Apert	0-30y	20	Compared to normal population.	No control group: normal population based on Lichtenberg 1960 (radiographs)	Intracranial volume is larger in Apert syndrome, from the age of 3.5 months
Posnick, 1994[69]	Apert, Crouzon	6-48m Apert: 34m (12-48m) Crouzon: 14m (6-46m)	21 Apert 8 Crouzon 13	Compared to normal population.	No control group: normal population based on Lichtenberg 1960 (radiographs)	Intracranial volume is normal or even larger in Crouzon and Apert syndromes, pre- and postoperatively

Table 2: Continued

Author	Diagnosis	Age	Number of patients	Methods	Limitation	Conclusion
Sgouros, 1999[67]	Nonsyndromic, syndromic	0-15y	84 Unicoronal 20 Metopic 11 Sagittal 7 Lambdoid 3 Bicoronal 17 Crouzon 8 Apert 7 Saethre-Chotzen 3 Complex 7 Pansynostosis 1	Slice thickness: 4mm, continuous slices Compared to controls.	Small subgroups Statistical analysis was performed for the total group, not for the subgroups The majority of the group had simple craniosynostosis Measurements in control group were performed in MRI	Smaller intracranial volume in patients with multisuture synostosis (pansynostosis), at the age of 1 month Normal volume around the age of 6 months *idem
Anderson, 2004[114]	Apert	0-7y	22	Intracranial region was outlined on each slice Compared to CT-measurements in controls		Intracranial volume is larger in Apert syndrome
Tovetjarn, 2014[115]	Bicoronal	0-3y	15 Apert 3 Crouzon 1 Muenke 6 Saethre-Chotzen 3 Nonsyndromic 2	0.6-mm slice thickness in craniosynostosis patients Data were compared with normative data (CT scans for neurological or posttraumatic reasons, 5mm slice thickness) Comparison were made at 5 months (preoperatively), 11months (postoperatively), and 3 years of age (follow-up)	Small subgroups	No difference between craniosynostosis patients and controls (pre- and postoperatively) Apert patients had a larger volume compared the rest of the group

in the prevention and treatment of increased ICP, because it creates a larger ICV compared to a fronto-orbital advancement. However this was never tested. Therefore, in **chapter 7** the OFC, the presence of papilledema and of tonsillar herniation, as well as visual acuity during 5 years of follow-up will be compared between patients who underwent a fronto-orbital advancement and those who underwent an occipital vault expansion.

An overview of factors that favor the development of ICH is shown in **figure 2**: some of them have been previously studied in the literature, while others have been evaluated first in this thesis.

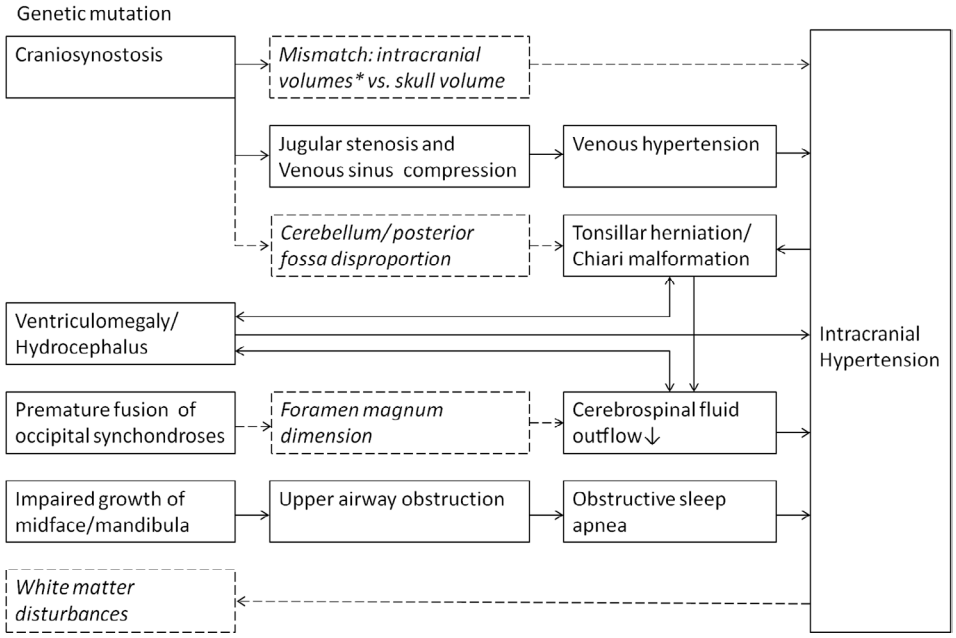

Figure 2: Pathophysiology of intracranial hypertension in patients with craniosynostosis syndromes. Dashed lines indicate contributors that are investigated in the thesis. * intracranial volumes include: brain, CSF and blood volumes.

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2

Brain and ventricular volume in patients with syndromic and complex craniosynostosis

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ABSTRACT

Purpose Brain abnormalities in patients with syndromic craniosynostosis can either be a direct result of the genetic defect or develop secondary to compression due to craniosynostosis, raised ICP or hydrocephalus. Today it is unknown whether children with syndromic craniosynostosis have normal brain volumes. The purpose of this study was to evaluate brain and ventricular volume measurements in patients with syndromic and complex craniosynostosis. This knowledge will improve our understanding of brain development and the origin of raised intracranial pressure in syndromic craniosynostosis.

Methods Brain and ventricular volumes were calculated from MRI scans of patients with craniosynostosis, 0.3 to 18.3 years of age. Brain volume was compared to age matched controls from the literature. All patient charts were reviewed to look for possible predictors of brain and ventricular volume.

Results Total brain volume in syndromic craniosynostosis equals that of normal controls, in the age range of 1 to 12 years. Brain growth occurred particularly in the first 5 years of age, after which it stabilized. Within the studied population, ventricular volume was significantly larger in Apert syndrome compared to all other syndromes and in patients with a Chiari I malformation.

Conclusions Patients with syndromic craniosynostosis have a normal total brain volume compared to normal controls. Increased ventricular volume is associated with Apert syndrome and Chiari I malformations, which is most commonly found in Crouzon syndrome. We advice screening of all patients with Apert and Crouzon syndrome for the development of enlarged ventricle volume and the presence of a Chiari I malformation.

Keywords Craniosynostosis, Syndrome, Brain volume, Ventricular volume.

INTRODUCTION

Children with craniosynostosis develop an abnormal head shape due to the premature closure of one or more cranial sutures. This congenital malformation occurs in one in 2100 to 2500 births. In up to 20% of these cases it is part of a syndrome, such as Apert, Crouzon, Muenke and Saethre-Chotzen, caused by mutations in the FGFR1, 2 and 3 and TWIST1 gene [9].

Different brain abnormalities are reported in patients with syndromic craniosynostosis including non-progressive ventriculomegaly, callosal agenesis or thinning, agenesis of the septum pellucidum, paucity of the antero-mesial temporal white matter, medial temporal lobe dysgenesis, pyramidal hypoplasia, venous malformations and Chiari I malformations [3, 4, 7, 8, 14, 15, 19]. In patients with syndromic craniosynostosis the origin of the abnormalities secondary to the craniosynostosis and associated hydrocephalus and increased intracranial pressure (ICP).

A mismatch between intracranial volume versus brain and ventricle volume is thought to be one of the causes of brain abnormalities and elevated ICP. However, in spite of the craniosynostosis the intracranial volumes are reported to be normal in patients with craniosynostosis or even enlarged in Apert and Crouzon syndrome [6, 13, 16]. Only one study reports on brain volume in syndromic craniosynostosis. They found that patients with Crouzon syndrome had a similar brain volume compared to normal controls [11]. This contradicts the assumption that a mismatch between intracranial and brain volume is the cause of raised ICP. To improve our understanding of the development of raised ICP, knowledge of brain and ventricular volume in this population is needed.

MATERIALS AND METHODS

Patients diagnosed with syndromic or complex craniosynostosis based on genetic testing and treated at the Dutch craniofacial center were invited to undergo MRI. Craniosynostosis was defined as complex if two or more sutures were closed and no mutation was found. The MRI were performed on a 1.5-T MR scanner (GE Healthcare, MR signa excite HD) between January 2004 and January 2011. Brain and ventricular volumes were calculated from the transversal 3D T1 weighted MR images with the use of Brainlab®. This is a post-processing programme developed for neuronavigation. The software automatically outlines the brain and ventricle contour in each slice. If the automatic contour was questionable, it was manually edited. After outlining the brain or ventricle volume slice by slice, the processing programme automatically computes the total volume. The within-rater and between-rater reliabilities were 0.99 and 0.97 respectively.

Brain volume was compared to that in normal controls at the age of 1, 4, 8 and 12 years, reported in literature [10, 12, 17]. Total ventricle volume could not be compared to that of normal controls because of the lack of normative data in the literature. A multivariate analysis was performed to look for potential predictors of brain and ventricular volume; age, gender, syndrome, Chiari I malformation and vault expansion. If patients had more than one MRI, only the first was used in the analysis, and patients with a ventriculoperitoneal shunt were excluded from the analysis. Syndromes were put in

the model as dummy variables. The intraclass correlation coefficient was calculated to compare the within-rater and betweenrater reliabilities of the volume measurements. All analyses were done with SPSS 16.0 for Windows. This study was approved by the medical ethical committee of the Erasmus University (MEC2005-273).

RESULTS

Between February 2004 and January 2011, 103 patients were invited to receive an MRI of whom 19 refused to participate. The 84 patient who received an MRI had a mean age of 8.1 years (range 0.3–18.3 years). Of the 84 patients, 13 had Apert syndrome, 31 Crouzon syndrome, 15 Muenke syndrome, 10 Saethre-Chotzen syndrome and 15 complex craniosynostosis. The total group consisted of 44 females and 40 males. A vault expansion was performed in 66 patients prior to the MRI, at a mean age of 1.1 years. A Chiari I malformation was found in 12 (14%) patients, one (8%) patient with Apert syndrome, 10 (32%) with Crouzon syndrome and one (7%) with Muenke syndrome. Three patients had a ventriculoperitoneal shunt and were excluded from the ventricular volume analysis. All three had Crouzon syndrome. The mean brain volumes at 1, 4, 8 and 12 years of patients with craniosynostosis and normal controls are shown in **table 1**.

TABLE 1: Mean brain volume of patients with syndromic craniosynostosis and of normal controls.

	Craniosynostosis	**Normal controls [10, 12, 17]**	***p*-Value**
1 Year			
n	4	29	
Age	0.90 (0.43)	1.06 (0.03)	0.048
Brain volume	924.25 (254.62)	855.54 (12.43)	0.118
4 Years			
n	8	26	
Age	3.95 (0.60)	3.96 (0.52)	0.960
Brain volume	1280.88 (162.05)	1210.62 (109.20)	0.166
8 years			
n	16	20	
Age	8.41 (0.83)	8.60 (0.70)	0.461
Brain volume	1403.44 (156.87)	1391.42 (23.54)	0.883
12 years			
n	16	20	
age	11.92 (0.60)	12.10 (0.60)	0.396
Brain volume	1464.50 (148.01)	1439.17 (23.54)	0.455

There was no significant difference between patients and normal controls. Age had a significant influence on brain volume ($p < 0.001$) but not on ventricular volume. The brain volume increased significantly in the first 5 years ($p = 0.004$) after which it stabilized. Patients with Apert syndrome ($p = 0.004$) had a significantly larger ventricular volume compared to all other patients. Patients with a Chiari I malformation ($p < 0.001$) had a significantly larger ventricular volume compared to patients without a Chiari I malformation. Unexpectedly, Crouzon syndrome as such was not significantly associated

with ventricular volume, although most patients (10 out of 12) with a Chiari I were diagnosed with Crouzon syndrome. Patients with Crouzon syndrome and a Chiari I malformation were significantly older compared to Crouzon patients without a Chiari I malformation, the mean age being 10.1 versus 8.0 years ($p = 0.018$). Furthermore, they had a larger ventricle volume ($p = 0.019$) and were less likely to have had a vault expansion ($p = 0.049$). The syndrome-specific relation between age and total ventricular and brain volume is shown in **figures 1** and **2**.

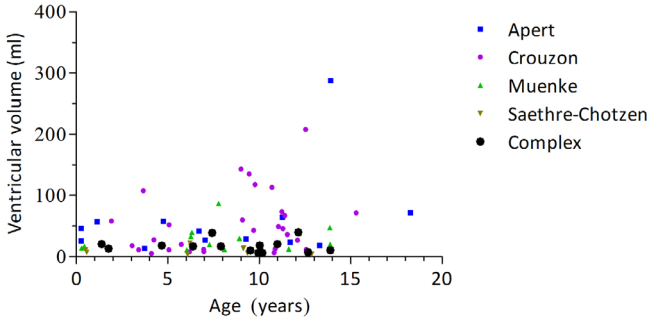

Figure 1: Syndrome-specific relation between age and ventricular volume.

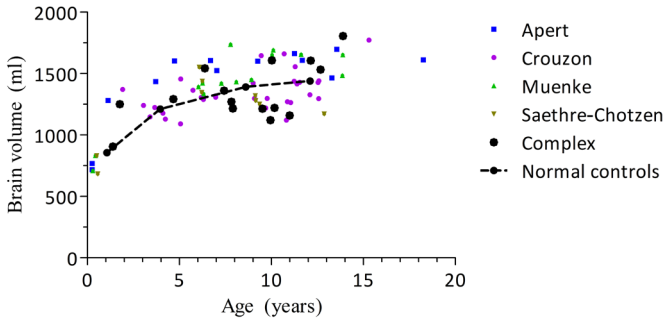

Figure 2: Syndrome-specific relation between age and brain volume.

DISCUSSION

In this study we compared the total brain volume of patients with complex or syndromic craniosynostosis to that of normal controls from the literature. Furthermore, we looked for predictors of brain and ventricular volume. We found that the total brain volume in patients with complex or syndromic craniosynostosis is similar to that in normal controls and that ventricular volume was significantly related to Apert syndrome and the presence of a Chiari I malformation. The majority of patients with syndromic and complex craniosynostosis have a normal or even enlarged intracranial volume, before as well as after vault expansion [6, 11, 13, 16]. The finding that brain volume is normal

suggests that the compensatory skull growth is sufficient, to allow normal brain growth. The excess of cerebrospinal fluid we observed may be the driving force behind this compensatory growth of the skull. Therefore, in these patients, raised ICP is more likely to result from raised CSF pressure than from a mismatch between intracranial and brain volume. In most patients this raised CSF pressure will have a communicating character with papilledema as the only sign [1].

Chiari I malformation is primarily seen in patients with Crouzon syndrome. In our population 32% of the patients with Crouzon syndrome had a Chiari I malformation, compared to 73% perviously reported by Cinnali et al.[2]. This difference can perhaps be explained by the fact that they performed an MRI in case of clinical signs, while we performed MRI as part of a prospective study and in most cases without a clinical indication. The diagnosis of Crouzon syndrome itself was not associated with an enlarged ventricular volume when it was corrected for Chiari I malformation. This means that Chiari I malformations have a stronger relation with ventricular volume than Crouzon syndrome by itself. With the lack of consecutive data, we are not able to tell whether Chiari I malformation precedes or follows the enlarged ventricular volume. Enlarged ventricular volume could be the consequence of reduced CSF outflow due to Chiari I but could also be the cause of downward pressure on the cerebellum due to raised ICP. Chiari I malformations and raised ICP are both prevalent in Crouzon syndrome [18]. In Apert syndrome larger ventricles are not related to Chiari I malformation, as only 2 to 8% of the patients with Apert syndrome have a Chiari I malformation [2]. Despite the larger ventricular volume, patients with Apert syndrome have a relatively low prevalence of increased ICP [5]. This could be due to their significantly larger intracranial volume before and after vault expansion [6, 16]. In Apert syndrome extra compensatory growth of the skull is facilitated by the enlarged anterior fontanelle that stays open for a relatively long period, preventing the development of increased ICP.

CONCLUSION

For the first time we show that patients with syndromic and complex craniosynostosis have a normal total brain volume. Therefore, it is unlikely that a mismatch between intracranial and brain volume is the main cause of raised ICP. Furthermore, we found enlarged ventricular volume to occur particularly in patients with Apert syndrome and patients with a Chiari I malformation. Patients with Crouzon syndrome are especially at risk for Chiari I, but those without a Chiari I have normal ventricular volumes. We advice screening of all patients with Apert and Crouzon syndrome for the development of enlarged ventricle volume and the presence a Chiari I malformation.

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3

The role of the posterior fossa in developing Chiari I malformation in children with craniosynostosis syndromes

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ABSTRACT

Objective Patients with craniosynostosis syndromes are at risk of increased intracranial pressure (ICP) and Chiari I malformation (CMI), caused by a combination of restricted skull growth, venous hypertension, obstructive sleep apnea (OSA), and an overproduction or insufficient resorption of cerebrospinal fluid. This study evaluates whether craniosynostosis patients with CMI have an imbalance between cerebellar volume (CV) and posterior fossa volume (PFV), that is, an overcrowded posterior fossa.

Methods Volumes were measured in 3D-SPGR T1-weighted MR scans of 28 'not-operated' craniosynostosis patients (mean age: 4.0 years; range: 0–14), 85 'operated' craniosynostosis patients (mean age: 8.0 years; range: 1–18), and 34 control subjects (mean age: 5.4 years; range: 0–15). Volumes and CV/PFV ratios were compared between the operated and not-operated craniosynostosis patients, between the individual craniosynostosis syndromes and controls, and between craniosynostosis patients with and without CMI. Data were logarithmically transformed and studied with analysis of covariance (ANCOVA).

Results The CV, PFV, and CV/PFV ratios of not-operated craniosynostosis patients and operated craniosynostosis patients were similar to those of the control subjects. None of the individual syndromes was associated with a restricted PFV. However, craniosynostosis patients with CMI had a significantly higher CV/PFV ratio than the control group (0.77 vs. 0.75; $p = 0.008$). The range of CV/PFV ratios for craniosynostosis patients with CMI, however, did not exceed the normal range.

Conclusion Volumes and CV/PFV ratio cannot predict which craniosynostosis patients are more prone to developing CMI than others. Treatment should focus on the skull vault and other contributing factors to increased ICP, including OSA and venous hypertension.

Keywords Cerebellum; Craniosynostosis syndromes; Chiari I malformation; Posterior fossa

INTRODUCTION

Syndromic craniosynostosis occurs in 1:8,750 newborns (Bannink et al., 2008, Johnson and Wilkie, 2011, Sharma et al., 2013 and Wilkie et al., 2010). Genes such as FGFR1, 2, 3 and TWIST1 are reported to be responsible for rare syndromes such as Apert, Crouzon–Pfeiffer, Muenke and Saethre–Chotzen syndrome. These patients are likely to develop a Chiari I malformation (CMI). Several processes are described as being responsible in CMI development (Barkovich and Raybaud, 2012), including an abnormally small bony posterior fossa (PF) (Aydin et al., 2005, Dagtekin et al., 2011, Furtado et al., 2009, Stovner et al., 1993 and Trigylidas et al., 2008) and more dynamic processes involving cerebrospinal fluid (CSF) circulation and venous hypertension (Di Rocco et al., 2011). In disorders other than craniosynostosis, CMI is associated with a smaller PF than controls (Aydin et al., 2005, Stovner et al., 1993 and Trigylidas et al., 2008), while other studies showed that cerebellar volume (CV) and posterior fossa volume (PFV) in non-craniosynostosis patients with CMI were similar to controls (Tubbs et al., 2008), and only the CV/PFV ratio was significantly higher (Nishikawa et al., 1997). In patients with syndromic craniosynostosis, volumetric data for the cerebellum and PF are lacking and it remains unclear whether their CMI results from a restricted PFV.

In the present study we want to explore the role of PFV in the development of CMI in patients with craniosynostosis syndromes. In this study we first compared these measurements between each craniosynostosis syndrome and controls. To investigate the role of the PFV in developing CMI in craniosynostosis patients, we then established whether CV, PFV and the CV/PFV ratio are related to the presence of CMI. We hypothesize that the PFV will be smaller and CV/PFV ratio will be higher in craniosynostosis patients compared with control subjects, as well as in craniosynostosis patients with CMI compared with patients without CMI.

MATERIALS AND METHODS

Patient population

For this study we enrolled genetically tested complex and syndromic craniosynostosis patients including Apert, Crouzon–Pfeiffer, Muenke, and Saethre–Chotzen syndrome treated at the Dutch Craniofacial Center, the single national referral center for syndromic craniosynostosis for a population of over 16 million inhabitants. Complex craniosynostosis refers to patients who have multisuture synostosis for which a responsible gene mutation has not been identified. Between October 2008 and December 2011, a subgroup of 130 syndromic and complex craniosynostosis patients were seen at the outpatient clinic and received an MR scan routinely, preoperatively at intake; postoperatively at age 4 years; and whenever patients had a downward deflection in the occipital frontal head circumference trajectory, papilledema on fundoscopy or for following-up ventriculomegaly or CMI. At our center, the protocol is to perform a cranial vault expansion within the first year of life (if referred on time). In Apert and Crouzon–Pfeiffer patients an occipital expansion is indicated; and in patients with Saethre–Chotzen and Muenke syndrome a fronto-supraorbital advancement; while in complex cases the choice depends on the involved sutures (occipital expansion with the involvement of the

lambdoid sutures). During an occipital decompression, the caudal osteotomy is made just above the level of the torcula without decompression of the PF, leaving its volume unchanged (de Jong et al., 2013). For all subjects, only the 3D T1-SPGR dataset (T1-weighted spoiled gradient-recalled-echo) of the first MR scan was measured, including scans from operated and not-operated children. This distinction within the patient population was kept to allow for appropriate comparisons.

In 12 of our craniosynostosis patients, a 3D T1-SPGR sequence was not obtained, while five scans were unusable because of incomplete scanning or artifacts due to head movements or braces. Consequently, 17 scans were excluded from the present study and 113 patients were included in the analyses. Thirty-four control subjects were identified by searching our pediatric radiology database. This group was scanned between October 2006 and December 2010 for various clinical indications, ranging from a dermoid cyst to epilepsy. Again, only MR scans including a 3D T1-SPGR sequence were included. Exclusion criteria for the control group were skull surgery, a medical history involving bone or brain maturation, and the presence of brain anomalies on their MR scan.

All imaging data were acquired using a 1.5 T MR Unit (GE Healthcare, MR Signa Excite HD, Little Chalfont, UK) and the imaging protocol included a 3D SPGR T1-weighted MR sequence. Imaging parameters for craniosynostosis patients were as follows: slice thickness 2 mm, no slice gap; field of view (FOV) 22.4 cm; matrix size 224 × 224; in plane resolution of 1 mm; echo time (TE) 3.1 ms, and repetition time (TR) 9.9 ms; these parameters were similar for controls.

Measurements

The total PFV was defined by the space bordered by the cerebellar tentorium, tentorial incisura, dural walls of the jugular foramen, clivus, foramen magnum and exoccipital bones. This volume included the brainstem (containing pons, medulla oblongata and inferior part of the midbrain), the 4th ventricle, two cisterns with their outlets, and the cerebellum. In cases where a mega cisterna magna was present (MCM; a large cisterna magna associated with a posterior midline tentorial defect), this was included in the PFV as well. CV did not include the 4th ventricle, but only the two cerebellar hemispheres and vermis.

The CV and PFV were automatically measured with the use of a multi-atlas-based segmentation method (Heckemann et al., 2006 and Klein et al., 2010). Because these atlases consisted of MR scans made of subjects without skull and brain deformities (Ikram et al., 2011), all automated segmentations in our study population were visually inspected and manually corrected per slice by an experienced doctor (first author) using the freely available ITK-SNAP software (Yushkevich et al., 2006). Manual correction was mainly performed in the sagittal plane (**figure 1**). Next, the ratio between CV and PFV was calculated.

The amount of tonsillar herniation (TH) of the cerebellum was measured in the mid-sagittal and adjacent MR slices, and assessed on the lowest position of one of the cerebellar tonsils. A TH was defined as a herniation of the tonsils of 1–5 mm below the foramen magnum, while CMI was classified as a herniation of ≥5 mm (classic definition) (Aboulezz et al., 1985, Amer and el-Shmam, 1997, Elster and Chen, 1992 and Wu et al., 1999). The PF of craniosynostosis patients was described as being

overcrowded when the mean CV/PFV ratio in these patients exceeded the mean ratio in the control group (Nishikawa et al., 1997).

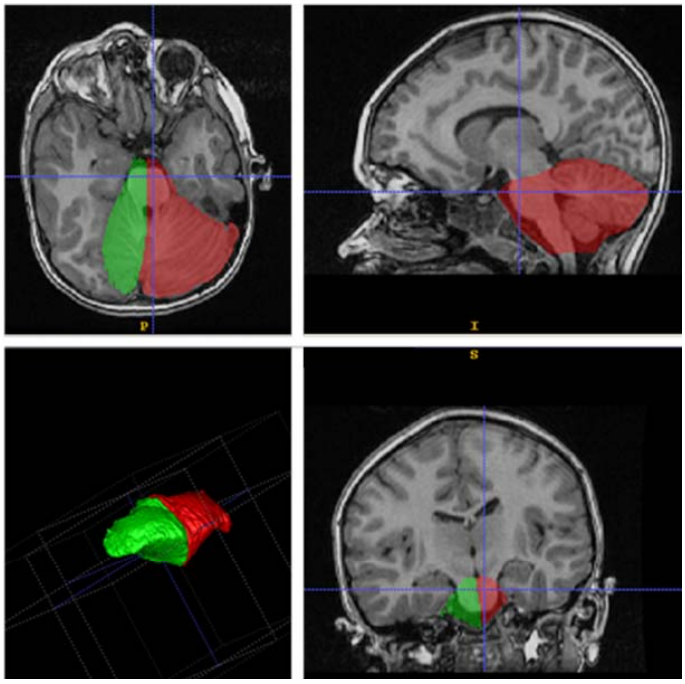

Figure 1: Measurements were performed in a 3D environment. This image shows the posterior fossa in a control subject (left side in red, right side in green).

Comparisons of CV, PFV and CV/PFV ratio were made between the following groups:

I. Craniosynostosis patients ('not-operated' and 'operated' subgroups) and controls.
II. Craniosynostosis patients (per syndrome) and controls.
III. Craniosynostosis patients with CMI and craniosynostosis patients without CMI.

Statistical analyses

Since human head growth demonstrates a logarithmic growth curve (Farkas et al., 1992), a logarithmic transformation (log10 of X and Y) of the data was required, so that relations became linear and an analysis of covariance (ANCOVA) (with post hoc comparisons if desired) could be performed to compare CV, PFV and CV/PFV ratios between the different groups. Subjects were not age- and sex-matched, but to control for possible effects these variables were included in the ANCOVA so that statistical analyses were corrected for these variables. Statistical analyses were performed in R Core (Team, 2014) and statistical significance was defined as $p < 0.05$.

RESULTS

Volumes in not-operated and operated craniosynostosis patients versus controls

This study included 28 not-operated, 85 operated craniosynostosis patients, and 34 controls. Age and sex both had a significant effect on CV and PFV ($p < 0.01$). In all subjects the cerebellum and PF grew most in the first 2.5 years of life. There was no significant difference between the CV and PFV of not-operated craniosynostosis patients, operated craniosynostosis patients, and control subjects (**table 1** and **table 2**). **Figure 2a, b** and **c** show the boxplots of PFV, CV, and their ratio presenting similar ranges between all three groups, for different age ranges (0–2 years, 2–5 years, 5–8 years, and 8–18 years old). Of the 85 surgical procedures, 56 (66%) were fronto-orbital expansions and 29 (34%) were occipital expansions, and a CSF diversion was performed in four patients (5%) (**table 1**). After correcting for age and sex there was no significant difference in PFV between craniosynostosis patients who underwent a fronto-orbital expansion (183 ml; mean age: 9 years), those who underwent an occipital expansion (170 ml; mean age: 6 years) and control subjects (153 ml; mean age: 5.4 years) (**table 1** and **table 2**).

Table 1: Cerebellar volume, posterior fossa volume and their ratio in relation to the position of the cerebellar tonsils, for not-operated craniosynostosis patients, operated craniosynostosis patients, and controls.

	Not-operated	Operated	Controls
MR imaging	n= 28	n= 85	n= 34
Gender (Male: Female)	14:14	42:43	16:18
Mean age in years (SD), range	4.0 (4.8), 0-14	8.0 (3.8), 1-18	5.4 (4.3), 0-15
[median]	[0.6]	[7.0]	[5.2]
Cranial vault surgery			
Fronto-orbital advancement	-	n= 56	-
Occipital expansion	-	n= 29	-
Cerebrospinal fluid diversion	-	n= 4	-
Normal cerebellar position	n= 20	n= 44	n= 34
Mean age (SD), range	2.4 (3.8), 0-12	7.6 (3.9), 1-18	5.4 (4.3)
Mean CV in ml (SD)	83 (28)	132 (23)	114 (34)
Mean PFV in ml (SD)	113 (37)	182 (33)	153 (44)
Mean ratio (SD)	0.73 (0.04)	0.73 (0.04)	0.75 (0.03)
Tonsillar herniation	n= 5	n= 26	-
Mean age (SD), range	9.8 (4.3), 3-14	8.6 (3.3)	-
Mean CV in ml (SD)	132 (14)	133 (13)	-
Mean PFV in ml (SD)	176 (24)	177 (19)	-
Mean ratio (SD)	0.75 (0.03)	0.75 (0.03)	-
Chiari I malformation	n= 3	n= 15	-
Mean age (SD), range	5.6 (4.7), 0-10	8.1 (4.2)	-
Mean CV in ml (SD)	112 (38)	134 (16)	-
Mean PFV in ml (SD)	142 (46)	173 (21)	-
Mean ratio (SD)	0.78 (0.02)	0.77 (0.03)	-

The not-operated craniosynostosis group included: 3 Apert, 8 Crouzon-Pfeiffer, 4 Muenke, 4 Saethre-Chotzen patients and 9 complex craniosynostosis patients. Operated craniosynostosis group included: 16 Apert, 23 Crouzon-Pfeiffer, 11 Muenke, 14 Saethre-Chotzen syndromes and 21 complex craniosynostosis patients. CV: cerebellar volume; PFV: posterioir fossa volume.

Table 2: Statistics showing which factors are associated with cerebellar volume, posterior fossa volume and volume ratio.

Cerebellar volume		***p*-value**
Age		<0.001*
Gender		0.009*
Syndrome	Apert	0.13
	Crouzon	0.57
	Muenke	0.02*
	Saethre-Chotzen	0.22
	Complex	0.54
Surgery	Cranial vault expansion	0.41
	-Fronto-orbital advancement	0.77
	-Occipital expansion	0.33
Tonsils	Normal cerebellum	0.86
	Tonsillar herniation	0.98
	Chiari I malformation	0.85
Posterior fossa volume		
Age		<0.001*
Gender		<0.001*
Syndrome	Apert	0.008*
	Crouzon	0.36
	Muenke	0.008*
	Saethre-Chotzen	0.37
	Complex	0.53
Surgery	Cranial vault expansion	0.25
	-Fronto-orbital advancement	0.41
	-Occipital expansion	0.30
Tonsils	Normal cerebellum	0.36
	Tonsillar herniation	0.98
	Chiari I malformation	0.53
Volume ratio		
Age		0.01*
Gender		0.09
Syndrome	Apert	0.003*
	Crouzon	0.31
	Muenke	0.46
	Saethre-Chotzen	0.27
	Complex	0.99
Surgery	Cranial vault expansion	0.55
	-Fronto-orbital advancement	0.15
	-Occipital expansion	0.90
Tonsils	Normal cerebellum	0.03*
	Tonsillar herniation	0.97
	Chiari I malformation	0.008*

Comparisons are made with the control group. The effect of syndrome, surgery and tonsils were tested in separate statistical models. The effect of age and gender was tested in the same model as for the effect of syndrome. All comparisons were corrected for age and gender. * Indicates significant association.

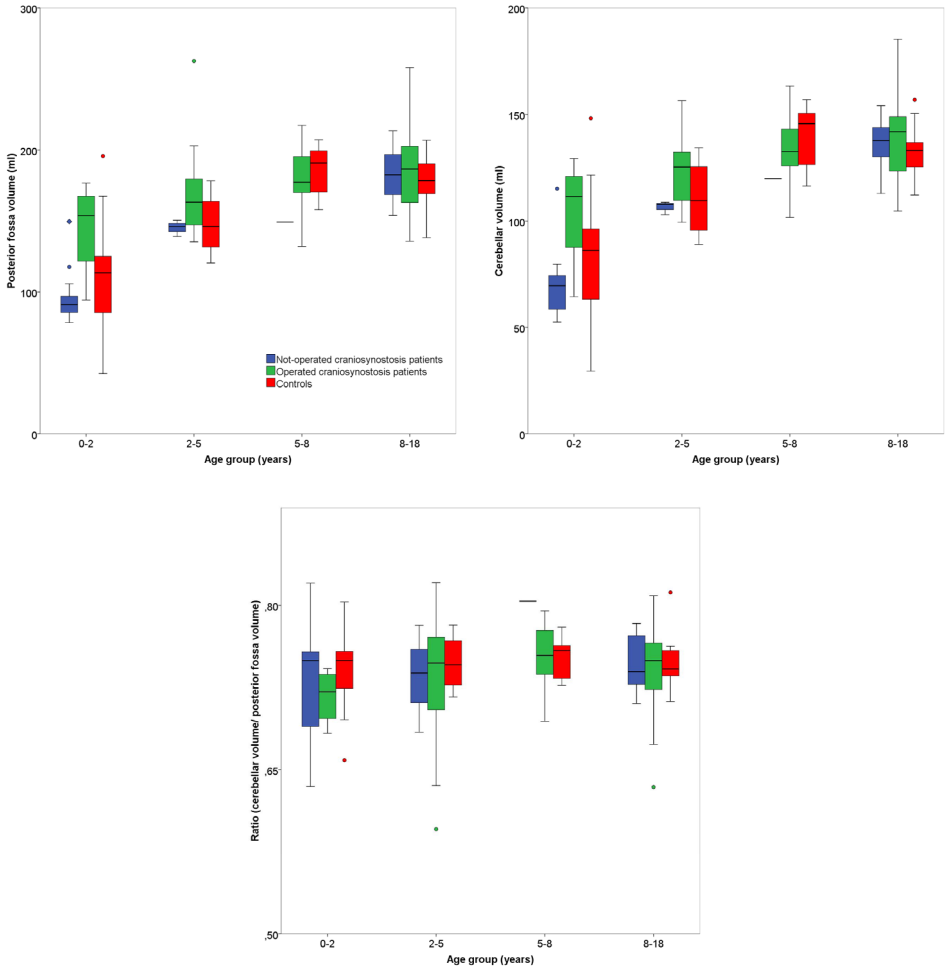

Figure 2. Boxplots showing: posterior fossa volume (a), cerebellar volume (b), and volume ratio (c) of not-operated craniosynostosis patients, operated craniosynostosis patients, and controls. Data is shown per age group, including 0-2 years, 2-5 years, 5-8 years, and 8-18 years. Colored dots represent outliers.

Craniosynostosis syndromes

Across the age range 0–18 years, Muenke patients had a larger CV and PFV, while Apert patients only had a larger PFV than control subjects. An MCM was most often seen in patients with Apert syndrome, who consequently showed a significantly lower CV/PFV ratio than control subjects. The volumetric measurements and presence of TH, CMI and MCM for each diagnosis and the control group are illustrated in **table 3**.

Table 3: Cerebellum and posterior fossa details per craniosynostosis syndrome and control group.

	Apert	Crouzon-Pfeiffer	Muenke	Saethre-Chotzen	Complex	Controls
MR imaging	n= 19	n = 31	n= 16	n= 18	n= 29	n= 34
Gender (Male, Female)	11M: 8F	14M: 17F	5M: 11F	9M: 9F	17M: 12F	16M: 18F
Mean age in years (SD)	7.4 (5.4)	8.3 (4.0)	6.8 (3.9)	6.9 (4.1)	5.6 (4.2)	5.4 (4.3)
[median]	[7.0]	[9.0]	[6.3]	[7.4]	[4.8]	[5.2]
Mean CV in ml (SD)	130 (35)	128 (19)	135 (31)	116 (27)	112 (29)	114 (34)
Mean PFV in ml (SD)	181 (47)	169 (26)	183 (46)	158 (36)	150 (38)	153 (44)
Mean ratio (SD)	0.72 (0.05)	0.76 (0.03)	0.74 (0.05)	0.74 (0.03)	0.75 (0.03)	0.75 (0.03)
Chiari I Malformation	10.5% (2)	22.6% (7)	6.7% (1)	5.6% (1)	23.3% (7)	-
Tonsillar Herniation	15.8% (3)	38.7% (12)	40.0% (6)	11.1% (2)	26.7% (8)	-
Mega Cisterna Magna	31.6% (6)	9.7% (2)	12.5% (2)	16.7% (3)	0% (0)	-

Volumetric measures, and presence of tonsillar herniation, Chiari I malformation and mega cysterna magna for each diagnosis and the control group. For Chiari I malformation, tonsillar herniation and mega cysterna magna, absolute numbers between parentheses.

Volumes in craniosynostosis patients with CMI versus craniosynostosis patients without CMI

TH and CMI were mainly observed after the age of 1.5 years (**figure 3**), and detected in both not-operated and operated craniosynostosis patients (**table 1**). Moreover, they were mostly seen in patients with Crouzon–Pfeiffer syndrome and complex craniosynostosis.

CV and PFV were not related to the position of the cerebellar tonsils; all groups, including craniosynostosis patients with a normal cerebellar position, TH and CMI and the control subjects, showed similar volumes to each other (**figure 3**). CV/PFV ratios were similar for not-operated and operated craniosynostosis patients, matched for the position of the cerebellar tonsils (**table 1**). However, patients with CMI had a significantly higher CV/PFV ratio than control subjects (0.77 vs. 0.75, $p = 0.008$).

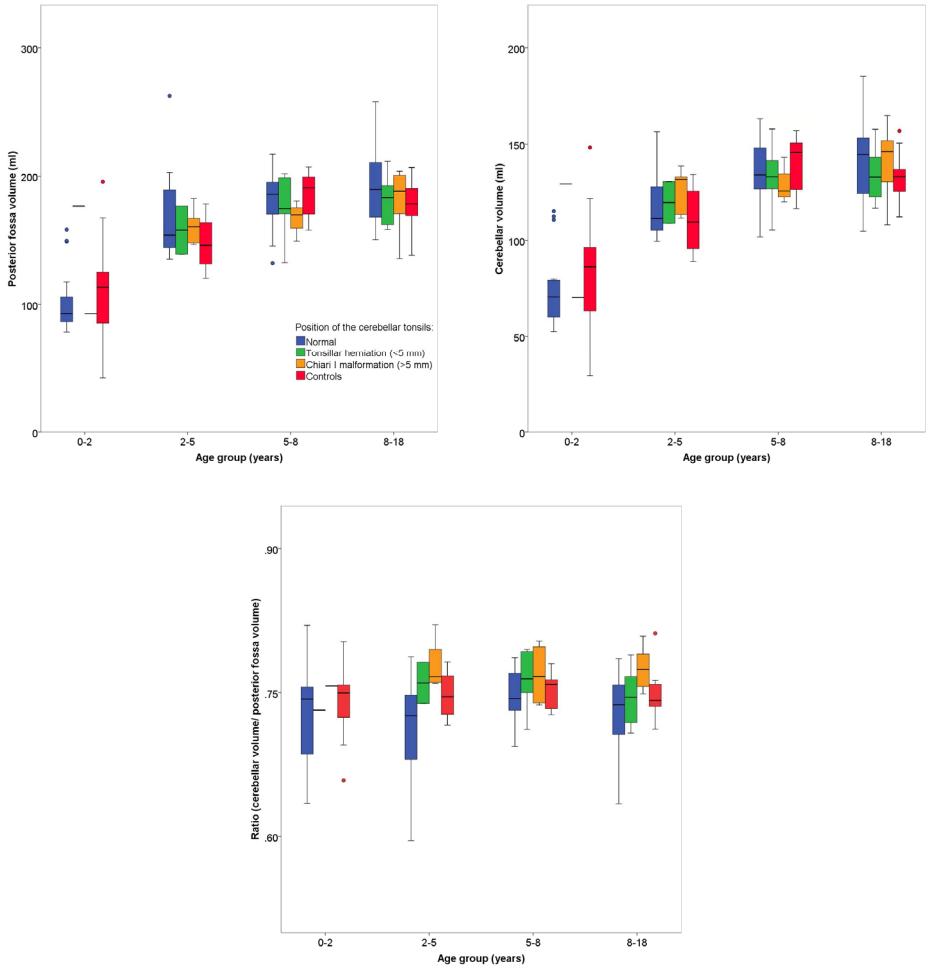

Figure 3. Boxplots showing: posterior fossa volume (a), cerebellar volume (b), and volume ratio (c) of craniosynostosis patients with a normal cerebellar position, those with a tonsillar herniation, those with Chiari I malformation, and control subjects. Data is shown per age group, including 0-2 years, 2-5 years, 5-8 years, and 8-18 years. Colored dots represent outliers.

DISCUSSION

The first hypothesis, stating that PFV is smaller and the CV/PFV ratio is higher in craniosynostosis patients compared with control subjects, was proven wrong. The present study showed that CV, PFV, and their ratio in not-operated craniosynostosis patients, operated craniosynostosis patients and control subjects are similar, and show matching growth curves. This means that these volumetric data play a minor role in causing CMI.

Volumetric studies in craniosynostosis patients are rare and focussed more on the anterior part of the skull than on the posterior part (Carinci et al., 1994, Posnick et al., 1993 and Posnick et al., 1994). Studies that included the cerebellum and PF consisted of cephalometric analyses of radiographs or CT scans. Those few studies that have focussed on the PF, presented a smaller anterior-posterior diameter in bicoronal craniosynostosis patients, suggesting its volume to be smaller (Richtsmeier et al., 1991 and Sgouros et al., 1999). However, since the skull is deformed in craniosynostosis patients, the brain and cerebellum are deformed as a consequence. Therefore, volumes might appear different on X-ray or conventional CT or MR scans. The discrepancy between our study and previous studies is probably caused by the low number of syndromic cases included in other studies, and more importantly by the fact that we performed a more accurate volumetric assessment in 3D MR images.

We believe that the CV/PFV ratio gives more information about an overcrowded PF than the volumes on their own; a reduced PFV does not have to induce problems when it incorporates a small cerebellum. In craniosynostosis patients with CMI, the CV/PFV ratio is significantly higher compared with control subjects, suggesting that the PF is overcrowded. However, the range of CV/PFV ratios in craniosynostosis patients with CMI (0.73–0.81 (mean ± 2 SD)) falls within the range of the control group (0.69–0.81). Other processes are probably involved in causing CMI, and an increased CV/PFV ratio seems to indicate a predisposition to develop CMI.

This study has some limitations: one could argue that only not-operated patients should have been included in this study, as the surgery might have affected our volumetric measurements. For this reason we have kept the data for not-operated and operated patients separately, and no difference was detected between these groups. One argument for the inclusion of operated patients is the fact that the majority of these children will receive surgery at an early age, and despite that still present with TH or CMI. To really assess the causes of TH or CMI development, we cannot leave them out, as they represent the true clinical course that syndromic craniosynostosis follows. Another limitation is the lack of age- and sex-matched controls. This can be explained by the fact that control MR data is scarce, because MRI is only performed when there is a clinical indication. Of those patients who underwent MRI, we included only patients without chronic diseases, and/or any abnormalities on MRI. Furthermore, we statistically corrected for age and sex, so that data was comparable between the groups.

Patients with craniosynostosis syndromes have an increased risk for elevated ICP, and the occurrence of CMI. The clinical message of this study is that CV, PFV, and their ratio are not predictive in determining which craniosynostosis patients are more prone to developing CMI than others.

Therefore, these volumetric measurements are not required as part of their standard treatment protocol. Moreover, the cause of CMI development is more likely to be supra-tentorial. This can be supported by the findings of Spruijt et al. (Spruijt et al., 2015); they found that impaired skull growth is a significant determinant in the development of increased ICP, beyond 1 year after surgery. Furthermore, the treatment of craniosynostosis patients should focus less on the posterior fossa, but more on the skull vault itself and other contributors to the development of increased ICP, such as OSA and venous hypertension.

CONCLUSION

Craniosynostosis patients with CMI have similar CV and PFV to control subjects, but they do have a significantly higher CV/PFV ratio. Since the range of the CV/PFV ratios for craniosynostosis patients with CMI fell within the range of controls, a higher CV/PFV ratio can be regarded as a predisposing factor for the development of CMI.

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4

Diffusion tensor imaging and fiber tractography in children with craniosynostosis syndromes

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ABSTRACT

Background and purpose: Patients with craniosynostosis syndromes caused by mutations in *FGFR-2*, *FGFR-3*, and *TWIST1* genes are characterized by having prematurely fused skull sutures and skull base synchondroses, which result in a skull deformity and are accompanied by brain anomalies, including altered white matter microarchitecture. In this study, the reliability and reproducibility of DTI fiber tractography was investigated in these patients. The outcomes were compared with those of controls.

Materials and methods: DTI datasets were acquired with a 1.5T MR imaging system with 25 diffusion gradient orientations (voxel size = 1.8 × 1.8 × 3.0 mm3, b-value = 1000 s/mm2). White matter tracts studied included the following: corpus callosum, cingulate gyrus, fornix, corticospinal tracts, and medial cerebellar peduncle. Tract pathways were reconstructed with ExploreDTI in 58 surgically treated patients with craniosynostosis syndromes and 7 controls (age range, 6–18 years).

Results: Because of the brain deformity and abnormal ventricular shape and size, DTI fiber tractography was challenging to perform in patients with craniosynostosis syndromes. To provide reliable tracts, we adapted standard tracking protocols. Fractional anisotropy was equal to that in controls (0.44 versus 0.45 ± 0.02, $p = .536$), whereas mean, axial, and radial diffusivity parameters of the mean white matter were increased in patients with craniosynostosis syndromes ($p < .001$). No craniosynostosis syndrome–specific difference in DTI properties was seen for any of the fiber tracts studied in this work.

Conclusions: Performing DTI fiber tractography in patients with craniosynostosis syndromes was difficult due to partial volume effects caused by an anisotropic voxel size and deformed brain structures. Although these patients have a normal fiber organization, increased diffusivity parameters suggest abnormal microstructural tissue properties of the investigated white matter tracts.

INTRODUCTION

Craniosynostosis occurs in 1:2100–2500 neonates, of which at least 20% is caused by an identified genetic mutation. *FGFR-2* (32%), *FGFR-3* (25%), and *TWIST1* (19%) are the most commonly involved genes, responsible for Apert and Crouzon-Pfeiffer, Muenke, and Saethre-Chotzen syndromes, respectively. Patients in whom ≥2 cranial sutures have fused prematurely but for whom no responsible gene mutation has been found are referred to as having complex craniosynostosis (5.5%).[1]

Patients with complex and syndromic craniosynostosis syndromes are characterized by the premature fusion of skull sutures and skull base synchondroses, which induces an abnormal growth of the skull, skull base, and midface. Not only are bony structures involved in craniosynostosis, but brain and CSF circulation appear to be directly affected by the genetic defect as well.[2–5] Because genes responsible for craniosynostosis syndromes are expressed during early embryonic development of the head,[6] it is likely that these intrinsic factors can also induce disturbances in microstructural WM organization.[4,7]

Structural or mechanical cerebral abnormalities such as Chiari malformation type I are often reported in these patients.[8] Additionally, ventriculomegaly, hypoplasia of the corpus callosum or hippocampus, agenesis of the septum pellucidum, and even aberrations in WM are seen.[4,9–13] Patients with craniosynostosis syndromes have a 2-fold higher risk for developing intellectual disability than the normative population, while they also have more behavioral and emotional functioning problems.[14]

In this study, we investigated whether diffusion tensor imaging and fiber tractography (FT) can be used for studying WM organization in patients with craniosynostosis syndromes. This technique should give more objective and anatomically complete information about WM tracts than the subjective single ROI approach that has been used before,[7] because parameters will be defined over the total length of a particular WM tract rather than at 1 certain location in the tract. Additionally, we wanted to focus on different types of fiber tracts (commissural, projection, and association) and to study whether DTI properties differ between patients with craniosynostosis syndromes and control subjects. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) are common diffusion properties for characterizing fiber structural features and providing information about axonal tissue organization.[15–17]

We hypothesized that FA would be reduced and diffusivity properties would be increased in patients with craniosynostosis syndromes compared with controls; these changes would indicate an abnormal microstructural tissue organization.

MATERIALS AND METHODS

The medical ethics committee approved this prospective study (MEC-2014–461), performed at the Dutch Craniofacial Center, the national referral center for patients with craniosynostosis syndromes in a population of 16 million inhabitants. MR imaging data were acquired between July 2006 and

October 2013 as part of the standard clinical follow-up protocol for patients with syndromic or complex craniosynostosis.

Subjects

In this study, we included 58 patients with craniosynostosis syndromes, including Apert, Crouzon-Pfeiffer, Muenke, and Saethre-Chotzen syndromes and patients with complex craniosynostosis. The latter group included patients who had at least 2 prematurely closed skull sutures, for which a responsible gene mutation has not yet been found. The study population incorporated that of Florisson et al[7] However, the inclusion period of this study was longer; therefore, we included more patients. In this study, we added 6 patients with Apert syndrome, 2 with Crouzon-Pfeiffer syndrome, 2 with Muenke syndrome, and 5 with complex craniosynostosis. Sixty-nine patients underwent both genetic testing and MR imaging, including DTI. Patients with craniosynostosis syndromes are at risk for developing episodes of increased intracranial pressure; therefore, they routinely underwent a cranial vault expansion within the first year of life to prevent or treat increased intracranial pressure. However, they still might develop enlarged ventricles, mostly because of disturbed CSF absorption due to venous hypertension.[2] Enlarged ventricles can induce periventricular WM atrophy but also affect the shape of surrounding brain structures. Therefore, we included the frontal occipital horn ratio in our analyses to correct for ventricular size.

Only the first MR image of our patients with craniosynostosis syndromes between 6 and 18 years of age was included. In addition, we included 7 healthy control subjects within the same age range who were previously neuropsychologically tested and scanned (identical scanner and MR imaging protocol) for another study.[18] Exclusion criteria for all subjects were the following: insufficient quality of the collected DTI dataset due to incomplete scanning, motion artifacts, or inhomogeneity of the MR imaging field due to braces or metallic remains from operations. In total, we excluded 7 patients with craniosynostosis syndromes: 1 had Apert syndrome, 1 had Crouzon-Pfeiffer syndrome, 2 had Muenke syndrome, 1 had Saethre-Chotzen syndrome, and 2 had complex craniosynostosis. In addition, 1 patient with Apert and 3 with Crouzon-Pfeiffer syndrome with a ventriculoperitoneal-shunt were also excluded from the study because this may influence the specificity of the collected DTI dataset. Consequently, the final study population included 58 patients with craniosynostosis syndromes and 7 control subjects.

Image Acquisition

All MR imaging data were acquired with a 1.5T unit (General Electric Healthcare, Milwaukee, Wisconsin), including 3D T1 spoiled gradient-recalled, 3D T2 Cube, and DTI sequences. DTI was obtained by using a multirepetition single-shot echo-planar sequence with a section thickness of 3 mm without a gap. Images were obtained in 25 gradient directions with the following parameters: sensitivity, b=1000 s/mm2; TR = 15,000 ms; TE = 82.1 ms; FOV = 240 × 240 mm2; and matrix = 128 × 128, resulting in a voxel size of 1.8 × 1.8 × 3.0 mm.[7] This protocol was identical throughout the entire study period.

Data Collection

All DTI processing was performed by using ExploreDTI (http://exploredti.com/).[19] In summary, processing consisted of correction of subject motion and eddy current distortions[20] and a weighted linear least-squares estimation of the diffusion tensor with the robust extraction of kurtosis indices with linear estimation (REKINDLE) approach.[21,22] The MRI Atlas of Human White Matter of Oishi et al[23] was used as a guideline to reconstruct the fiber pathways. WM tracts for tractography included projection fibers (corticospinal tract), commissural/callosal fibers (corpus callosum, anterior commissure), association fibers (uncinate fasciculus), tracts of the limbic system (fornix, cingulate gyrus), and tracts in the brain stem (medial cerebellar peduncle).

Tractography was performed by placing ROIs on each dataset by using "OR/SEED" and "AND" operators to allow tracts to pass through, and "NOT" operators when tracts were not allowed to pass through.[24] In addition, "NOT" operators were occasionally placed in the midline to avoid crossing fibers from other bundles. Furthermore, 2 ANDs were placed to extract a certain segment of a WM tract; thereby, identical tract parts of each subject were measured. The FA threshold was set at 0.1, and the maximum angle threshold, at 45°. For all included WM tracts, ROI definitions were adjusted to established publications presenting good validity and reliability.[25,26] The adapted protocol for DTI FT was exactly the same in both control and craniosynostosis groups and is described in more detail below.

Commissural Fibers

Corpus Callosum. The genu, corpus, and splenium of the corpus callosum were measured separately; for all 3 parts, a OR/SEED was placed similarly in the midsagittal plane around the relevant part of the corpus callosum. To exclude regions of crossing fibers and partial volume effects, we set the maximum fiber length at 10 mm; thus, only the midsagittal segment of the corpus callosum was selected (**figure 1**).[27]

Projection Fibers

Corticospinal Tracts. Fiber tracts of the corticospinal tracts (**figure 2**) were generated for both sides, by placing a OR/SEED at the level of the medial cerebellar peduncle, where it was clearly separated from the pontine crossing tract and corticospinal tracts. An AND was placed at the same level, 1 additional AND at the level of the decussation of the superior cerebellar peduncle, and 1 AND around the posterior limb of the internal capsule.

Limbic System Fibers

Cingulate Gyrus. The cingulate gyrus was divided into central and hippocampal parts (**figure 3a, -b**). For the first part, a OR/SEED was placed in the coronal plane above the middle part of the corpus of the corpus callosum. Additionally, 1 AND was placed posterior to it, while another AND was placed anterior to the splenium; therefore, only the middle part of the cingulate gyrus was tracked. The hippocampal part was measured by a OR/SEED placed in the coronal plane underneath the splenium,

followed by 1 AND placed in the transverse plane just below the splenium and a second AND, over the cingulate gyrus at the temporal lobe, which was already labeled by tracking.

Fornix. With regard to FT of the fornix, a OR/SEED was placed in the transverse plane around the turquois body of the fornix located at the level of the thalamus. An AND was placed at the body of the fornix in the coronal plane and separately in the transverse plane around the left or right bundle that was labeled by tracking. By placing 2 additional ANDs, 1 around the fornix at the level of the anterior commissure and the other at the level of the temporal lobe, an identical segment of the fornix was labeled in all patients (**figure 3c**).

Tracts in the Brain Stem

Medial Cerebellar Peduncle. Fiber tracts of the medial cerebellar peduncle (**figure 4**) were tracked by placing a OR/SEED around the relevant structure in the coronal view and by placing 2 ANDs around each peduncle at the level of the pontine crossing tract and posterior from the pons.

Statistical Analysis

A linear regression analysis was performed for each dependent variable: FA, MD, AD, and RD of each WM structure, while tract volume and the frontal occipital horn ratio were added to the model as independent variables to correct for tract volume and ventricular size. Similar to findings in the study of Florisson et al,[7] age did not have a statistically significant effect on DTI parameters and was therefore excluded from our model. In total, we tested 4 diffusion properties (FA, MD, AD, and RD) and 11 WM structures (corpus callosum [genu, corpus, splenium, and total], bilateral cingulate gyrus, fornix, bilateral corticospinal tracts, medial cerebellar peduncle, and mean WM), resulting in 44 comparisons between patients with craniosynostosis syndromes and controls. A Bonferroni correction was performed, and a p-value < .001 (p-value = .05/44) was considered statistically significant. The intra- and interobserver reliability was tested by average-measures 2-way mixed intraclass correlation coefficients.

RESULTS

Subjects This study included 7 control subjects (mean age, 10.7 years; range, 7.5–15 years) and 58 patients with syndromic or complex craniosynostosis (mean age, 9.4 years; range, 6–18 years). The distribution for the different syndromes is presented in **table 1**.

Table 1: Patient characteristics

Syndrome	Apert	Crouzon-Pfeiffer	Muenke	Saethre-Chotzen	Complex	Total cranio-synostosis	Controls
Subjects #	10	16	10	9	13	58	7
Gender M: F	5:5	9:7	4:6	6:3	7:6	31:27	2:5
Mean age (years)	11.1	10.1	7.9	8.9	8.9	9.4	10.7

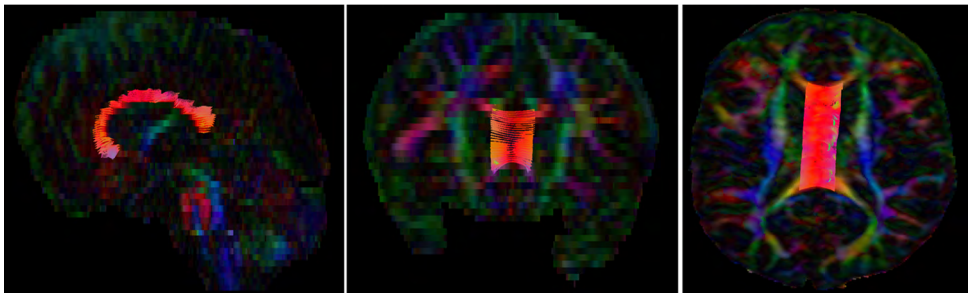

Figure 1: Mid-sagittal 10 mm of the corpus callosum in a 6 year old female Muenke patient.

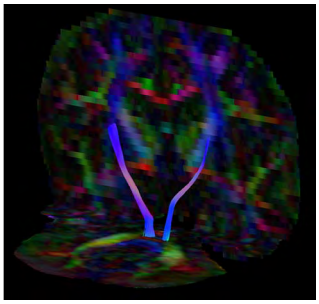

Figure 2: Mid-segment of bilateral corticospinal tracts in a 6 year old female Muenke patient.

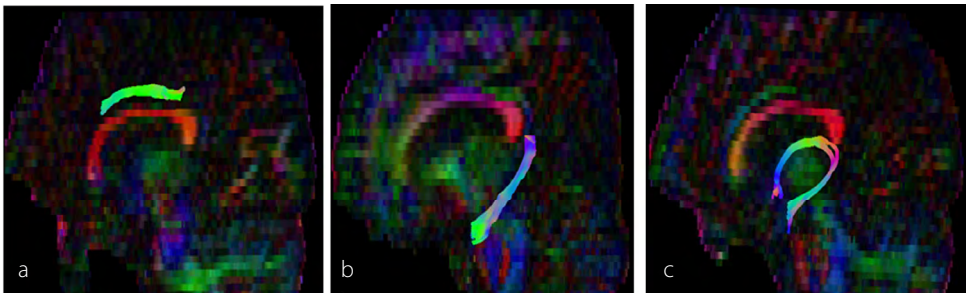

Figure 3: Central (a) and hippocampal (b) segment of the cingulum. Segmental part of the fornix (c).

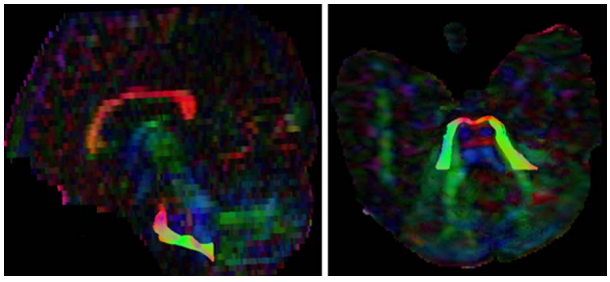

Figure 4: Segmental part of the medial cerebellar peduncle.

Measurement: Reliability and Reproducibility

DTI FT in patients with craniosynostosis syndromes was challenging because of partial volume effects due to the brain deformity and abnormal ventricular size and shape. Therefore, standard FT protocols could not be used, and measurements of all tracts needed to be adapted to track reliable and comparable fiber tracts in all subjects. Although an FA threshold of 0.2 is commonly used, an FA threshold of 0.1 made it possible to track all structures in the control group and almost all included structures in the craniosynostosis group. Consequently, by using an FA threshold of 0.1, more aberrant tracts were generated and additional AND and NOT ROIs were required to exclude aberrant fibers. Additionally, by extracting particular segments from a WM tract (by using 2 AND operators), we could measure identical WM structures and make fair comparisons between patients with craniosynostosis syndromes and control subjects. Unfortunately, the anterior commissure was not measurable in either controls or patients with craniosynostosis syndromes. Probably the anisotropic voxel size used in our protocol was too large to reconstruct such a small structure. The uncinate fasciculus showed implausible tractography in patients with craniosynostosis syndromes; therefore, both structures were excluded from the study. Furthermore, in different patients with craniosynostosis syndromes, fiber tracts could not be measured due to partial volume effects, mainly involving the cingulate gyrus and fornix (13 patients with Apert syndrome and 1 with Crouzon-Pfeiffer syndrome).

Intra- and Interobserver Reliability

Observers (B.F.M.R. and Y.L.) had 2 years of experience in DTI-FT and were supervised by A.L. with 12 years of experience in DTI and by M.H.L. with 20 years of experience in pediatric neuroradiology. Intraobserver reliability of measurements was determined by observer 1 (Y.L.), who performed all structural measurements twice in 10 subjects, 5 patients and 5 control subjects. This process resulted in an intraclass correlation coefficient of 0.93. Interobserver reliability was measured by comparing the results of observer 1 with those of a second observer (B.F.M.R.), who measured the same 10 subjects; this procedure resulted in an interclass correlation coefficient of 0.94.

WM Tracts and Ventriculomegaly

The frontal occipital horn ratio was more constant in control subjects (range, 0.31–0.37; mean, 0.35 ± 0.02) than in patients with craniosynostosis syndromes (range, 0.25–0.53; mean, 0.38 ± 0.05) and was highest in patients with Apert and Crouzon-Pfeiffer syndromes, indicating that these patients had the largest ventricles. The frontal occipital horn ratio was not significantly correlated to the FA, MD, AD, and RD of mean WM. However, it was significantly correlated to a reduced FA and increased diffusivity properties of the genu and corpus of the corpus callosum ($p < .001$), but it had no significant effect on the splenium.

WM Measures and Craniosynostosis

Mean WM DTI properties were calculated by the sum of the properties of the individual structures and divided by the number of brain structures that could be measured.

FA. The mean FA of the total group of patients with craniosynostosis syndromes showed an FA of the mean WM similar to that of control subjects (0.44 versus 0.45, $p = .536$), as well as for the separate WM tracts.

Diffusivity Properties. MD, AD, and RD of the mean WM were significantly higher in patients with craniosynostosis syndromes compared with the control group ($p < .001$). Whereas all diffusivity properties were significantly increased in the cingulate gyrus and corticospinal tracts, only AD was significantly increased in the corpus and splenium of the corpus callosum (**table 2**).

With regard to the different craniosynostosis syndromes, FA of mean WM and separate WM tracts was equal to that of control subjects (**On-line table 1**). However, MD, AD, and RD of mean WM were significantly higher in each syndrome compared with controls ($p < .001$). While the cingulate gyrus and corticospinal tracts were affected the most, diffusivity properties of the fornix and medial cerebellar peduncle were similar between each craniosynostosis group and the control group. For an overview see **On-line tables 2–4**.

DISCUSSION

Following DTI studies on ROIs, we now performed DTI FT to study WM tracts in patients with syndromic and complex craniosynostosis. The aim of the study was to investigate the reliability of this technique in an unusual patient group with skull and brain deformities and to compare DTI properties between these patients and controls. Due to the premature fusion of skull sutures, patients with craniosynostosis syndromes develop abnormal skull and brain shapes. For instance, when coronal sutures are involved, a brachycephalic skull shape will develop. Consequently, brain structures running in the anteroposterior direction will be bent or even compressed, while structures running from left to right might be stretched out by the compensatory growth of the skull and brain parallel to the premature fused skull suture. Patients with craniosynostosis syndromes often develop ventriculomegaly, which may induce periventricular WM atrophy but also changes the shape of surrounding brain structures. Particularly the corpus callosum is at risk for CSF contamination, and DTI FT has previously been described as being difficult to conduct in patients with hydrocephalus.[28] Hence, difficulties in fiber tracking is (among others) caused by partial volume effects, we discovered that DTI FT in patients with craniosynostosis syndromes is more challenging than in controls; the combination of structural brain abnormalities and anisotropic voxels gives rise to less realistic fiber tract reconstructions. Unfortunately less is known about the effects of anisotropic voxels on the outcome of the FT, though it is assumed that isotropic voxels may be more beneficial for FT.[29] The use of an anisotropic voxel size in our study might be seen as a limitation; however, FT in our control group without skull shape abnormalities did not cause any difficulties. Therefore, we believe that the deformity of WM structures itself caused by the genetic defect, prematurely fused skull sutures, and/or large CSF spaces nearby has a greater influence on fiber tract reconstructions than the anisotropic voxel size. Another limitation of our study includes the inability for total blinding of the observers; the altered brain shape in our patient population could often be visually detected during the measurements. In addition, we were able to include only

a small number of control subjects within the same age range as our patients with craniosynostosis syndromes, who were not age and sex matched. However, because the age of all subjects ranged from 6 to 18 years and the brain has matured thoroughly enough from 6 years of age to yield stable anisotropic indexes, DTI properties seem to change only slightly afterward.

Regarding DTI properties between controls and patients with craniosynostosis syndromes, we found that FA was similar between both groups, in contrast to the findings in the study of Florisson et al.[7] Our study showed lower FA in almost all structures of both controls and patients with craniosynostosis syndromes, probably caused by the different postprocessing pipeline and data-acquisition protocol. In addition, placing a single ROI may be more subjective and could cause an overestimate of the FA of the structure of interest. Furthermore, the FA is typically underestimated in areas with crossing fibers and is further affected by an anisotropic voxel size.[29,30] Comparable with results of the study of Florisson et al,[7] diffusivity properties of the mean WM in our study were significantly higher in the total group of patients with craniosynostosis syndromes than in the control group. Although diffusivity parameters per craniosynostosis syndrome were higher than those in controls as well, regarding particular WM tracts there was no clear distinction between any craniosynostosis syndrome and the control group. One could argue that this is remarkable because *fgfr* genes have a major influence on myelinization of WM tracts by involving the development of oligodendrocytes,[31] while the *twist1* gene responsible for Saethre-Chotzen syndrome is important in mesenchymal cell lineage.[32,33]

Similar to the findings in the study of Yuan et al[34] regarding DTI in infants with hydrocephalus, the frontal occipital horn ratio (ie, ventricular size) was significantly related to a lower FA and higher diffusivity properties in the genu and corpus of the corpus callosum in our study. This finding might be caused by the increased amount of water or edema in the extracellular space,[35,36] because these structures are located closest to the ventricles. We assume that the role of the central CSF spaces is at least as big as the genetic influence in causing WM alterations. As in patients with sagittal craniosynostosis in whom altered DTI parameters may underlie their neuropsychological deficits,[37] WM abnormalities of the cingulate gyrus and corpus callosum in syndromic patients with craniosynostosis syndromes may be responsible for existing attention and memory problems.14 However, neurologic assessment of our patients with craniosynostosis syndromes cannot explain diffusivity abnormalities in the corticospinal tracts, and motor deficits might rather be caused by impairment of the frontal WM.[38] Remarkably, the fornix seems to be spared by the mechanical pressure or stretching caused by ventriculomegaly and altered brain shape. By contrast, Hattori et al[13] did show reduced FA values in the fornix of patients with normal pressure hydrocephalus compared with controls.

If we take these results together, our findings demonstrate that patients with craniosynostosis syndromes have a normal fiber organization but exhibit abnormal diffusivity values that may be related to differences in microstructural tissue properties. Performing DTI FT in very young patients with craniosynostosis syndromes without an operation, in whom secondary changes of the WM microarchitecture are unlikely to have occurred yet, would be interesting, to relate WM disturbances to either genetic influences or secondary changes including enlarged ventricles.

CONCLUSIONS

DTI FT is challenging to perform in patients with craniosynostosis syndromes, most likely because of their deformed brain and abnormal ventricular size and shape. This study showed that patients with craniosynostosis syndromes have FA equal to that in control subjects, while MD, AD, and RD were significantly higher in different brain structures in these patients. Although these differences may indicate abnormalities in tissue microstructural properties, such as myelin deficiency and axonal loss, we cannot exclude confounding contributions of partial volume effects related to the enlarged CSF spaces. No craniosynostosis syndrome–specific differences in DTI properties were seen in any particular type of fiber tract.

Table 2: DTI-parameters in the total craniosynostosis group compared to the control group.

	FA			MD (mm^2/s)			AD (mm^2/s)			RD (mm^2/s)		
	Cranio-synostosis	**Controls**	***p*-value**	**Cranio-synostosis**	**Controls**	***p*-value**	**Cranio-synostosis**	**Controls**	***p*-value**	**Cranio-synostosis**	**Controls**	***p*-value**
White matter	0.44 (0.03)	0.45 (0.01)	0.536	$9.93*10^{-4}$	$8.76*10^{-4}$	**0.000***	$15.06*10^{-4}$	$13.43*10^{-4}$	**0.000***	$7.37*10^{-4}$	$6.42*10^{-4}$	**0.000***
Corpus callosum	0.55 (0.07)	0.59 (0.03)	0.521	$10.39*10^{-4}$	$9.17*10^{-4}$	0.030	$17.66*10^{-4}$	$16.14*10^{-4}$	0.013	$6.76*10^{-4}$	$5.68*10^{-4}$	0.097
-Genu	0.56 (0.06)	0.62 (0.03)	0.068	$10.20*10^{-4}$	$8.84*10^{-4}$	0.005	$17.71*10^{-4}$	$16.21*10^{-4}$	0.001	$6.54*10^{-4}$	$5.15*10^{-4}$	0.019
-Corpus	0.50 (0.07)	0.51 (0.05)	0.799	$11.42*10^{-4}$	$9.62*10^{-4}$	0.001	$18.25*10^{-4}$	$15.71*10^{-4}$	**0.000***	$8.00*10^{-4}$	$6.58*10^{-4}$	0.050
-Splenium	0.62 (0.07)	0.63 (0.04)	0.774	$9.93*10^{-4}$	$9.04*10^{-4}$	0.081	$17.84*10^{-4}$	$16.50*10^{-4}$	**0.001***	$5.98*10^{-4}$	$5.31*10^{-4}$	0.335
Cingulate gyrus left	0.34 (0.04)	0.36 (0.02)	0.148	$8.95*10^{-4}$	$7.58*10^{-4}$	**0.000***	$12.39*10^{-4}$	$10.74*10^{-4}$	**0.000***	$7.23*10^{-4}$	$5.99*10^{-4}$	**0.000***
Cingulate gyrus right	0.33 (0.04)	0.36 (0.01)	0.067	$8.97*10^{-4}$	$7.54*10^{-4}$	**0.000***	$12.27*10^{-4}$	$10.66*10^{-4}$	**0.000***	$7.32*10^{-4}$	$5.98*10^{-4}$	**0.000***
Fornix	0.28 (0.03)	0.29 (0.03)	0.789	$13.69*10^{-4}$	$11.85*10^{-4}$	0.024	$17.87*10^{-4}$	$15.62*10^{-4}$	0.021	$11.60*10^{-4}$	$9.97*10^{-4}$	0.028
Corticospinal tract left	0.58 (0.04)	0.56 (0.05)	0.294	$8.24*10^{-4}$	$7.17*10^{-4}$	**0.000***	$14.43*10^{-4}$	$12.22*10^{-4}$	**0.000***	$5.15*10^{-4}$	$4.64*10^{-4}$	0.012
Corticospinal tract right	0.58 (0.04)	0.57 (0.04)	0.955	$8.22*10^{-4}$	$7.22*10^{-4}$	**0.000***	$14.35*10^{-4}$	$12.55*10^{-4}$	**0.000***	$5.16*10^{-4}$	$4.56*10^{-4}$	**0.001***
Medial cerebellar peduncle	0.44 (0.04)	0.45 (0.06)	0.93	$11.10*10^{-4}$	$10.78*10^{-4}$	0.856	$16.41*10^{-4}$	$16.08*10^{-4}$	0.831	$8.44*10^{-4}$	$8.13*10^{-4}$	0.877

Mean values of DTI properties, with standard deviation between parentheses (SD). * indicates a significant difference (i.e. $p < 0.0011$) between the craniosynostosis group and the control group.

ONLINE TABLES

Online table 1. FA values in WM structures according to craniosynostosis syndrome.

	Apert (n=10)	*p*-value	Crouzon (n=16)	*p*-value	Muenke (n=10)	*p*-value	Saethre-Chotzen (n=9)	*p*-value	Complex (n=13)	*p*-value	Control (n=7)
White matter	0.45 (0.02)	0.420	0.44 (0.03)	0.527	0.45 (0.02)	0.661	0.45 (0.02)	0.682	0.44 (0.03)	0.527	0.45 (0.01)
Corpus callosum	0.52 (0.10)	0.387	0.53 (0.09)	0.398	0.58 (0.04)	0.656	0.58 (0.02)	0.679	0.56 (0.05)	0.427	0.59 (0.03)
-Genu	0.51 (0.08)	0.016	0.56 (0.06)	0.088	0.59 (0.05)	0.376	0.59 (0.02)	0.009	0.57 (0.04)	0.027	0.62 (0.03)
-Corpus	0.48 (0.10)	0.833	0.48 (0.06)	0.907	0.51 (0.05)	0.170	0.52 (0.05)	0.783	0.50 (0.08)	0.950	0.51 (0.05)
-Splenium	0.57 (0.14)	0.543	0.60 (0.04)	0.434	0.65 (0.04)	0.520	0.64 (0.04)	0.719	0.62 (0.04)	0.720	0.63 (0.04)
Cingulate gyrus left	0.32 (0.04)	0.014	0.35 (0.04)	0.180	0.32 (0.03)	0.012	0.36 (0.03)	0.684	0.35 (0.05)	0.700	0.36 (0.02)
Cingulate gyrus right	0.31 (0.05)	0.016	0.34 (0.04)	0.121	0.31 (0.03)	0.064	0.34 (0.01)	0.036	0.33 (0.05)	0.163	0.36 (0.01)
Fornix	0.30 (0.03)	0.197	0.27 (0.02)	0.412	0.28 (0.05)	0.926	0.29 (0.02)	0.786	0.28 (0.02)	0.457	0.29 (0.03)
Corticospinal tract left	0.58 (0.04)	0.530	0.58 (0.05)	0.716	0.59 (0.04)	0.065	0.59 (0.04)	0.282	0.57 (0.05)	0.478	0.56 (0.05)
Corticospinal tract right	0.60 (0.03)	0.718	0.57 (0.04)	0.710	0.59 (0.03)	0.328	0.58 (0.03)	0.781	0.56 (0.05)	0.581	0.57 (0.04)
Medial cerebellar peduncle	0.44 (0.04)	0.999	0.42 (0.05)	0.890	0.44 (0.04)	0.513	0.44 (0.05)	0.856	0.44 (0.05)	0.712	0.45 (0.06)

Mean FA with standard deviation between parentheses. There were no significant differences in FA between individual craniosynostosis groups and the control group.

Online table 2. MD (mm^2/s) in WM structures according to craniosynostosis syndrome.

	Apert (n=10)	*p*-value	Crouzon (n=16)	*p*-value	Muenke (n=10)	*p*-value	Saethre-Chotzen (n=9)	*p*-value	Complex (n=13)	*p*-value	Controls (n=7)
White matter	$9.94*10^{-4}$	**0.000***	$9.94*10^{-4}$	**0.000***	$9.88*10^{-4}$	**0.000***	$9.90*10^{-4}$	**0.000***	$9.98*10^{-4}$	**0.000***	$8.76*10^{-4}$
Corpus callosum	$11.00*10^{-4}$	0.089	$10.19*10^{-4}$	0.116	$10.19*10^{-4}$	0.005	$10.30*10^{-4}$	**0.000***	$10.43*10^{-4}$	0.002	$9.17*10^{-4}$
-Genu	10.76*10-4	0.223	10.48*10-4	0.020	9.77*10-4	0.079	$9.73*10^{-4}$	0.002	$10.14*10^{-4}$	0.002	$8.84*10^{-4}$
-Corpus	11.59*10-4	0.127	11.63*10-4	0.002	11.21*10-4	0.002	$11.31*10^{-4}$	0.005	$11.28*10^{-4}$	0.004	$9.62*10^{-4}$
-Splenium	10.66*10-4	0.078	9.83*10-4	0.008	9.57*10-4	0.144	$9.86*10^{-4}$	0.002	$9.88*10^{-4}$	0.012	$9.04*10^{-4}$
Cingulate gyrus left	$8.97*10^{-4}$	**0.000***	$8.96*10^{-4}$	**0.000***	$9.039*10^{-4}$	**0.000***	$8.88*10^{-4}$	**0.000***	$8.91*10^{-4}$	**0.000***	$7.58*10^{-4}$
Cingulate gyrus right	$9.09*10^{-4}$	0.003	$8.81*10^{-4}$	0.005	$9.27*10^{-4}$	**0.000***	$8.95*10^{-4}$	**0.000***	$8.91*10^{-4}$	**0.000***	$7.54*10^{-4}$
Fornix	$13.30*10^{-4}$	0.084	$14.05*10^{-4}$	0.114	$12.95*10^{-4}$	0.106	$13.96*10^{-4}$	0.007	$13.91*10^{-4}$	0.002	$11.85*10^{-4}$
Corticospinal tract left	$8.31*10^{-4}$	**0.000***	$8.16*10^{-4}$	**0.000***	$8.30*10^{-4}$	**0.000***	$8.24*10^{-4}$	**0.000***	$8.25*10^{-4}$	**0.000***	$7.17*10^{-4}$
Corticospinal tract right	$8.15*10^{-4}$	**0.000***	$8.12*10^{-4}$	**0.000***	$8.26*10^{-4}$	**0.000***	$8.38*10^{-4}$	**0.000***	$8.29*10^{-4}$	**0.000***	$7.22*10^{-4}$
Medial cerebellar peduncle	$10.89*10^{-4}$	0.886	$11.61*10^{-4}$	0.333	$11.12*10^{-4}$	0.048	$10.24*10^{-4}$	0.828	$11.32*10^{-4}$	0.944	$10.78*10^{-4}$

* Shows significant differences ($p<0.0011$) in MD between craniosynostosis patients and control group (last column).

Online table 3. AD (mm^2/s) in WM structures according to craniosynostosis syndrome.

	Apert (n=10)	*p*-value	Crouzon (n=16)	*p*-value	Muenke (n=10)	*p*-value	Saethre-Chotzen (n=9)	*p*-value	Complex (n=13)	*p*-value	Controls (n=7)
White matter	$15.10*10^{-4}$	**0.000***	$14.98*10^{-4}$	**0.000***	$15.08*10^{-4}$	**0.000***	$15.13*10^{-4}$	**0.000***	$15.08*10^{-4}$	**0.000***	$13.43*10^{-4}$
Corpus callosum	$17.82*10^{-4}$	0.005	$17.16*10^{-4}$	0.302	$17.80*10^{-4}$	**0.000***	$18.01*10^{-4}$	**0.000***	$17.80*10^{-4}$	**0.000***	$16.14*10^{-4}$
-Genu	$17.43*10^{-4}$	0.802	$17.90*10^{-4}$	0.004	$17.23*10^{-4}$	0.006	$17.17*10^{-4}$	0.010	$17.56*10^{-4}$	**0.000***	$16.21*10^{-4}$
-Corpus	$18.02*10^{-4}$	0.008	$18.37*10^{-4}$	**0.000***	$18.27*10^{-4}$	**0.000***	$18.53*10^{-4}$	**0.000***	$18.06*10^{-4}$	**0.000***	$15.71*10^{-4}$
-Splenium	$18.00*10^{-4}$	0.004	$17.49*10^{-4}$	0.027	$17.90*10^{-4}$	0.011	$18.33*10^{-4}$	**0.000***	$17.78*10^{-4}$	**0.000***	$16.50*10^{-4}$
Cingulate gyrus left	$12.17*10^{-4}$	**0.000***	$12.46*10^{-4}$	**0.000***	$12.26*10^{-4}$	**0.000***	$12.50*10^{-4}$	**0.000***	$12.47*10^{-4}$	**0.000***	$10.74*10^{-4}$
Cingulate gyrus right	$12.22*10^{-4}$	0.009	$12.15*10^{-4}$	0.011	$12.46*10^{-4}$	0.004	$12.43*10^{-4}$	**0.000***	$12.19*10^{-4}$	**0.000***	$10.66*10^{-4}$
Fornix	$17.62*10^{-4}$	0.044	$18.14*10^{-4}$	0.119	$16.99*10^{-4}$	0.116	$18.29*10^{-4}$	0.004	$18.09*10^{-4}$	0.003	$15.62*10^{-4}$
Corticospinal tract left	$14.56*10^{-4}$	**0.000***	$14.23*10^{-4}$	**0.000***	$14.69*10^{-4}$	**0.000***	$14.59*10^{-4}$	**0.000***	$14.30*10^{-4}$	**0.000***	$12.22*10^{-4}$
Corticospinal tract right	$14.47*10^{-4}$	**0.000***	$14.07*10^{-4}$	**0.000***	$14.61*10^{-4}$	**0.000***	$14.69*10^{-4}$	**0.000***	$14.21*10^{-4}$	**0.000***	$12.55*10^{-4}$
Medial cerebellar peduncle	$16.28*10^{-4}$	0.918	$16.87*10^{-4}$	0.285	$16.53*10^{-4}$	0.034	$15.34*10^{-4}$	0.748	$16.51*10^{-4}$	0.865	$16.08*10^{-4}$

* Shows significant differences ($p<0.0011$) in AD between craniosynostosis patients and control group (last column).

Online table 4. RD (mm^2/s) in WM structures according to craniosynostosis syndrome.

	Apert (n=10)	*p*-value	Crouzon (n=16)	*p*-value	Muenke (n=10)	*p*-value	Saethre-Chotzen (n=9)	*p*-value	Complex (n=13)	*p*-value	Controls (n=7)
White matter	$7.36*10^{-4}$	**0.000***	$7.42*10^{-4}$	**0.001***	$7.28*10^{-4}$	**0.000***	$7.29*10^{-4}$	**0.000***	$7.42*10^{-4}$	**0.000***	$6.42*10^{-4}$
Corpus callosum	$7.59*10^{-4}$	0.182	$6.70*10^{-4}$	0.057	$6.38*10^{-4}$	0.191	$6.45*10^{-4}$	0.007	$6.75*10^{-4}$	0.028	$5.68*10^{-4}$
-Genu	$7.42*10^{-4}$	0.174	$6.77*10^{-4}$	0.054	$6.04*10^{-4}$	0.267	$6.01*10^{-4}$	0.002	$6.43*10^{-4}$	0.006	$5.15*10^{-4}$
-Corpus	$8.38*10^{-4}$	0.300	$8.26*10^{-4}$	0.041	$7.69*10^{-4}$	0.088	$7.70*10^{-4}$	0.059	$7.89*10^{-4}$	0.067	$6.58*10^{-4}$
-Splenium	$6.99*10^{-4}$	0.160	$6.01*10^{-4}$	0.042	$5.40*10^{-4}$	0.949	$5.63*10^{-4}$	0.398	$5.93*10^{-4}$	0.151	$5.31*10^{-4}$
Cingulate gyrus left	$7.37*10^{-4}$	**0.000***	$7.21*10^{-4}$	**0.000***	$7.43*10^{-4}$	**0.000***	$7.07*10^{-4}$	**0.000***	$7.13*10^{-4}$	**0.000***	$5.99*10^{-4}$
Cingulate gyrus right	$7.52*10^{-4}$	0.002	$7.14*10^{-4}$	0.005	$7.68*10^{-4}$	**0.000***	$7.21*10^{-4}$	**0.000***	$7.27*10^{-4}$	**0.000***	$5.98*10^{-4}$
Fornix	$11.14*10^{-4}$	0.136	$12.01*10^{-4}$	0.115	$10.93*10^{-4}$	0.102	$11.79*10^{-4}$	0.011	$11.82*10^{-4}$	0.003	$9.97*10^{-4}$
Corticospinal tract left	$5.19*10^{-4}$	0.024	$5.12*10^{-4}$	0.057	$5.10*10^{-4}$	0.273	$5.07*10^{-4}$	0.021	$5.22*10^{-4}$	0.033	$4.64*10^{-4}$
Corticospinal tract right	$4.99*10^{-4}$	0.017	$5.14*10^{-4}$	0.015	$5.08*10^{-4}$	0.077	$5.23*10^{-4}$	0.015	$5.33*10^{-4}$	0.012	$4.56*10^{-4}$
Medial cerebellar peduncle	$8.20*10^{-4}$	0.875	$8.98*10^{-4}$	0.387	$8.42*10^{-4}$	0.075	$7.69*10^{-4}$	0.880	$8.44*10^{-4}$	0.990	$8.13*10^{-4}$

* Shows significant differences ($p<0.0011$) in RD between craniosynostosis patients and control group (last column).

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5a

Foramen magnum size and involvement of its intra-occipital synchondroses in Crouzon syndrome

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ABSTRACT

Background: Cranial sutures and synchondroses tend to close prematurely in patients with Crouzon syndrome. This influences their skull vault and skull base development and may involve in common disturbances such as increased intracranial pressure and cerebellar tonsillar herniation. The authors' hypothesis was that Crouzon patients have a smaller foramen magnum than controls because of premature fusion of the intraoccipital synchondroses, putting them at risk for cerebellar tonsillar herniation. Therefore, foramen magnum size and time of intraoccipital synchondroses closure were evaluated and were related to the presence and degree of cerebellar tonsillar herniation.

Methods: The foramen magnum surface area and anteroposterior diameter were measured on three-dimensional computed tomographic scans of 27 Crouzon patients and 27 age-matched controls. Scans had a slice-thickness between 0.75 and 1.25 mm and were aligned in a three-dimensional reformatting platform. The t-test was used to study size differences. Synchondroses were graded as described by Madeline and Elster and studied with ordinal logistic regression analysis.

Results: Crouzon patients had a smaller foramen magnum surface area (602 mm2 versus 767 mm2, $p < 0.001$) and anteroposterior diameter (31 mm versus 35 mm, $p < 0.001$) compared with controls. Differences stayed constant over time. Intraoccipital synchondroses closed 3 to 9 months earlier in Crouzon patients than in controls ($p < 0.05$).

Conclusions: Since intraoccipital synchondroses close earlier in Crouzon patients, from early life on their foramen magnum is smaller compared with controls. Within Crouzon patients, the presence of cerebellar tonsillar herniation could not be related to foramen magnum size.

INTRODUCTION

Crouzon syndrome is most commonly caused by mutations of the fibroblast growth factor receptor 2 (FGFR2) gene, with craniosynostosis and exorbitism being common phenotypic features.[1,2] Patients are particularly at risk for developing intracranial problems such as ventriculomegaly, venous hypertension, disturbed cerebrospinal fluid outflow, and cerebellar tonsillar herniation.[3–6] A cranial vault expansion is indicated in nearly all Crouzon patients to prevent or treat increased intracranial pressure, although precise interactions with and contribution of previously mentioned intracranial problems to increased intracranial pressure remain unclarified. Besides prematurely closed calvarial sutures, synchondroses of the skull base might be involved also in these patients.[7–10] The most important synchondroses of the foramen magnum are the intraoccipital synchondroses. These four cartilaginous joints allow the foramen magnum to grow in the first period of life. This growth is necessary for the development of a normal size and shape of the foramen magnum and to provide a sufficient passage of cerebrospinal fluid between the cranial cavity and the spinal sac.[11,12]

Studies have shown that the posterior and anterior intraoccipital synchondroses are completely fused in early childhood.[13,14] More specific are the studies by Madeline and Elster and the study by Mann et al., in which the authors describe that posterior intraoccipital synchondroses will be completely fused between 3 and 6 years of age and anterior intraoccipital synchondroses will be totally closed between 7 and 10 years of age.[15–17] Growth disturbances at the level of the foramen magnum can influence the passage of cerebrospinal fluid and therefore play a role in the development of ventriculomegaly, increased intracranial pressure, and cerebellar tonsillar herniation.[18–20]

Our hypothesis is that the foramen magnum in patients with Crouzon syndrome is smaller than in controls because of premature fusion of the intraoccipital synchondroses, and this might increase the risk of cerebellar tonsillar herniation. In this study, we therefore investigated (1) surface area and anteroposterior diameter of the foramen magnum; (2) timing of closure of posterior and anterior intraoccipital synchondroses separately; and (3) presence and degree of cerebellar tonsillar herniation in Crouzon patients and in agematched controls.

PATIENTS AND METHODS

All genetically confirmed Crouzon patients (n = 29) between the ages of 0 and 10 years who had undergone three-dimensional computed tomographic scanning from November of 2004 to December of 2011 at the Dutch craniofacial center were included. The exclusion criteria were the insertion of a shunt (n = 2) and any operation involving the foramen magnum (n = 0). Only the first available three-dimensional computed tomographic scan was used for statistical analysis. In 14 Crouzon patients (52 percent), a cranial vault expansion was performed before their computed tomographic scans were obtained, of which 11 (41 percent) consisted of a frontoorbital advancement, two (7 percent) consisted of an occipital cranial vault expansion, and one (4 percent) consisted of a frontobiparietal remodulation. Because cerebellar tonsillar herniation in Crouzon patients generally develops between

the ages of 2 and 4 years irrespective of early vault expansion, computed tomographic scans obtained before and after surgery were included. A possible effect of vault surgery was examined by comparing the measurements taken on the presurgical and postsurgical scans. Age-matched controls were enrolled from the pediatric radiology database; trauma patients without a medical history of bone maturation disturbances who underwent three-dimensional computed tomographic scanning that did not show any skull or skull base deformities were included in the study.

Size of the Foramen Magnum

The area and anteroposterior diameter of the foramen magnum were measured in a threedimensional reformatting platform (AquariusNET; TeraRecon, Inc., Melbourne, Victoria, Australia), where images were aligned in sagittal and coronal planes to optimize the area measurement made in the transverse plane, and aligned in coronal and transverse planes to measure anteroposterior diameter in the sagittal plane; thus, the foramen magnum of all patients was measured in the same manner **figure 1**). All measurements were performed twice by the same investigator (B.F.M.R.) at separate occasions, and the mean surface area and mean anteroposterior diameter were used for analysis.

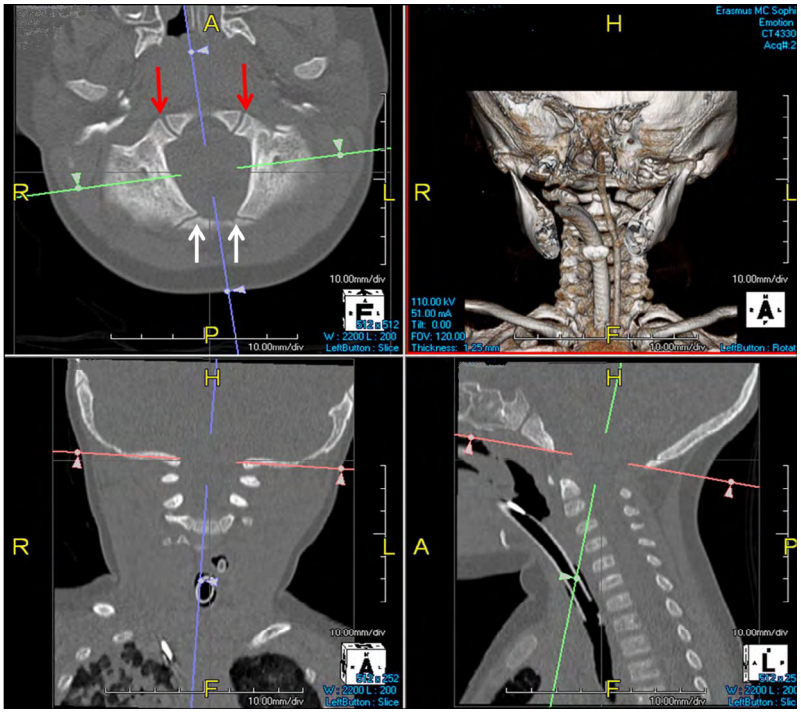

Figure 1: All measurements were performed using a multiplane platform (AquariusNET). These four photographs show the alignment in a 1-year-old control subject with open posterior intraoccipital synchondroses (*white arrows*) and open anterior intraoccipital synchondroses (*red arrows*).

Grade and Timing of Closure of Posterior and Anterior Intraoccipital Synchondroses

The anterior and posterior intraoccipital synchondroses were studied in the same three-dimensional computed tomographic scans of Crouzon patients and age-matched controls and divided into five closing grades according to the Madeline and Elster system[16] (**Table 1**).

Cerebellar Tonsillar Herniation

The presence and degree of cerebellar tonsillar herniation was examined in midsagittal and adjacent computed tomographic slices and divided into three groups: (1) no cerebellar tonsillar herniation below the foramen magnum; (2) herniation of less than 5 mm below the foramen magnum; and (3) herniation of 5 mm and more below the foramen magnum (classic definition of Chiari type I malformation).

Imaging Data

All imaging data were acquired using a multidetector computed tomographic scanner (Siemens, Erlangen, Germany). Scan protocol parameters were set according to the required image quality. For craniosynostosis patients, almost all scans had a slice thickness of 1.25 mm (H10s kernel). In nearly all control subjects, a three-dimensional computed tomographic scan with a slice thickness of 0.75 mm (B60s or B70s kernel) was acquired. Radiation dose used was adapted to the patient size (CARE Dose; Siemens).

Statistical Analysis

Data were distributed normally and controls were age-matched; therefore, we used an independent-samples t-test to investigate size differences of the foramen magnum between controls and Crouzon patients. To study differences in closure of the intraoccipital synchondroses, we performed ordinal logistic regression analysis. Statistical significance in all tests was defined as $p < 0.05$.

RESULTS

Twenty-seven Crouzon patients (13 male patients) with a mean age of 4.5 years and 27 agematched controls (14 male) with a mean age of 4.4 years were used for analyses.

Size of the Foramen Magnum

Within Crouzon patients, there were no differences in foramen magnum size between patients who were operated on (area, 584.25 mm2; anteroposterior diameter, 31.06 mm; mean age, 2.4 years) and subjects who were not (area, 633.73 mm2; anteroposterior diameter, 32.07 mm; mean age, 6.4 years), corrected for age and sex ($p = 0.405$). Therefore, these data were pooled for the comparison between Crouzon patients and normal controls. The intraclass correlation coefficient for calculating the within-rater reliability of the measurements was 0.99.

In both Crouzon patients and control subjects, most foramen magnum growth took place within the first 4 years of life, after which it slowed considerably. However, the foramen magnum in Crouzon patients was smaller than in controls already within the first few months of life, which did not change over time (mean area, 602 mm2 versus 767 mm2, $p < 0.001$; anteroposterior diameter, 31 mm versus 35 mm, $p < 0.001$) (**figure 2**).

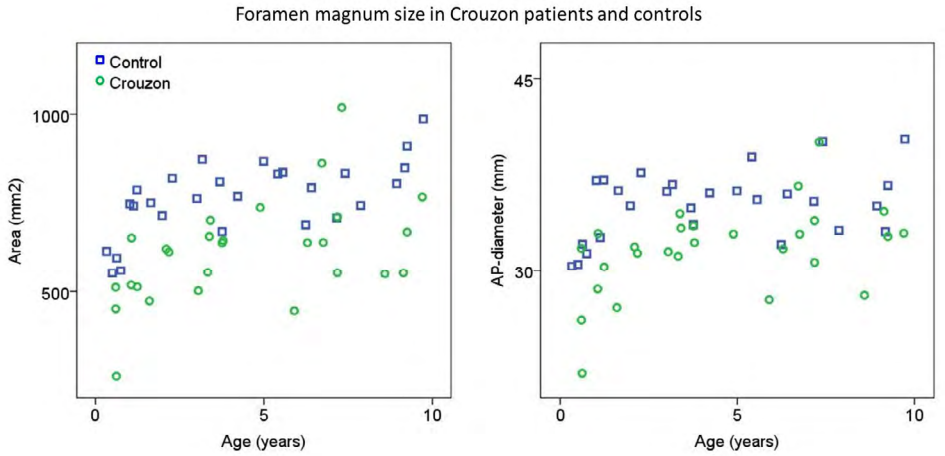

Figure 2: Size of the foramen magnum in Crouzon patients (*green circles*) and controls (*blue squares*) regarding surface area (*left*) and anteroposterior diameter (*right*). *AP*, anteroposterior.

Grade and Timing of Closure of Posterior and Anterior Intraoccipital Synchondroses

Although posterior intraoccipital synchondroses closed earlier than anterior intraoccipital synchondroses in both groups, both anterior and posterior intraoccipital synchondroses closed earlier in Crouzon patients than in controls (**figure 3**). Remarkably, posterior intraoccipital synchondroses were partially closed in Crouzon patients already within the first 2 years of life. Furthermore, posterior intraoccipital synchondroses in Crouzon patients were completely closed at a mean age of 3.3 years, whereas they closed at 4.2 years in controls and thus 9 months earlier ($p = 0.002$) (Fig. 3). In Crouzon patients, anterior intraoccipital synchondroses showed more progressive fusion than controls starting from the age of 3 to 4 years, compared with 4 to 5 years of age in the control group ($p = 0.039$).

Cerebellar Tonsillar Herniation

Four Crouzon patients (15 percent) showed a cerebellar tonsillar herniation greater than or equal to 5 mm below the foramen magnum, and eight patients (30 percent) showed a cerebellar tonsillar herniation of less than 5 mm on their scans. This means that 15 patients (56 percent) showed normal position of the cerebellar tonsils (**figure 4**).

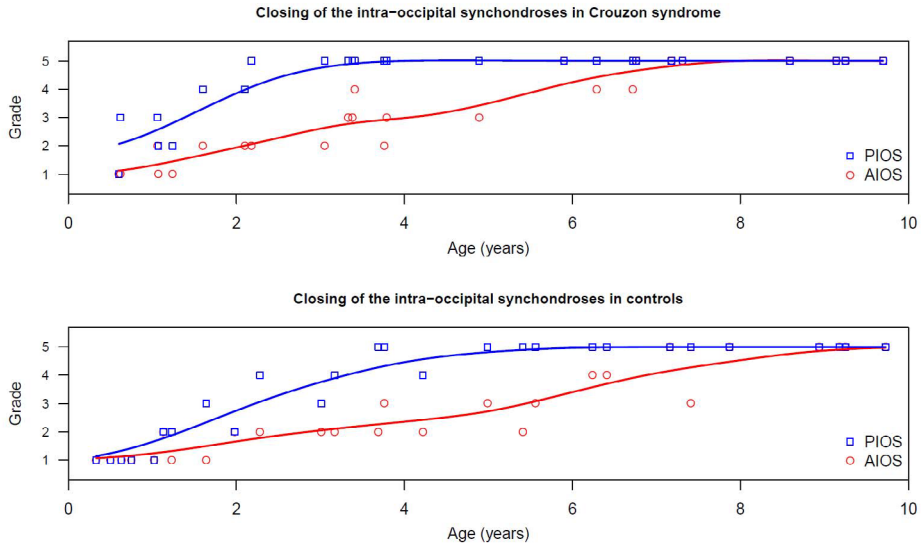

Figure 3: Closing of the intraoccipital synchondroses in Crouzon syndrome (*above*) and controls (*below*). *Red line* indicates anterior intraoccipital synchondroses (*AIOS*), *blue line* indicates posterior intraoccipital synchondroses (*PIOS*). Note that posterior intraoccipital synchondroses are already fusing in the first year of life in Crouzon patients but not in controls.

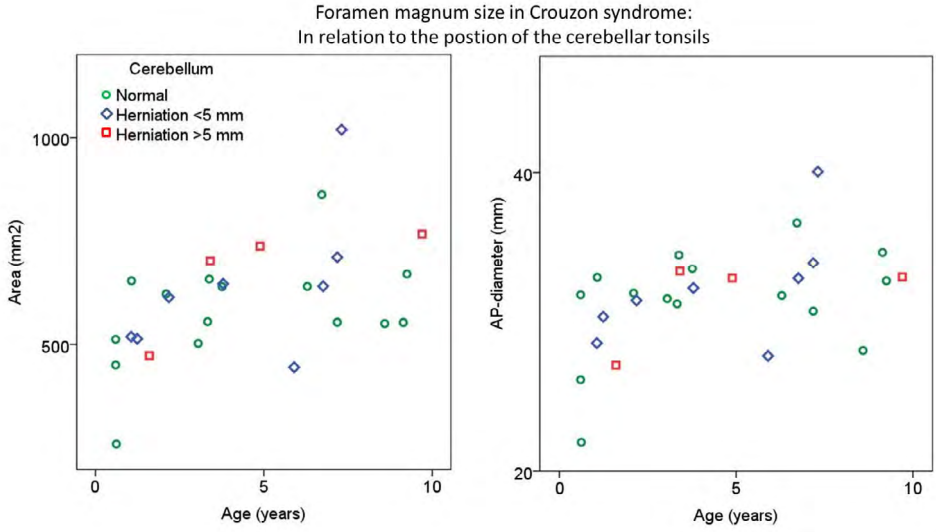

Figure 4: Foramen magnum size in Crouzon patients; patients with normal position of the cerebellar tonsils are indicated by *green circles*, those with cerebellar tonsillar herniation less than 5 mm are indicated by *blue diamonds*, and those with cerebellar tonsillar herniation greater than 5 mm are indicated by *red squares*. *AP*, anteroposterior.

5a

Foramen Magnum Size versus Cerebellar Tonsillar Herniation

Within Crouzon patients, foramen magnum size of those without cerebellar tonsillar herniation (area, 578.60 mm2; anteroposterior diameter, 31.30 mm; mean age, 4.38 years) was not different from patients with cerebellar tonsillar herniation of greater than or equal to 5 mm (area, 670.40 mm2; anteroposterior diameter, 31.56 mm; mean age, 4.90 years; $p = 0.283$) or patients for whom both degrees of herniation (<5 mm and >5 mm) were considered together (area, 609.90 mm2; anteroposterior diameter, 31.58 mm; mean age, 4.47 years; $p = 0.672$) (**figure 4**).

DISCUSSION

We found that Crouzon patients had a smaller foramen magnum size than control subjects already in early life and that this size difference stayed constant over time. It is unclear whether this difference was caused only by premature closure of the synchondroses or whether an intrinsic impairment in development plays a role as well. The latter seems likely considering the function of the *FGFR2* gene in embryogenesis. During embryogenesis, the brain and brainstem start to develop in the fourth week of gestation, followed by formation of a cartilaginous neurocranium. The cranial base is the onset of skull development, starting around the fifth week of gestation by endochondral ossification. During this process, a cartilage template has been formed and vascularized, and osteoclasts and osteoblasts are recruited to replace the cartilage scaffold with bone.[17,21] Subsequently, this basal plate will grow around the cranial end of the notochord and later will form the foramen magnum, including two pairs of cartilaginous synchondroses that accommodate its expansion.[22,23] In addition, animal studies have revealed that *FGFR2* is expressed at the neural tube and cranial base during embryogenesis.[24–27]

Several studies reported abnormalities of the skull[2,5,9,28,29] and skull base[9,13,30] in Crouzon syndrome in humans and in mice.[31–33] Thus, it is likely that *FGFR2* gene mutations have an effect on hindbrain development and give rise to abnormal growth of its surrounding bone plates (i.e., the foramen magnum). Although there are various publications concerning the cranial base in mice and humans, little has been written about the cranial base in Crouzon patients, not to mention about the intraoccipital synchondroses in these patients. In this study, foramen magnum size was measured in a multiplane environment, because it is crucial to align all scans in sagittal, coronal, and transverse planes. Particularly in Crouzon patients, who might have a deformed cranial base, it is critical to measure the foramen magnum of all patients in the same plane. Only then can reliable sizes be achieved and differences between groups studied. Although Crouzon patients did not undergo scans identical to those of control subjects, it resulted in an equal scan quality and could not have had any influence on the foramen magnum size measurements. Moreover, influence on grading anterior intraoccipital synchondroses and posterior intraoccipital synchondroses is assumed to be negligible. Here, all synchondroses were assumed to close within the normal age range described in the literature, namely, complete fusion of intraoccipital synchondroses in early childhood[13,14] or, more specifically, complete fusion of posterior intraoccipital synchondroses between 3 and 6 years and of anterior intraoccipital synchondroses between 7 and 10 years of age.[15–17] However,

these ranges are wide and therefore we studied the closure in more detail in Crouzon patients and age-matched controls. Thus, we discovered that posterior intraoccipital synchondroses and anterior intraoccipital synchondroses closed significantly earlier in Crouzon patients than in controls. Because posterior intraoccipital synchondroses in Crouzon syndrome already started to fuse before the second year of life, it seems that synchondroses are constructed prenatally, but that they show premature fusion in accordance with cranial vault sutures in Crouzon syndrome patients.[34] This means that fusion might start before birth. Because posterior intraoccipital synchondroses seem to be affected earlier than anterior intraoccipital synchondroses in Crouzon syndrome, it is likely that the shape of the foramen magnum is altered into a relatively small posterior part compared with the anterior part (**figure 5**).

A study by Coll et al.[19] regarding foramen magnum size in Crouzon syndrome indeed described the posterior sagittal diameter of the foramen magnum as being most affected. This was probably caused by early fusion of posterior intraoccipital synchondroses as well. Thus, premature fusion of the intraoccipital synchondroses in Crouzon syndrome seems to be causally related to a smaller foramen magnum. Patients with Crouzon syndrome are prone to develop cerebellar tonsillar herniation which, in our presented series, occurred in 44 percent, with a variable degree of herniation.

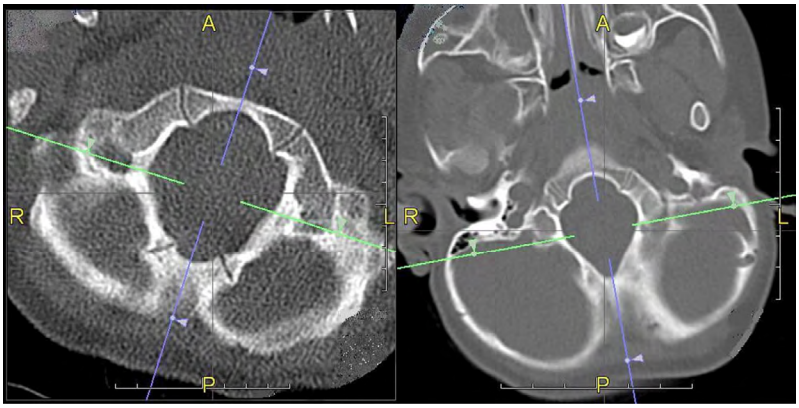

Figure 5: Foramen magnum in a 3-year-old control subject (*left*) and a 3-year-old Crouzon patient (*right*). Notice that the anterior intraoccipital synchondroses are open in both subjects, whereas posterior intraoccipital synchondroses are already closed in the Crouzon patient.

With regard to foramen magnum size and cerebellar tonsillar herniation in Crouzon syndrome, our finding is in line with the study of Coll et al., in which also an association between foramen magnum size and cerebellar tonsillar herniation could not be found. Unfortunately, there were no more studies in Crouzon syndrome available with which to compare our results. However, there were studies regarding foramen magnum and cerebellar tonsillar herniation in patients with diagnoses other than craniosynostosis. For instance, the combined computed tomographic/magnetic resonance imaging study of Furtado et al.[35] showed equal foramen magnum sizes in symptomatic pediatric cerebellar

tonsillar herniation patients compared with controls, similar to a magnetic resonance imaging study of Noudel et al. that presented equal anteroposterior diameter of the foramen magnum in symptomatic cerebellar tonsillar herniation in adults and controls.[36] However, other magnetic resonance imaging studies showed even larger foramen magnum sizes in symptomatic cerebellar tonsillar herniation patients compared with controls.[20,37,38] This implies that a smaller foramen magnum size is typical for Crouzon syndrome rather than for cerebellar tonsillar herniation patients. Therefore, it is possible that foramen magnum size is affected in other craniosynostosis syndromes as well. Based on our results, we conclude that a smaller foramen magnum by itself does not directly increase the risk for developing cerebellar tonsillar herniation. Other factors are involved in Crouzon patients, causing cerebellar tonsillar herniation to occur in approximately half of them. Possibly, a smaller foramen magnum restricts normal cerebellar tonsillar herniation outflow locally; this may initiate a vicious circle with first a rise in intracranial pressure, resulting in cerebellar tonsillar herniation, which impairs cerebrospinal fluid outflow even more. Obstructive sleep apnea has been demonstrated to cause elevated intracranial pressure; perhaps its effect on intracranial pressure is more pronounced in Crouzon patients with a smaller foramen magnum. Therefore, this study will be continued to discover which associated factors determine whether an individual Crouzon patient will develop cerebellar tonsillar herniation and elevated intracranial pressure.

CONCLUSIONS

Patients with Crouzon syndrome have a smaller foramen magnum than controls. Intraoccipital synchondroses and, in particular, posterior intraoccipital synchondroses close earlier in Crouzon patients than in controls; therefore, timing of closure of the intraoccipital synchondroses appears to be the causal factor for the reduced foramen magnum size in Crouzon syndrome. Within the group of Crouzon patients, the presence of cerebellar tonsillar herniation could not be related to foramen magnum size.

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5b

The formation of the foramen magnum and its role in developing ventriculomegaly and Chiari I malformation in children with craniosynostosis syndromes

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ABSTRACT

Object Craniosynostosis syndromes are characterized by prematurely fused skull sutures, however, less is known about skull base synchondroses. This study evaluates how foramen magnum (FM) size, and closure of its intra-occipital synchondroses (IOS) differ between patients with different craniosynostosis syndromes and control subjects; and whether this correlates to ventriculomegaly and/or Chiari malformation type I (CMI), intracranial disturbances often described in these patients.

Methods Surface area and anterior–posterior (A–P) diameter were measured in 175 3D-CT scans of 113 craniosynostosis patients, and in 53 controls (0–10 years old). Scans were aligned in a 3D multiplane-platform. The frontal and occipital horn ratio was used as an indicator of ventricular volume, and the occurrence of CMI was recorded. Synchondroses were studied in scans with a slice thickness ≤1.25 mm. A generalized linear mixed model and a repeated measures ordinal logistic regression model were used to study differences.

Results At birth, patients with craniosynostosis syndromes have a smaller FM than controls ($p < 0.05$). This is not related to the presence of CMI ($p = 0.36$). In Crouzon–Pfeiffer patients the anterior and posterior IOS fused prematurely ($p < 0.01$), and in Apert patients only the posterior IOS fused prematurely ($p = 0.028$).

Conclusion The FM is smaller in patients with craniosynostosis syndromes than in controls, and is already smaller at birth. In addition to the timing of IOS closure, other factors may influence FM size.

Keywords Chiari I malformation; Craniosynostosis syndromes; Foramen magnum; Ventriculomegaly

INTRODUCTION

Patients with craniosynostosis syndromes such as Apert, Crouzon–Pfeiffer, Muenke and Saethre–Chotzen syndrome are known to have prematurely closed skull sutures, of which the coronal sutures are most often involved. In addition to the cranial sutures, the synchondroses of the skull base also tend to be involved (Kreiborg et al., 1993, Laurita et al., 2011 and Morriss-Kay and Wilkie, 2005). The timing of fusion of the skull base synchondroses varies, and a unique pattern for each synchondrosis exists; for example, the spheno-occipital synchondrosis (SOS) normally closes during adolescence (Madeline and Elster, 1995a), while the intra-occipital synchondroses (IOS) fuse in early childhood (Furuya et al., 1984 and Madeline and Elster, 1995a). Moreover, a distinction can be made between the fusion of the posterior intra-occipital synchondroses (PIOS), which normally close between 3 and 6 years, and the anterior ones (AIOS), that close between 7 and 11 years of age (Madeline and Elster, 1995b and Mann et al., 2000).

Studies have shown that the SOS fuses prematurely in patients with Apert (McGrath et al., 2012) and Crouzon–Pfeiffer syndromes (Tahiri et al., 2013). In Crouzon–Pfeiffer patients also the intra-occipital synchondroses fuse prematurely, resulting in a smaller foramen magnum (FM) compared with age matched controls (Coll et al., 2012 and Rijken et al., 2013). It remains unknown whether FM size and the timing of the closure of its intra-occipital synchondroses are also affected in craniosynostosis syndromes other than Crouzon–Pfeiffer syndrome, and if so, whether this is related to the presence of ventriculomegaly and CMI. Therefore this study was to investigate: 1) FM size in relation to specific craniosynostosis syndromes, and 2) FM size in relation to the presence of ventriculomegaly and/or CMI. These data may give more insight into the role of the FM in developing intracranial disturbances. Besides, it may explain why certain craniosynostosis patients have a higher risk of developing these intracranial problems than others.

MATERIALS AND METHODS

Subjects All genetically tested craniosynostosis patients between the age of 0 and 10 years old, who obtained a 3D-CT scan between November 2001 and June 2013 at the Dutch Craniofacial Center were included in this study (n = 113). Syndromes included were: Apert, Crouzon–Pfeiffer, Muenke and Saethre–Chotzen syndrome. In addition, patients with two or more prematurely fused cranial sutures in which no responsible gene mutation was found (complex craniosynostosis) were included. At our center, patients are routinely scheduled for a cranial vault expansion within their first year of life, or shortly after their first presentation when older than 1 year old. Exclusion criteria were any surgery involving the FM (none) and the insertion of a shunt (n = 2; one had Apert syndrome and one had Crouzon syndrome).

Control subjects were recruited from the pediatric radiology database; 53 trauma patients without a medical history of bone maturation disturbances, who received a 3D-CT scan between January 2006 and June 2012 which did not show any skull or skull base fractures, were included in the study.

Imaging data All imaging data were acquired using a multi-detector CT scanner (Siemens, Erlangen Germany). Scan protocol parameters were set according to the required image quality. The radiation dose used was adapted to the patient size (CareDose, Siemens Healthcare) (Rijken et al., 2013). Craniosynostosis patients received at least one CT scan, while control subjects only had one CT scan, which resulted in an inclusion of 175 CT scans for the craniosynostosis patients and 53 control CT scans. Scans had a slice thickness maximum of 3 mm. Only CT scans which could be reformatted in sagittal, coronal and transverse planes using our 3D multiplane platform (AquariusNET) were included; as a result, the FM of all patients and controls could be measured in the same manner (**figure 1**).

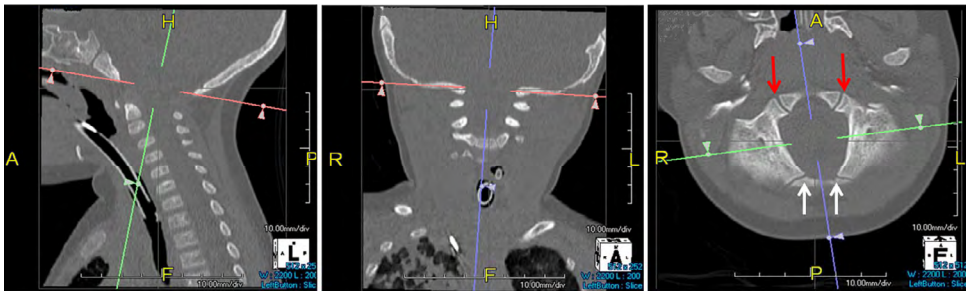

Figure 1: All measurements were performed using a multiplane platform (AquariusNET). These three photographs show the alignment in a 1-year-old control subject with open posterior intra-occipital synchondroses (white arrows) and open anterior intra-occipital synchondroses (red arrows).

Foramen magnum

Size: For the FM size assessment all CT scans of the 113 craniosynostosis patients and 53 control subjects were included. Measurement methodology was identical to that reported in our previous study on the FM in Crouzon syndrome; AquariusNET was used to align all scans, so that all measurements were performed in the same 3D orientation for all patients and controls (i.e., the surface area was measured in the transverse plane, while the A–P diameter was measured in the sagittal plane). All measurements were performed twice and the mean value was used for analysis. The intra-class correlation coefficient for calculating the within-rater reliability of the measurements was 0.99 (Rijken et al., 2013).

Intra-occipital synchondroses: For studying closure of the intra-occipital synchondroses, only CT scans with a slice thickness of ≤1.25 mm were included. Consequently, 19 craniosynostosis patients and one control subject were excluded from this analysis. The closure grade of AIOS and PIOS was studied separately with the support of a 3 scale grading system: 1 = open, 2 = partially closed, and 3 = totally closed (McGrath et al., 2012 and Tahiri et al., 2013).

Cerebellar tonsillar herniation and ventricular size

The presence and degree of cerebellar tonsillar herniation within craniosynostosis patients was assessed in the midsagittal and adjacent slices in all CT scans. The following groups were defined by the amount of tonsillar herniation: 1) No cerebellar tonsillar herniation below the level of the FM, 2) Tonsillar herniation (TH) of less than 5 mm below the FM and 3) TH of 5 mm and more below the FM (classic definition of Chiari type I malformation).

The frontal and occipital horn ratio (FOHR), known as: (frontal horn width + occipital horn width)/2 × biparietal width, was examined in the same CT scans to evaluate ventricular size (Kulkarni et al., 1999 and O'Hayon et al., 1998).

Statistical analysis

Because craniosynostosis patients had multiple CT scans and control subjects had only one CT scan, size differences as well as the relation between FM size and CMI or ventriculomegaly were studied with a generalized linear mixed model, in order to take into account the repeated measurements. Closure of the intra-occipital synchondroses was examined by a repeated measures ordinal logistic regression model. Outcomes were corrected for age and sex. Statistical significance in all tests was defined as $p < 0.05$.

RESULTS

A total of 175 CT scans from 113 craniosynostosis patients with a mean age of 2.9 years were evaluated on FM size and closure of the intra-occipital synchondroses. Of these patients, 19 had Apert syndrome, 28 had Crouzon–Pfeiffer syndrome, 18 had Muenke syndrome, 15 had Saethre–Chotzen syndrome and 33 had complex craniosynostosis. Half of the CT scans (56%) were obtained pre-operatively. The control group included 53 trauma patients with a mean age of 3.1 years.

The FOHR could not be assessed in nine of the CT scans, because of incomplete scanning of the ventricles, an inefficient filter that was used for scanning, or because of corpus callosum agenesis (n = 1, Apert syndrome). Of those nine scans, one could also not be assessed for the presence of CMI because a suboptimal filter was used.

Foramen magnum

Size: Patients with all types of syndromic and complex craniosynostosis have a significantly smaller FM surface area compared with control subjects ($p < 0.05$) (**figures 2** and **3**). The A–P diameter is also smaller in syndromic craniosynostosis patients ($p < 0.05$) (**table 1**). The FM surface area of the craniosynostosis group is already smaller within the first period of life compared with controls (below 400 mm2 and above 400 mm2 respectively). Besides the initially smaller surface area of the FM, its growth curve has a more downward deflection as well (**figure 3**). The same applies for the A–P diameter, but to a lesser extent (**figure 4**).

Table 1. Foramen magnum surface area and ap-diameter

	Apert n= 19	Crouzon n= 29	Muenke n= 18	Saethre-Chotzen n= 15	Complex n=33	Controls n=54
Mean age in years (SD)	2.8 (3.0)	5.4 (3.2)	1.6 (2.8)	1.9 (1.9)	0.9 (1.1)	3.7 (3.1)
Mean area in mm^2 (SD)	562 (197)	619 (161)	545 (137)	513 (81)	537 (127)	723 (144)
p-value	0.001*	<0.001*	0.013*	<0.001*	0.015*	
Mean AP-diameter in mm (SD), *p*-value	31 (4.3) 0.009*	31 (4.1) <0.001*	30 (3.8) 0.019*	30 (1.5) 0.003*	31 (3.8) 0.152	34 (3.5)

* $p < 0.05$ was considered significant. Mean age, area and A–P diameter per craniosynostosis group. Craniosynostosis groups were compared with control subjects (last column).

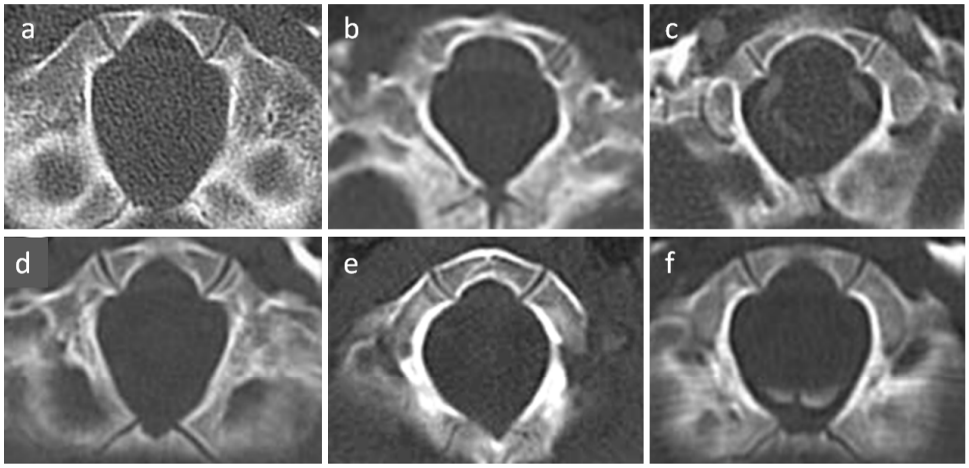

Figure 2: Foramen magnum in: a) Control subject, b) Apert patient, c) Crouzon patient, d) Muenke patient, e) Saethre-Chotzen patient, f) complex craniosynostosis patient. All subjects were at the age of approximately 1.5 years.

Intra-occipital synchondroses: Similar to controls, the PIOS closed before AIOS in all syndromic and complex craniosynostosis patients. We observed that the FM surface area was still increasing when the PIOS were totally closed (grade 3), however once the AIOS were also totally closed, FM growth stopped. Posterior intra-occipital synchondroses: In Crouzon–Pfeiffer syndrome, the PIOS began to close earlier than in controls; partial and even total closure was already seen within the first year of life, while it was not in the control group. Therefore, total closure of the PIOS (grade 3) was significantly earlier than in controls (2.3 years old vs. 2.7 years old, $p < 0.001$). In Apert syndrome closure of the PIOS was also significantly earlier than in controls (2.5 years old vs. 2.7 years old, $p = 0.028$). In patients with Muenke, Saethre–Chotzen and complex craniosynostosis closure of PIOS was similar to control subjects ($p > 0.05$) (**figure 5**). Anterior intra-occipital synchondroses: Only patients with Crouzon–Pfeiffer syndrome showed a premature fusion of the anterior synchondroses compared with the control group; the AIOS were totally closed (grade 3) at the age of 5.5 years in Crouzon–Pfeiffer patients vs. 7.5 years in controls, $p = 0.001$. Patients with other craniosynostosis syndromes had a similar closing pattern of the intra-occipital synchondroses to controls (**figure 6**).

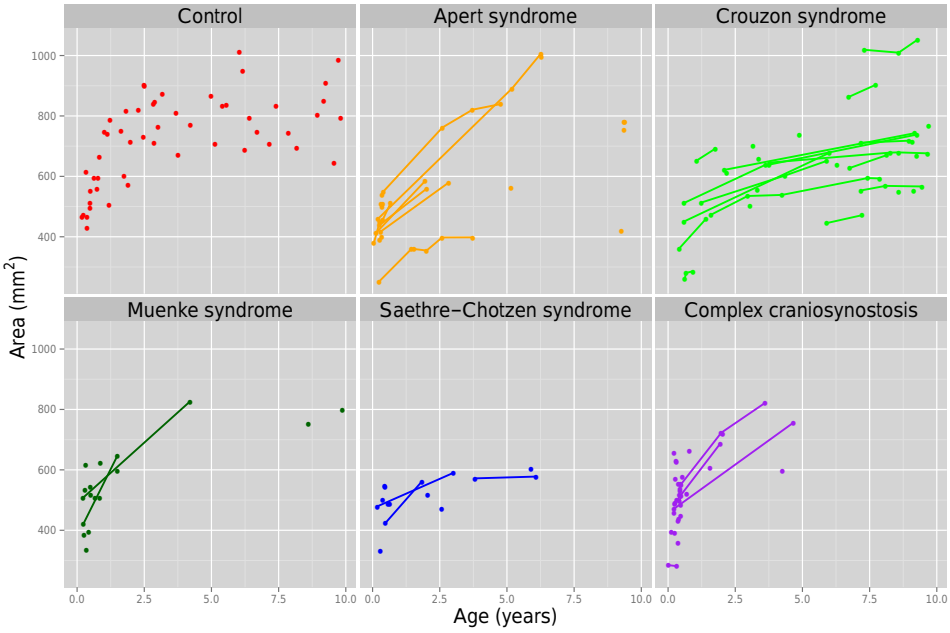

Figure 3: Scatter plots showing the area per craniosynostosis group and control group. Where a patient has multiple measurements, the dots are connected.

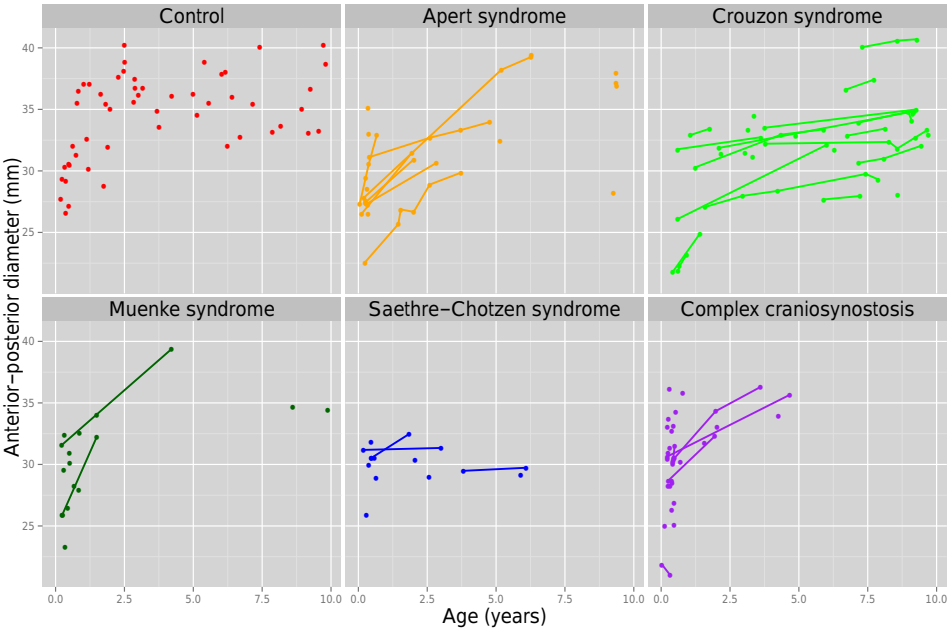

Figure 4: Scatter plots showing the A-P diameter per craniosynostosis group and control group. Where a patient has multiple measurements, the dots are connected.

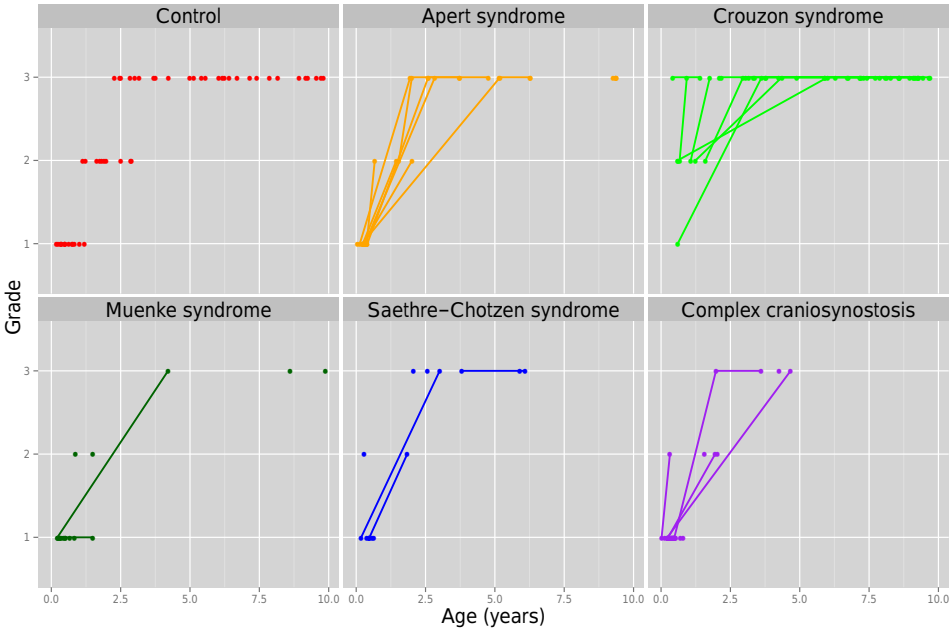

Figure 5: Scatter plots showing the closure of the posterior intra-occipital synchondroses per craniosynostosis group and control group. Where a patient has multiple measurements, the dots are connected.

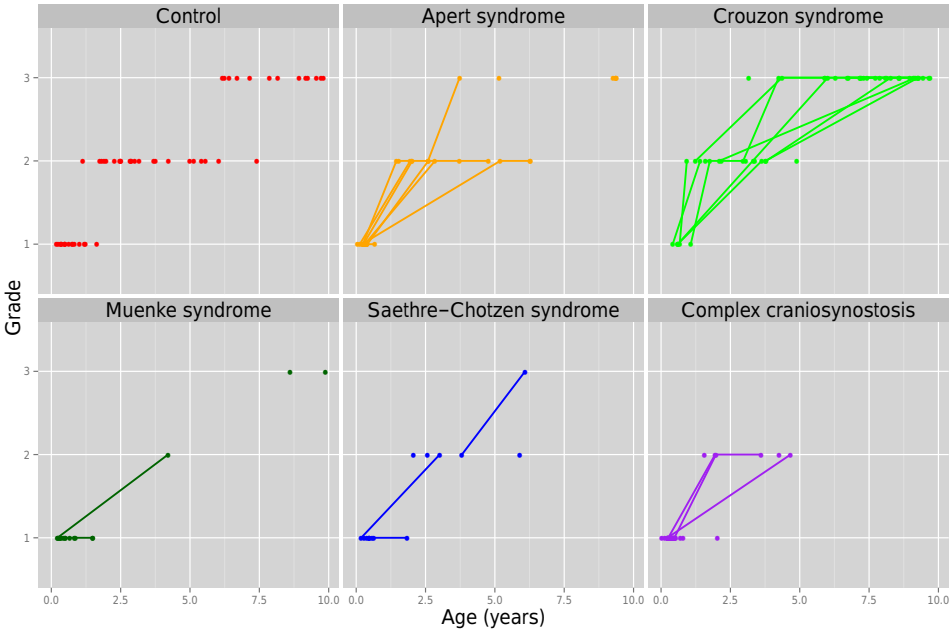

Figure 6: Scatter plots showing the closure of the anterior intra-occipital synchondroses per craniosynostosis group and control group. In case of multiple measurements within one subject, dots are connected.

Foramen magnum size in relation to the position of the cerebellar tonsils and ventricular size

In 14 craniosynostosis patients (20 scans) CMI was detected on the CT scan, and in 16 patients (35 scans) a TH (**table 2**). FM surface area was not related to the position of the cerebellar tonsils (p = 0.36); that is, FM sizes did not vary between craniosynostosis patients with a normal position for the cerebellar tonsils, those with TH and those with CMI (**figure 7**).

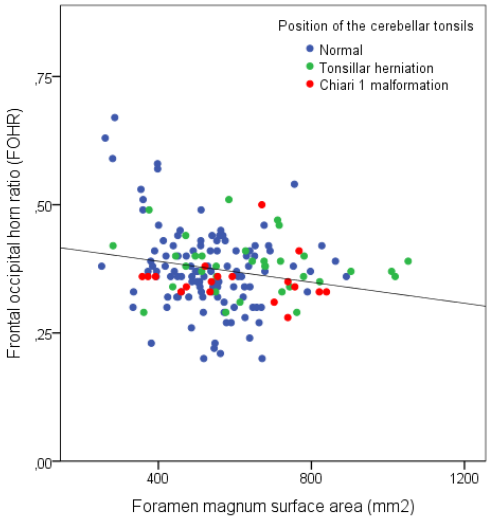

Figure 7: Foramen magnum size in relation to the position of the cerebellar tonsils and ventricular size.

Table 2. Cerebellar position and ventricular size per craniosynostosis syndrome

	Apert n= 39	Crouzon n= 56	Muenke n= 20	Saethre-Chotzen n= 19	Complex n= 41
Normal cerebellar position	31	27	20	19	23
Mean age in years (range)	2.6 (0-10)	4.5 (0-10)	1.6 (0-10)	1.9 (0-6)	0.7 (0-4.5)
Tonsillar herniation	5	18	-	-	12
Mean age (range)	4.7 (0-10)	6.7 (0-10)			1 (0-4)
Chiari I malformation	3	11	-	-	6
Mean age (range)	4.8 (3.5-6)	5.5 (1.5-10)			1.1 (0-5)
FOHR	0.43	0.39	0.35	0.29	0.36
(range)	(0.29-0.58)	(0.24-0.67)	(0.29-0.42)	(0.20-0.40)	(0.27-0.49)

Distribution of normal cerebellar position, tonsillar herniation, Chiari I malformation, and FOHR per craniosynostosis syndrome. FOHR in the control group: mean of 0.34 (range: 0.26–0.40).

The FOHR remained stable over time (i.e., independent of age) and was highest in patients with Apert syndrome, followed by Crouzon–Pfeiffer patients, indicating that these patients had the largest ventricular volume. They were followed by patients with complex craniosynostosis, Muenke and

Saethre–Chotzen syndrome (**table 2**). Nevertheless, control subjects had the smallest FOHR (mean 0.34; range: 0.26–0.40).

Within the total group of craniosynostosis patients, a smaller FM surface area was significantly related to a higher FOHR ($p < 0.001$), however this relation was very weak (R^2 of 0.04).

DISCUSSION

This study showed that the FM surface area is smaller in patients with different types of syndromic or complex craniosynostosis compared with control subjects, which is in line with studies reporting on patients with Crouzon–Pfeiffer syndrome (Coll et al., 2012 and Rijken et al., 2013) and Muenke syndrome (Di Rocco et al., 2014). Moreover, we found that this difference is already present at birth and increases over time.

FGFR2 and FGFR3-genes responsible for Apert, Crouzon–Pfeiffer and Muenke syndrome are expressed in the neural tube and cranial base already at the fifth week of gestation and involved in the endochondral ossification process (Bansal et al., 2003, Saarimaki-Vire et al., 2007, Walshe and Mason, 2000 and Wright et al., 2003). While FGFR2 is highly expressed in both the osteogenic and chondrogenic cell lineage, FGFR3 is especially expressed in the proliferating chondrocytes. Therefore, these genes play a major role in skull base development and may induce premature fusion of different skull base synchondroses (McGrath et al., 2012, Rijken et al., 2013 and Tahiri et al., 2013). Although less is known about the influence of the TWIST1-gene on fusion of the skull base synchondroses in Saethre–Chotzen patients, TWIST1 is important in morphogenesis of the cephalic neural tube (Soo et al., 2002) and promotes intramembranous ossification in the skull (Hermann et al., 2012) in mouse models. We observed in the total group of craniosynostosis patients that when the PIOS were totally fused the FM surface area was still increasing, but once the AIOS were totally fused FM growth stopped. This shows the involvement of the intra-occipital synchondroses in FM development. Nevertheless, premature fusion could only be proven in patients with Crouzon–Pfeiffer (AIOS and PIOS) and Apert syndrome (only PIOS). In Saethre–Chotzen, Muenke and complex craniosynostosis patients this pattern of premature fusion could not be proved. Furthermore, since the FM is already smaller at birth, our findings indicate that FM growth does not only depend on the timing of fusion of the intra-occipital synchondroses, but that it might be influenced by other factors such as hypoplasia of the occipital bones.

Normal development and growth of the FM is necessary to accommodate the brain stem and allow sufficient space for CSF passage between the cranial cavity and spinal sac (Greitz et al., 1992 and Neff and Subramaniam, 1996). Therefore, a reduced FM size may result in a hindered CSF passage around the posterior skull base. Consequently, it may play a role in the development of ventriculomegaly and increased ICP. Our study shows that FOHR is higher in craniosynostosis patients than in controls and, as in the normal population, it is age-independent (O'Hayon et al., 1998). Apert patients had the largest ventricles, followed by Crouzon–Pfeiffer, Muenke, Saethre–Chotzen and complex craniosynostosis patients. The relation we found between FOHR and FM surface area was, however, very weak and thus the smaller FM does not appear to obstruct cerebrospinal fluid outflow.

A limitation of our study is the low number of cases, particularly for patients with complex craniosynostosis over 2 years old for whom scans were lacking. The reason for this is that in our institution 3D-CT scans are only made on clinical indication, to prevent patients being unnecessarily exposed to radiation.

CONCLUSION

Patients with different types of craniosynostosis syndromes have a smaller FM compared with control subjects. The reduced size of the FM could only be partially related to premature closure of the PIOS and AIOS, in Crouzon–Pfeiffer and Apert syndrome. Moreover, a reduced FM size is not related to the presence of CMI.

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6

The occipito-frontal circumference: reliable prediction of the intracranial volume in children with syndromic and complex craniosynostosis

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ABSTRACT

Object Patients with syndromic and complex craniosynostosis are characterized by the premature fusion of one or more cranial sutures. These patients are at risk for developing elevated intracranial pressure (ICP). There are several factors known to contribute to elevated ICP in these patients, including craniocerebral disproportion, hydrocephalus, venous hypertension, and obstructive sleep apnea. However, the causal mechanism is unknown, and patients develop elevated ICP even after skull surgery. In clinical practice, the occipitofrontal circumference (OFC) is used as an indirect measure for intracranial volume (ICV), to evaluate skull growth. However, it remains unknown whether OFC is a reliable predictor of ICV in patients with a severe skull deformity. Therefore, in this study the authors evaluated the relation between ICV and OFC.

Methods Eighty-four CT scans obtained in 69 patients with syndromic and complex craniosynostosis treated at the Erasmus University Medical Center–Sophia Children's Hospital were included. The ICV was calculated based on CT scans by using autosegmentation with an HU threshold < 150. The OFC was collected from electronic patient files. The CT scans and OFC measurements were matched based on a maximum amount of the time that was allowed between these examinations, which was dependent on age. A Pearson correlation coefficient was calculated to evaluate the correlations between OFC and ICV. The predictive value of OFC, age, and sex on ICV was then further evaluated using a univariate linear mixed model. The significant factors in the univariate analysis were subsequently entered in a multivariate mixed model.

Results The correlations found between OFC and ICV were r = 0.908 for the total group ($p < 0.001$), r = 0.981 for Apert ($p < 0.001$), r = 0.867 for Crouzon-Pfeiffer ($p < 0.001$), r = 0.989 for Muenke ($p < 0.001$), r = 0.858 for Saethre-Chotzen syndrome ($p = 0.001$), and r = 0.917 for complex craniosynostosis ($p < 0.001$). Age and OFC were significant predictors of ICV in the univariate linear mixed model ($p < 0.001$ for both factors). The OFC was the only predictor that remained significant in the multivariate analysis ($p < 0.001$).

Conclusions The OFC is a significant predictor of ICV in patients with syndromic and complex craniosynostosis. Therefore, measuring the OFC during clinical practice is very useful in determining which patients are at risk for impaired skull growth.

INTRODUCTION

Craniosynostosis involves the premature fusion of one or more cranial sutures, which results in deformation of the skull due to lack of growth perpendicular to the affected suture and compensatory overgrowth at the nonaffected sutures.[17] This rare condition, with a prevalence of 1 in 2100–2500 births,[17] is classified as syndromic in up to 24% of cases.[27] Syndromes associated with craniosynostosis include Apert, Crouzon-Pfeiffer, Muenke, and Saethre-Chotzen.[17] Patients in whom more than one suture is affected, but for which no responsible gene mutation has been found, are called complex cases.[18,19]

The treatment of craniosynostosis consists of skull vault surgery. This procedure is performed to prevent or to treat elevated intracranial pressure (ICP) by enlarging the intracranial volume (ICV). Surgery is preferably performed within 1 year after birth, because the risk of developing raised ICP is higher when the operation is performed later in life.[24] Furthermore, the mental outcome is better compared with patients who undergo a cranial vault expansion later in life.[24] Moreover, the skull deformity is corrected and its progression is prevented.[17] In general, patients with Apert and Crouzon-Pfeiffer syndromes underwent an occipital vault expansion, which might be followed by a frontoorbital advancement later in life, whereas patients with Muenke and Saethre-Chotzen syndromes underwent a frontoorbital advancement as the first (and often the only) surgical procedure. For patients with multisuture synostosis, the surgical procedure depends on the cranial sutures involved; occipital expansion when lambdoid sutures are involved, and frontoorbital advancement when coronal sutures are involved.

Preoperatively, 40%–50% of the patients with Apert syndrome, 50%–70% of those with Crouzon-Pfeiffer syndrome, 35%–45% of those with Saethre-Chotzen syndrome, 50%–80% of the patients with complex craniosynostosis, and none of those with Muenke syndrome develop increased ICP.[5,12,13,15,18,21,24,25,29,30,32] Postoperatively, 35%–43% of patients still develop raised ICP.[12,13,15,18,25,29,30] Factors influencing ICP in these patients include craniocerebral disproportion (a condition in which the brain grows faster than the skull), hydrocephalus, venous hypertension, and obstructive sleep apnea syndrome.[8,11,14] During follow-up of the surgically treated patient, the occipitofrontal circumference (OFC) is used as a derivative of ICV to evaluate whether craniocerebral disproportion might be present. However, it is unknown whether OFC and ICV correlate in patients with a severe skull deformity. Although OFC and ICV have been shown to correlate in healthy individuals,[6,7] a small study (n = 7) in infants with an abnormal head shape, including 5 with craniosynostosis, could not find any correlation.[7] The aim of the present study is to evaluate the correlation between OFC and ICV in children with different craniosynostosis syndromes, and to assess the predictive value of OFC in these patients.

METHODS

Data Acquisition

The volume measurements were performed using 3D CT scans. These scans were assembled via the radiology department of the Erasmus University Medical Center–Sophia Children's Hospital. All digitally available 3D CT scans of the skull (slice thickness 1.25–3 mm) in all children (age 0–18 years) with syndromic and complex craniosynostosis that were obtained between January 2000 and January 2014 were initially included. The exclusion criteria were as follows: incomplete scans (scans that did not totally include the area between the vertex and the foramen magnum), and scans with artifacts caused by the presence of distractors. Scans including contrast media were also excluded from the study, due to the highly time-consuming measurement. Data on OFC were collected from electronic patient files. The 3D CT scans and OFCs were paired based on the time interval between the CT scan and OFC measurement; because the human skull grows mostly in the first months of life,[10] the OFC had to be measured within 1 month before or after the CT scan for children 0–1 years, within 3 months for patients 1–2 years, within 6 months for those 2–4 years of age, and 12 months for those > 4 years (**table 1**). Additionally, the OFC and CT scan were not paired when the patient underwent skull surgery between the measurement of OFC and acquisition of the CT scan.

Table 1. Matching criteria for CT scans and OFC measurements.

Age (yrs)	Interval Allowed (mos)*
0–1	1
1–2	3
2–4	6
>4	12

* The time interval between CT scans and OFC measurements.

The ICV Measurement

The ICV was calculated from 3D CT scans by using Brainlab, a neuronavigation program. Within this software, autosegmentation with a soft-tissue/bone Hounsfield unit (HU) threshold of < 150 HU[1–4] was performed to outline the ICV. Parts with an HU value below 150, such as skin, that did not contribute to the ICV were manually excluded using axial, sagittal, and coronal images (**figure 1**). These planes were also used to outline the foramen magnum manually, using the area between the clivus and the occipital bone as a cutoff point in the sagittal plane (**figure 2**). When the outlining was finished on each slice, the software program automatically calculated the ICV (**figure 3**). The intrarater reliability was based on the intraclass correlation coefficient, which was 1.000.

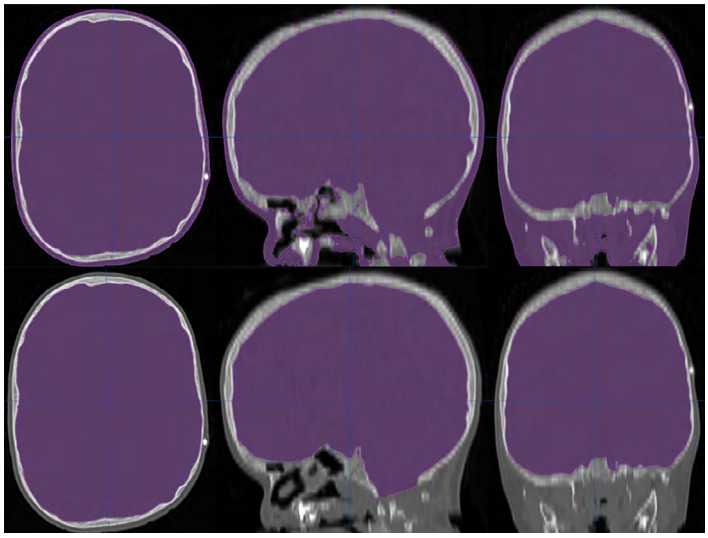

Figure 1. Upper Row: Axial, sagittal, and coronal 3D CT scans showing results after autosegmentation, which includes all tissue with an HU value < 150. This excludes bone, but includes brain, eyes, skin, mucosa, and other soft tissue (for example, that of the nasopharyngeal area). **Lower Row:** Axial, sagittal, and coronal 3D CT scans showing results after manual correction, whereby soft tissues other than brain, ventricles containing CSF, and blood vessels containing blood were manually erased. Consequently, only the ICV remained, of which the lower border was defined by the foramen magnum.

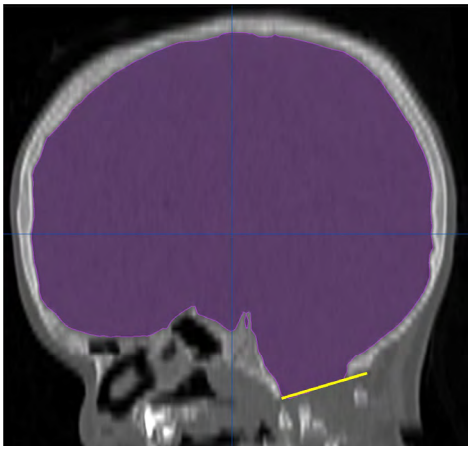

Figure 2. A 3D CT scan on which the foramen magnum between the clivus and occipital bone is outlined *(yellow line)*.

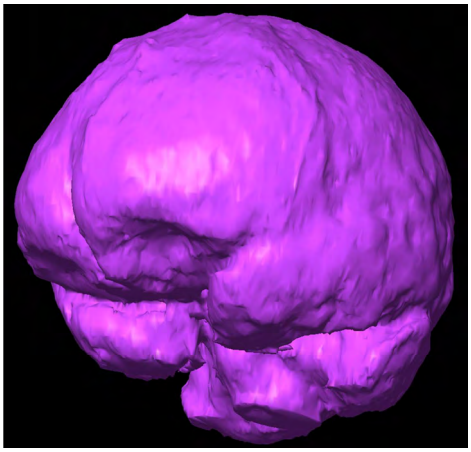

Figure 3. A 3D reconstruction of the ICV, after manually correcting the automatic measurement. This included the brain, ventricles with CSF, cerebellum, upper part of the brainstem (above the foramen magnum), and blood vessels.

Statistical Analysis

To study the correlation between OFC and ICV, a Pearson correlation coefficient was calculated for all patients combined, and per syndrome. Additionally, correlations were calculated as follows: 1) preoperatively; 2) postoperatively; 3) for Apert syndrome patients with a turricephaly; or 4) those without a turricephaly. Only the first 3D CT scan for each patient was used for the calculation of the correlations, because correlation coefficients do not allow the use of multiple measurements. For further analysis of the predictive value of OFC, a linear mixed model correcting for multiple measurements, age, and sex was used. The OFC, age, and sex were first entered separately into the model. Variables that were significant in the univariate analysis were subsequently entered into a multivariate linear mixed model. Statistical significance was defined as $p < 0.05$.

RESULTS

One hundred fifty-nine of 229 CT scans remained eligible when the inclusion and exclusion criteria were applied, of which 84 were paired with an OFC measurement (**figure 4**). These 84 scans were obtained in 69 patients with craniosynostosis, including Apert (n = 11), Crouzon-Pfeiffer (n = 24), Muenke (n = 7), and Saethre-Chotzen (n= 10) syndromes, and complex craniosynostosis (n = 17) (**table 2**).

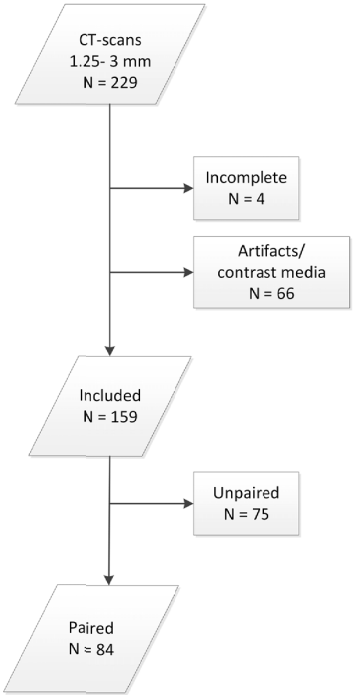

Figure 4. Flowchart of the scans included in the study.

Three patients with Apert, 6 with Crouzon-Pfeiffer, and 1 with Saethre-Chotzen syndrome, and 1 with complex craniosynostosis underwent multiple scans. The mean age of our patient population was 5.7 years (range 2 months to 18 years), and 34 of the patients were female (49%). The correlation coefficient between OFC and ICV was r = 0.908 for all patients combined; r = 0.981 for those with Apert; r = 0.867 for those with Crouzon-Pfeiffer; r = 0.989 for those with Muenke; r = 0.858 for those with Saethre-Chotzen syndrome; and r = 0.917 for those with complex craniosynostosis (**tables 3** and **4**). Preoperatively, the correlation between OFC and ICV for all patients combined was r = 0.903 ($p < 0.001$), and it was r = 0.815 postoperatively ($p < 0.001$). The correlation in patients with Apert syndrome with a turricephaly (n = 4) was r = 0.984 ($p < 0.031$), and for patients with Apert syndrome without a turricephaly (n = 7) it was r = 0.969 ($p < 0.001$). In the univariate analysis, OFC and age were significant predictors of ICV ($p < 0.001$ for both factors), whereas sex had no significant contribution ($p = 0.238$). When OFC and age were entered into a multivariate model, OFC remained the only significant predictor of the ICV ($p < 0.001$ for OFC and $p = 0.136$ for age).

Table 2. Characteristics in 69 with syndromic and complex craniosynostosis.

Characteristics	No. of Patients (%)	No. of Scans (%)
Total	69	84
Craniosynostosis group		
Apert	11 (16)	17 (20)
Crouzon-Pfeiffer	24 (35)	31 (37)
Muenke	7 (10)	7 (8)
Saethre-Chotzen	10 (14)	11 (13)
Complex	17 (25)	18 (21)
Sex		
Male	35 (51)	44 (52)
Female	34 (49)	40 (48)
Age in yrs		
0–1	25 (36)	25 (30)
1–2	8 (12)	9 (11)
2–4	10 (14)	15 (18)
4–8	6 (9)	7 (8)
8–12	9 (13)	10 (12)
12–18	11 (16)	18 (21)

Table 3. The mean ICV, OFC, and age per craniosynostosis group.

Group	Age at CT (yrs)	ICV (cm^3)	Age at OFC (yrs)	OFC (cm)
Total	5.7	1242	5.7	48.3
Apert	8.5	1590	8.5	50.6
Crouzon-Pfeiffer	8.2	1357	8.2	51.6
Muenke	3.1	1082	3.2	45.2
Saethre-Chotzen	3.1	1070	3.0	45.7
Complex	1.5	884	1.5	43.1

Table 4. Correlations between OFC and ICV per craniosynostosis group.

Group	Correlation	*p*-Value
Total	0.908	<0.001
Apert	0.981	<0.001
Crouzon-Pfeiffer	0.867	<0.001
Muenke	0.989	<0.001
Saethre-Chotzen	0.858	0.001
Complex	0.917	<0.001

DISCUSSION

In this study we evaluated the predictive value of OFC for ICV, and the correlation between OFC and ICV in patients with syndromic and complex craniosynostosis. The OFC and ICV were highly correlated when evaluating all patients combined, but also for subgroups per syndrome, pre- and postoperatively, and in patients with Apert syndrome with a turricephaly. Furthermore, when corrected for age, OFC was a significant predictor of ICV. The OFC and ICV were highly correlated in our study population. A previous study in which the correlation between OFC and ICV was evaluated could not find any correlation.[7] However, we believe that our study has several strengths in comparison with the previous one. For example, the study population of Buda et al. consisted of only 7 infants with a deviated skull form, of whom 5 patients had craniosynostosis, whereas our study consisted of a much larger cohort. Additionally, ICVs in the previous study were calculated using radiographs, whereas in this study we calculated the ICV on 3D CT scans, which is a more established method for ICV measurements.26 There are 2 studies in which the correlation between OFC and ICV was evaluated in healthy individuals.[6,7] They found correlations of r = 0.97 and r = 0.98, which is slightly higher than the correlation of r = 0.91 that we found in our study population. Apparently, although the skull shape is altered in children with craniosynostosis, it turns out that the OFC is still a reliable tool to evaluate ICV. For each syndrome separately, OFC and ICV were highly correlated as well. We believed that the correlation might be altered in children with Apert syndrome, due to the presence of patients with a turricephaly in this group. However, we found that the correlation in Apert syndrome was one of the highest of all syndrome subgroups, and additionally that the presence or absence of a turricephaly did not alter the correlation substantially. Whether OFC and ICV have a good correlation in patients with Crouzon-Pfeiffer syndrome with only sagittal suture synostosis was evaluated in 2 patients. Remarkably, the correlation coefficient of these 2 patients was almost identical to the rest of the group (0.867 and 0.865, respectively). However, this might be explained by the fact that both patients were measured postoperatively, indicating that the configuration of the skull in these patients was altered, and was more similar to those without sagittal suture involvement. Therefore, it is uncertain whether the OFC is as good a predictor for ICV in patients with Crouzon-Pfeiffer syndrome with only sagittal suture synostosis prior to correction. In addition, ICV depends on the diagnosis; ICV is normal in unicoronal suture synostosis,[16] normal or slightly enlarged in sagittal suture synostosis,[20,23]

and enlarged in patients with Apert and Crouzon-Pfeiffer syndromes.[22] Increasing ICV is caused by increasing brain mass or CSF, which both might contribute to elevated ICP. The incidence of increased ICP differs between different craniosynostosis syndromes, with the highest percentage in patients with Crouzon-Pfeiffer syndrome.[5] In addition, patients with different craniosynostosis syndromes show different OFC curves, and some are regarded as more likely to develop a deflecting OFC growth curve than others.[28] For example, stagnating skull growth is more often seen in patients with Crouzon-Pfeiffer syndrome than in patients with Muenke syndrome. Therefore we studied the OFC curves per syndrome, and investigated the relation between OFC and ICV per syndrome as well. For each craniosynostosis syndrome, the relation between ICV and OFC was high, which means that the OFC curve is a reliable measurement to study ICV in different craniosynostosis syndromes. This makes it a clinically useful tool to study skull growth. Moreover, it turns out that a deflecting growth curve (OFC not changing or showing growth of < 0.5 SD within 2 years) is a very important risk factor for developing papilledema, which is an indirect sign of increased ICP.[9,28,31]

A limitation of our study includes its retrospective design. The OFC was often not measured on the day that the CT scan was performed. To evaluate the influence of our variables more precisely, these measurements would preferably be made on the same day. Another point of attention might be the human factor when measuring the OFC; for example, measurement errors or noncooperative children. However, the data collection was done by experienced professionals at every visit of the patient to the clinic, which limits those factors as much as possible.

CONCLUSIONS

Taken together, craniocerebral disproportion contributes to the development of elevated ICP in children with syndromic and complex craniosynostosis. The ICV measurements can be used to monitor skull growth. However, because this is time consuming and therefore not feasible for use in clinical practice, OFC is often used as an alternative to ICV. We found that OFC is indeed a reliable predictor of ICV in the total group of patients with craniosynostosis, in the individual syndromes as well as in surgically and nonsurgically treated patients with craniosynostosis. This makes it a rapid and accurate method to monitor skull growth during follow-up and to help determine which patients are lacking in ICV.

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7

First vault expansion in Apert and Crouzon-Pfeiffer syndromes: front or back?

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ABSTRACT

Background: Children with Apert and Crouzon-Pfeiffer syndromes are at risk of intracranial hypertension. Until 2005, when we switched to occipital expansion, our institution's preferred treatment was fronto-orbital advancement (FOA). However, it was still unclear whether 1.) occipital-frontal head circumference (OFC; i.e. intracranial volume) was greater after occipital expansion than after FOA; 2.) the incidences of tonsillar herniation and papilledema were lower; and 3.) visual acuity was better during follow-up. In these patients we therefore compared FOA with occipital expansion as first surgical procedure.

Methods: Measurements included repeated OFC as a measure for intracranial volume; neuroimaging to evaluate tonsillar herniation; fundoscopy to identify papilledema; and visual acuity testing.

Results: We included 37 patients (18 Apert, 19 Crouzon-Pfeiffer). Eighteen underwent FOA and 19 underwent occipital expansion (age at surgery: 1.0 versus 1.5 years, P=0.13). Follow-up time in both groups was 5.7 years. The increase in OFC (+1.09SD) was greater after occipital expansion than after FOA (+0.32SD), p =0.03. After occipital expansion, fewer patients with Crouzon-Pfeiffer syndrome had tonsillar herniation (occipital: 3 of 11 versus FOA: 7 of 8, $p = 0.02$); for both syndromes together, fewer patients had papilledema (occipital: 4 of 19 versus FOA: 11 of 18; $p = 0.02$). Visual acuity was similar after FOA (0.09 logMAR) and occipital expansion (0.13 logMAR), $p = 0.28$.

Conclusions: Our preference for occipital expansion as the initial craniofacial procedure in Apert and Crouzon-Pfeiffer syndromes is supported by the greater increase it produces in intracranial volume (as evidenced by the OFC), which reduces the incidences of tonsillar herniation and papilledema.

INTRODUCTION

Apert and Crouzon-Pfeiffer syndromes are congenital disorders characterized by the premature fusion of skull sutures and facial anomalies. They are associated with a significant risk of developing intracranial hypertension, mainly in the first six years of life.[1] In Apert syndrome, the incidence of intracranial hypertension before cranial vault expansion is 45%; in Crouzon-Pfeiffer syndrome it is 63%.[2,3] One sign of intracranial hypertension is papilledema, which, in a clinical setting, is screened using fundoscopy.[4] Prolonged intracranial hypertension can impair neuropsychological development, cause behavioral disturbances, and may ultimately lead to optic nerve atrophy with visual loss.[5] Many patients, especially those with Crouzon-Pfeiffer syndrome, also develop tonsillar herniation, which is associated with the presence of intracranial hypertension.[6] To prevent or treat episodes of intracranial hypertension, patients routinely undergo vault expansion within their first year of life. Until 2005, the first choice of treatment in our hospital—the Netherlands' only national referral center for syndromic craniosynostosis—was fronto-orbital advancement (FOA). After a presentation by Professor Hayward during a consensus meeting,[7] the protocol was changed to occipital expansion as the first operation for Apert and Crouzon-Pfeiffer syndromes. By creating a larger intracranial volume than FOA, this was expected to prevent or treat intracranial hypertension more effectively.

The aim of this study was to determine not only whether occipital expansion does indeed lead to a greater increase in intracranial volume than FOA, and consequently to a lower incidence of tonsillar herniation and papilledema, but also to better visual acuity within the timeframe in which patients are at risk, i.e., the first six years of life.

METHODS

Patients

We included patients with Apert and Crouzon-Pfeiffer syndromes born between January 1999 and December 2013 who had been treated at the Dutch Craniofacial Center (Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands). The diagnosis of Crouzon-Pfeiffer syndrome is a spectrum of varying severity; nevertheless we considered them as a homogeneous group since they can be considered as phenotypic variations of the same genetic defect.[8, 9] The Institutional Human Research Ethics Board approved this research (Erasmus MC, MEC-2005-273) and in all patients, parents provided written-informed consent. Patients were divided into two groups on the basis of the craniofacial procedure, i.e., FOA or occipital expansion. Patients who had not received cranial vault surgery, or who had incomplete follow-up, were excluded. In both groups, the follow-up time after surgery was 5.7 years, thereby covering the period during which these patients were most likely to develop tonsillar herniation and/or papilledema.[1]

Cranial vault expansion

Our treatment protocol includes vault expansion within the first year of life, or shortly after referral if the child is older at first presentation. The choice of the type of surgery performed had been based solely

on the protocol that had applied at that time, with a change from FOA to occipital expansion in 2005. The only exception covered patients who suffered from severe obstructive sleep apnea and/or severe exorbitism: a monobloc was then performed.

Fronto-orbital advancement: For fronto-orbital advancement,[10] the frontal bone is removed in one piece with the osteotomies situated 2 cm behind the coronal sutures. After that, the supraorbital bar is taken out with lateral extensions to allow for a tongue in groove. The remodeling of the supraorbital bar is performed depending on the deformity and is replaced with advancement. The frontal bone is subsequently replaced at the same advanced level as the supraorbital bar. Bone grafts are positioned in between the posterior edge of the frontal bone and the parietal bone to secure the level of advancement. Fixation is usually done with resorbable plates and screws, or resorbable sutures. The advancement achieved by FOA is approximately 1.5–2.0 cm, although we note that while it is feasible to obtain 2 cm advancement with FOA this might result in a significant disturbance of the facial profile.

Occipital expansion (conventional method): For occipital expansion with the conventional method,[11] the occipital bone is removed in one piece with the horizontal osteotomies situated cranially just behind the coronal sutures and caudally just above the torcula. From the most anterior part of the bone flap a bandeau is taken out. The bandeau is placed horizontally, just above the occipital osteotomy. The remaining bone flap is rotated 180 degrees, remodeled and fixed to the bandeau. Bone grafts are positioned in between the parietal bone and the replaced bone flap to secure the level of expansion. Fixation is usually done with resorbable plates and screws, or resorbable sutures. The expansion achieved by conventional occipital expansion is approximately 3.0–3.5 cm, depending on the stretch that the skin of the scalp allows.

Occipital expansion (springs): For occipital expansion using springs,[11] the horizontal osteotomies are situated cranially just behind the coronal sutures and caudally just above the torcula. A bone strip of 1 cm in the midline of the caudal osteotomy is left intact to act as hinge. The bone flap is left attached to the dura, except when the lambdoid sutures are patent in which case the dura was detached to prevent hinging of the bone flap at the site of the sutures. Springs are placed, usually two to four of them. We use springs (Active Spring Co., Ltd., UK), which produce a force of 3.11 Nmm/°. Springs are left in place on average 12 weeks. The expansion achieved by occipital expansion with springs varies between 4.0–5.0 cm.

Skull growth

Occipital-frontal head circumference (OFC) was measured during each visit to the outpatient clinic (i.e., at intake, 1 day before surgery, 3 months after surgery, 6 months after surgery, then every other 6 months until age 3; and then annually). Since OFC and intracranial volume are highly correlated in patients with syndromic craniosynostosis,[12] the OFC was used as a measure of intracranial volume.

Neuroimaging

MR scan imaging data were acquired using a 1.5 Tesla MR Unit (GE Healthcare, MR signa excite HD); the imaging protocol included a 3D SPGR T1-weighted MR sequence, with a slice thickness of 2 mm without slice gap, FOV= 22.4 cm, matrix size= 224*224, in plane resolution of 1 mm, TE= 3.1 ms and TR= 9.9 ms. If no MR scan was available, the CT-scan was evaluated. These CT data were acquired using a

multi-detector CT scanner (Siemens, Erlangen, Germany); scans had a slice thickness of 1.25 mm (H10s kernel). All MR and CT scans were reviewed in a 3D reformatting platform (AquariusNET; TeraRecon, Inc., Melbourne, Victoria, Australia), in which scans were aligned in the sagittal, coronal and transvers planes to optimize the examination. The presence and degree of cerebellar tonsillar herniation was examined in midsagittal and adjacent scan slices. Patients were divided into three groups: (1) those with no tonsillar herniation; (2) those with herniation of less than 5 mm below the foramen magnum; and (3) those with herniation of 5 mm and more below the foramen magnum (classic definition of Chiari type I malformation[13]).

Fundoscopy

The presence of papilledema was used to indicate intracranial hypertension, and therefore elevated intracranial pressure. A pediatric ophthalmologist performed fundoscopy in all patients at least biannually.

Visual acuity testing

An orthoptist tested visual acuity, either with a Snellen chart or the Tumbling E-chart, or, in young children and patients with psychomotor retardation, with the Amsterdam Picture Chart (APK).[14] Due to the possible long-term effect of papilledema on vision, visual acuity was evaluated on the basis of the latest available follow-up.5 The eye with best visual acuity was used in the analysis, to prevent confounding caused by strabismus and/or amblyopia. Visual acuity was expressed using the logMAR scale; a visual acuity of 0.30 logMAR was regarded as the minimum vision necessary for adequate functioning in everyday life.

Statistical analysis

Since our protocol had changed from FOA to occipital expansion in 2005, the FOA group had a longer follow-up time. To account for this, we determined the latest available follow-up in the occipital expansion group, and applied the same follow-up time to the FOA group. Continuous variables are expressed as the mean (95% confidence interval), and an independent sample T-test was used for comparisons. Since the expected value in one of the cells of the 2x2 contingency table was below 5, categorical variables were compared using the Fisher exact test. Statistical significance was defined as a p-value of < 0.05.

RESULTS

Thirty-seven children were included (Apert syndrome n=18, and Crouzon-Pfeiffer syndrome n=19); 18 of them had undergone FOA, and 19 had undergone occipital expansion (9 with springs). One patient with Apert syndrome and four patients with Crouzon-Pfeiffer syndrome were excluded as they had not had vault surgery. Age at surgery (1.0 years [range: 0.4 – 2.5] versus 1.5 years [range: 0.4 – 3.9] respectively, $p = 0.13$) and diagnoses were equal between the groups. In both groups, follow-up time after surgery was 5.7 years. An overview of the demographics and patient characteristics can be seen in **tables 1, 2, 3**. A representative pre- and post-operative skull X-ray for each type of surgery is shown in **figure 1**.

Table 1: Demographics

	FOA (n=18)	Occipital (n=19)
Syndrome		
-Apert	10	8
-Crouzon-Pfeiffer	8	11
Gender (male)	10 (55.5%)	11 (57.8%)
Age at surgery (years)	1.0 (range 0.4 – 2.5)	1.5 (range: 0.4 – 3.9)
Follow-up time (years)	5.7	5.7

Numbers represent absolute patient numbers, unless stated otherwise.

Table 2: Patient characteristics: Apert syndrome

#	Diagnosis	Mutation		Synostosis	Surgery	Exorbitsm	OSA	Tracheostomy
1	Apert	p.P253R	FGFR2	Bicoronal	FOA	Mild	Mild	No
2	Apert	p.P253R	FGFR2	Bicoronal	FOA	Mild	No	No
3	Apert	p.S252W	FGFR2	Bicoronal	FOA	Mild	No	No
4	Apert	p.S252W	FGFR2	Bicoronal	FOA	Severe	Moderate	No
5	Apert	p.S252W	FGFR2	Bicoronal	FOA	Severe	Moderate	No
6	Apert	p.P253R	FGFR2	Bicoronal	FOA	Mild	No	No
7	Apert	p.P253R	FGFR2	Right coronal, sagittal	FOA	Mild	Mild	No
8	Apert	p.S252W	FGFR2	Bicoronal	FOA	Mild	No	No
9	Apert	p.P253R	FGFR2	Bicoronal, right lambdoid	FOA	Mild	Mild	No
10	Apert	p.S252W	FGFR2	Bicoronal, metopic	FOA (monobloc)	No	Moderate	No
11	Apert	p.P253R	FGFR2	Bicoronal	OE (springs)	Mild	No	No
12	Apert	p.P253R	FGFR2	Bicoronal	OE	Mild	Mild	No
13	Apert*	N/A	FGFR2	Bicoronal	OE	Mild	Mild	No
14	Apert	p.S252W	FGFR2	Bicoronal	OE (springs)	Severe	Mild	No
15	Apert	p.S252W	FGFR2	Bicoronal	OE	Severe	Severe	Yes
16	Apert	p.P253R	FGFR2	Bicoronal	OE (springs)	Mild	Mild	No
17	Apert	p.P253R	FGFR2	Bicoronal	OE (springs)	Mild	No	No
18	Apert	p.S252W	FGFR2	Bicoronal	OE (springs)	Mild	Mild	No

*One patient with Apert syndrome did not undergo genetic analysis. Surgery: FOA: fronto-orbital advancement; OE: occipital expansion (with or without springs). OSA: Obstructive sleep apnea, categorized based on the oAHI-index: mild (oAHI 1 and <5), moderate (oAHI ≥5 and <25) or severe OSA (oAHI ≥25).[32, 33]

Table 3: Patient characteristics: Crouzon-Pfeiffer syndrome

#	Diagnosis	Mutation		Synostosis	Surgery	Exorbitsm	OSA	Tracheostomy
1	Crouzon	p.Q289P	FGFR2	Right coronal, metopic, sagittal, bi-lambdoid	FOA	Mild	Mild	No
2	Crouzon	p.S267P	FGFR2	Bicoronal	FOA	Severe	No	No
3	Crouzon	p.C342W	FGFR2	Pansynostosis	FOA (monobloc)	Severe	Severe	Yes
4	Crouzon	p.C342Y	FGFR2	Pansynostosis	FOA	Severe	Moderate	No
5	Crouzon	p.C278F	FGFR2	Metopic, sagittal, bicoronal	FOA	Severe	Mild	No
6	Crouzon	p.S267P	FGFR2	Bicoronal	FOA	Mild	No	No
7	Crouzon	p.C342Y	FGFR2	Bicoronal, sagittal	FOA	Mild	Mild	No
8	Crouzon	p.C342Y	FGFR2	Bicoronal	FOA	Severe	Mild	No
9	Crouzon	p.S354C	FGFR2	Bicoronal	OE	Mild	No	No
10	Pfeiffer	c.1084+3 A>G	FGFR2	Pansynostosis	OE	No	No	No
11	Crouzon	p.W290R	FGFR2	Pansynostosis	OE	No	No	No
12	Crouzon	p.Y340H	FGFR2	Pansynostosis	OE	Mild	Mild	No
13	Crouzon	p.L327V	FGFR2	Pansynostosis	OE (springs)	Severe	Mild	No
14	Pfeiffer	p.W290C	FGFR2	Right coronal, metopic, sagittal, bi-lambdoid	OE (springs)	Severe	Severe	Yes
15	Pfeiffer	p.E565G	FGFR2	Pansynostosis	OE (springs)	Mild	Mild	No
16	Crouzon	p.C278F	FGFR2	Pansynostosis	OE	Severe	Mild	No
17	Pfeiffer	p.P252R	FGFR2	Bicoronal	OE (springs)	Mild	No	No
18	Crouzon	p.G338R	FGFR2	Bicoronal, sagittal	OE	Mild	No	No
19	Crouzon	p.L357V	FGFR2	Bicoronal, right lambdoid	OE	Mild	No	No

Surgery: FOA: fronto-orbital advancement; OE: occipital expansion (with or without springs). OSA: Obstructive sleep apnea, categorized based on the oAHI-index: mild (oAHI 1 and <5), moderate (oAHI ≥5 and <25) or severe OSA (oAHI ≥25).[32, 33]

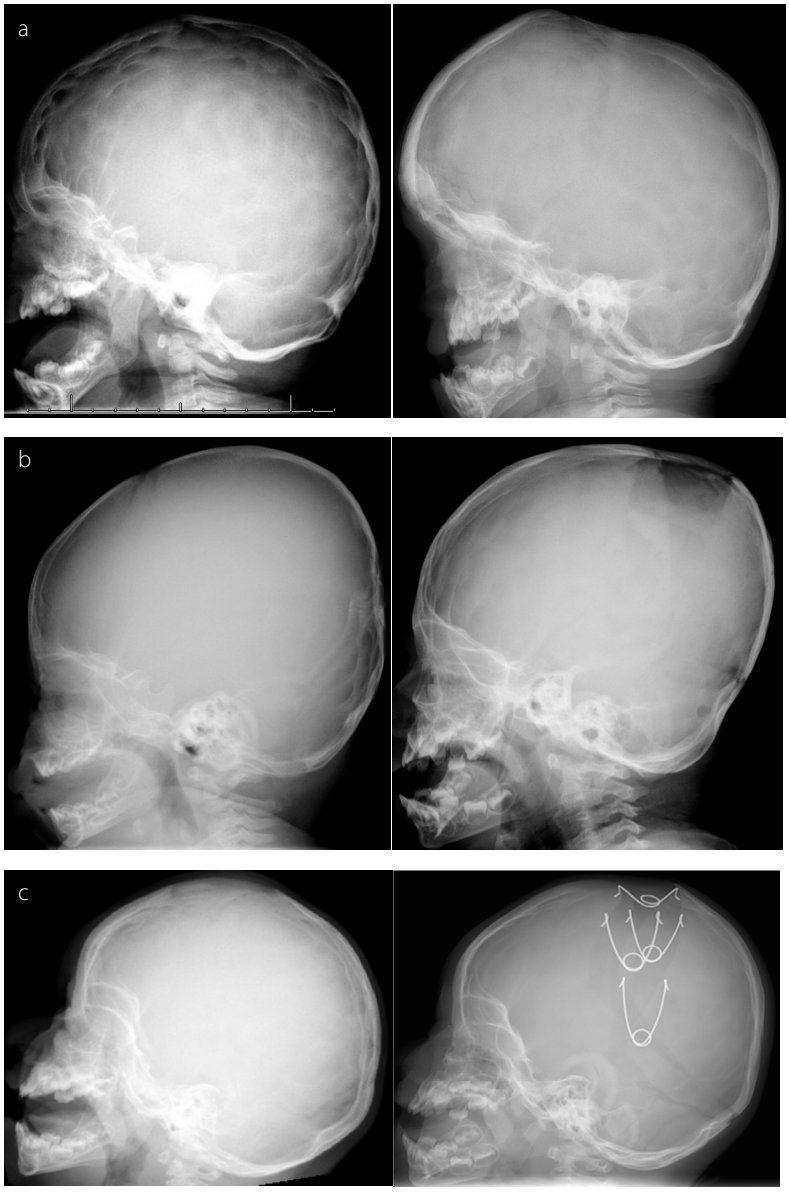

Figure 1: Pre- vs. post-operative skull X-rays: a) FOA; b) conventional occipital expansion; c) occipital expansion with springs.

a. FOA: After surgery the impressiones digitatae have decreased, although a vertex bulge has developed, which is a sign of lack of intracranial volume and possible intracranial hypertension.[34] Additionally, the facial profile is disturbed. The advancement achieved is approximately 1.5–2.0 cm.

b. Conventional occipital expansion: The facial profile is preserved. The expansion achieved is approximately 3.0–3.5 cm.

c. Springs: The facial profile is preserved. In this patient four springs are in situ. The expansion achieved varies between 4.0–5.0 cm.

Before surgery

The OFC was similar between children who had been scheduled for FOA (OFC-SD score: -0.28 [-0.96 – 0.40]) and occipital expansion (-0.04 [-0.77 – 0.68]), $p = 0.62$. The prevalence of papilledema was 35.1%. Regarding the presence of tonsillar herniation or papilledema, there was no difference between the two groups; see **table 4**.

Table 4: Occipital-frontal head circumference, tonsillar herniation, papilledema and visual acuity

	Fronto-orbital advancement N=18 (Apert 10, Crouzon-Pfeiffer 8)		**Occipital expansion** N=19 (Apert 8, Crouzon-Pfeiffer 11)		*p*-value	
	PRE-OP	**POST-OP**	**PRE-OP**	**POST-OP**	**PRE-OP**	**POST-OP**
OFC SD-score						
Overall	-0.28 (-0.96 – 0.40)	0.04 (-0.39 – 0.47)	-0.04 (-0.77 – 0.68)	1.05 (0.43 – 1.67)	0.62	<0.01*
- Apert	*0.41 (-0.33 – 1.14)*	*0.27 (-0.31 – 0.84)*	*0.42 (-0.53 – 1.36)*	*1.58 (0.75 – 2.42)*	*0.99*	*<0.01**
- Crouzon-Pfeiffer	*-1.15 (-1.91 – -0.39)*	*-0.29 (-1.03 – 0.46)*	*-0.38 (-1.51 – 0.75)*	*0.66 (-0.25 – 1.58)*	*0.28*	*0.12*
OFC increase after surgery						
Overall		+0.32		+1.09		0.03*
- Apert		*–0.14*		*+1.17*		*0.04**
- Crouzon-Pfeiffer		*+0.86*		*+1.04*		*0.57*
Tonsillar herniation†						
Overall	4	9	3	4	0.38	0.09
- Apert	*0*	*2*	*0*	*1*	*1.00*	*1.00*
- Crouzon-Pfeiffer	*4*	*7*	*3*	*3*	*0.38*	*0.02**
Papilledema						
Overall	7	11	6	4	0.74	0.02*
- Apert	*2*	*5*	*0*	*2*	*0.48*	*0.37*
- Crouzon-Pfeiffer	*5*	*6*	*6*	*2*	*1.00*	*0.02**
Visual acuity‡						
Overall		0.09		0.13		0.28
- Apert		*0.09*		*0.17*		*0.29*
- Crouzon-Pfeiffer		*0.08*		*0.09*		*0.83*

Values represent absolute patient numbers, unless stated otherwise; PRE-OP: pre-operative; POST-OP: post-operative P-value (PRE-OP): PRE-OP fronto-orbital advancement versus PRE-OP occipital expansion; p-value (POST-OP): POST-OP fronto-orbital advancement versus POST-OP occipital expansion; *p-value <0.05

†A MR- or CT-scan was not performed or not available in all patients. Pre-operatively, in the FOA group 11 scans were available (i.e. 7 missing), in the occipital group 17 scans were available (i.e. 2 missing); post-operatively, in the FOA group for all 18 patients a scan was available, while in the occipital group 17 scans were available (i.e. 2 missing).

‡Values for visual acuity are expressed in logMAR. After FOA, 13 of 18 patients had their visual acuity measured (6 *Snellen Chart*, 5 *Tumbling E-chart*, 2 *APK*), 11 had strabismus, 2 of whom also had amblyopia. Following occipital expansion, 12 of 19 patients had their visual acuity measured (5 *Snellen Chart*, 1 *Tumbling E-chart*, 6 *APK*), 9 had strabismus, 4 of whom also had amblyopia.

After surgery

Occipital-frontal head circumference: OFC in the overall Apert and Crouzon-Pfeiffer group increased more after occipital expansion than after FOA (OFC-SD score: +1.09 versus +0.32, $p = 0.03$), especially in patients with Apert syndrome (OFC-SD score: +1.17 versus -0.14, $p = 0.04$). See **table 4**.

Tonsillar herniation: The number of patients in the overall group who had tonsillar herniation was similar after FOA and occipital expansion ($p= 0.09$, **table 4**). However, tonsillar herniation was present in fewer patients with Crouzon-Pfeiffer syndrome who had undergone occipital expansion (3 patients of 11) than in those who had undergone FOA (7 patients of 8; 2 of whom had a Chiari type I malformation); $p = 0.02$.

Papilledema: In the overall group, fewer patients who had undergone occipital expansion had papilledema (4 patients of 19) than those who had undergone FOA (11 patients of 18); $p = 0.02$, **table 4**. This association was particularly prominent in patients with Crouzon-Pfeiffer syndrome: $p = 0.02$.
Visual acuity: After FOA and occipital expansion, the visual acuity of the eye with greatest vision was similar not only in the overall group (0.09 and 0.13 logMAR respectively, $p = 0.28$; see **table 4**), but also for Apert and Crouzon-Pfeiffer syndromes separately. In the occipital expansion group, three patients had a visual acuity of 0.30 logMAR; one of these patients also had papilledema.

Follow-up

Follow-up after primary vault expansion showed that papilledema could, post-operatively, occur for the first time (FOA: n= 6, occipital: n= 3), re-occur (FOA: n= 2, occipital: 1), or persist (FOA: n= 3, occipital: n= 0). The mean age at occurrence/re-occurrence in the overall group was 3.5 years (range: 1.5 – 4.8 years), which was similar for FOA and occipital expansion. Subsequent treatment was initiated, and all patients had normalization of intracranial hypertension within 3-6 months of final treatment. A flowchart of the patients with papilledema is shown in **figure 2**, the details of the follow-up and the initiated treatments are given in **table 5**.

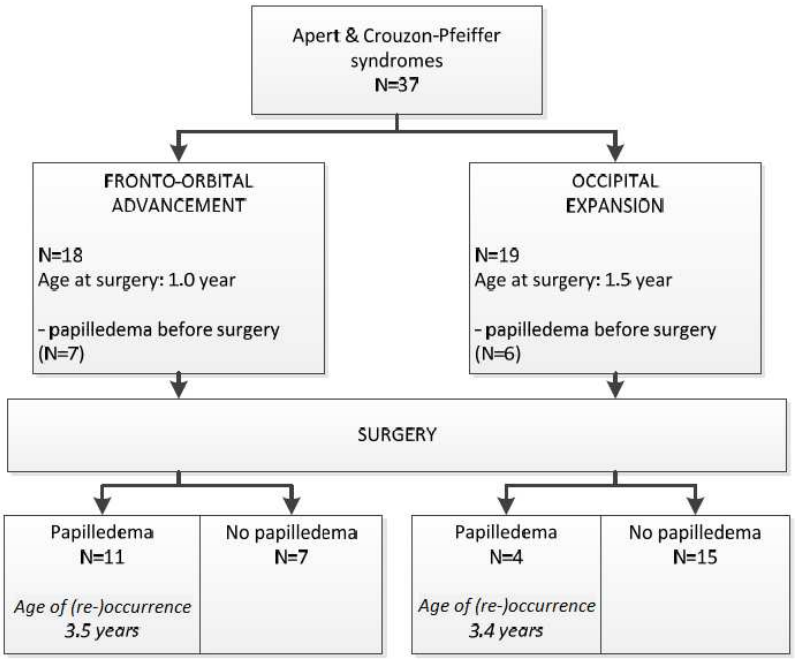

Figure 2: Flowchart showing the distribution of patients with papilledema in the study.

Table 5: Follow-up after the primary vault expansion, for the patients who had papilledema postoperatively

	FOA (n=18)	**Occipital (n=19)**
Patients with papilledema after surgery	11	4
- pre-op: no / post-op: yes (occurrence)	6	3
- pre-op: yes / post-op: yes (reoccurrence)	2	1
- pre-op: yes / post-op: yes (persistent)	3	0
Age at occurrence / reoccurrence of papilledema after surgery (years)	3.5 (range: 1.5-4.7)	3.4 (range: 1.9-4.8)
Treatment	-Occipital expansion (n=7); 3 of whom needed additional intervention: 1x facial bipartition, 1x VP-shunt, 1x CPAP - FOA + monobloc (n=1) - Monobloc + mandibular distraction (n=1) - LeFort III + CPAP (n=1) - ICP monitoring for mild papilledema: borderline raised ICP. No treatment was prescribed (n=1)	- Monobloc (n=1) - Biparietal widening (n=1) - FOA + third ventriculostomy (n=1) - Wait-and-see approach for mild papilledema and psychomotor retardation, requested by the parents (n=1)

Numbers represent absolute patient numbers, unless stated otherwise.

DISCUSSION

This study indicates that occipital expansion is preferred as the initial type of surgery in patients with Apert and Crouzon-Pfeiffer syndromes. After occipital expansion, the increase in OFC—a strong predictor of intracranial volume in these children[12]—was greater in these patients than in those who had undergone FOA. Subsequently, after occipital expansion, fewer patients had tonsillar herniation and papilledema. This was particularly the case in patients with Crouzon-Pfeiffer syndrome, probably because the prevalence of tonsillar herniation and papilledema is intrinsically higher than in Apert syndrome. Since tonsillar herniation and papilledema are both indirect signs of intracranial hypertension,[4, 6] our findings confirm the superiority of occipital expansion in the treatment of intracranial hypertension as the first craniofacial procedure. During follow-up after vault expansion, cranio-cerebral disproportion is one of the main contributors to the development of intracranial hypertension.[15] Here, we show that occipital expansion leads to a greater increase in OFC-SD score than FOA does, even at five years after surgery. We hypothesize that, due to the smaller increase in intracranial volume after FOA, patients are less able to compensate for any other risk factors for intracranial hypertension that are present (e.g., hydrocephalus, venous outflow obstruction or obstructive sleep apnea[16-19]); they are therefore at greater risk of developing intracranial hypertension, which is confirmed by the higher incidences of tonsillar herniation and papilledema.

Tonsillar herniation is not present at birth in patients with craniosynostosis, but acquired during life. There are several theories to explain the mechanism by which it develops.[20-22] The ongoing debate focuses on whether it is a cause or consequence of intracranial hypertension.[6] In our view, it is likely that tonsillar herniation is secondary to prolonged intracranial hypertension. This is due to the facts that 1.) the incidences of tonsillar herniation and papilledema are both higher after FOA, and 2.) these two conditions tend to co-occur: in our study, 83% of the children who had tonsillar herniation also had papilledema. The mean age at which papilledema occurred after surgery was 3.5 years; in most patients it occurred between 2 and 4.5 years. This confirms the observations of Marucci et al., who found that after an average period of 3 years and 4 months after vault expansion, 35% of patients with Apert syndrome developed a second period of intracranial hypertension.[23] Other authors have also stated that, despite early treatment, intracranial hypertension might still relapse or persist.[1, 5, 24, 25] Spruijt et al. demonstrated that a falling-off in the OFC growth curve is an important factor in the occurrence or re-occurrence of intracranial hypertension after surgery, as is obstructive sleep apnea during longer follow-up.[15] After the age of 6 years, the re-occurrence of papilledema is rare in these patients.[1, 15] At 5.7 years, the length of follow-up in our study can therefore be seen as sufficient.

Visual acuity—which might be affected by prolonged intracranial hypertension—was similar between the FOA and occipital expansion groups. Once intracranial hypertension has been detected, treatment is quickly undertaken on the basis of assessment of the OFC growth curve, polysomnography and MR scan. Our visual acuity results seem to suggest that our protocol is effective in preventing visual loss: only one child with papilledema in the occipital expansion group—who also had psychomotor retardation—had a visual acuity of 0.30 logMAR, which is usually seen as the

minimum for adequate functioning. However, visual acuity in these patients might also be affected by other disturbances, such as abnormalities of the optic nerve or visual pathways, and/or by the strabismus or amblyopia that can result from structural alterations or absence of the extraocular muscles.[26, 27] We should also add that visual loss is a severe complication, which might be too crude as study endpoint, as it only develops after prolonged intracranial hypertension.[5, 28]

The advancement/expansion achieved by vault expansion is greatest for the springs method, followed by conventional occipital expansion, and then by FOA. The significantly greater increase in OFC after occipital expansion compared to FOA indicates that, given the strong relationship between OFC and intracranial volume,[12] the resulting greater increase in intracranial volume leads to lower incidences of tonsillar herniation and papilledema. An additional advantage is that the frontal-orbital area remains untouched, thereby facilitating a monobloc or facial bipartition procedure later in life. However, even after occipital expansion the prevalence of recurrent papilledema was 21%, although due to our center's preference in recent years for springs this percentage might fall further in the future.[11] This recurrence nevertheless highlights these patients' need for close follow-up by a multidisciplinary team. We use the presence of papilledema as the primary approach to indicate intracranial hypertension.[15] Screening for it by means of fundoscopy is not only practical, but also useful and clinically relevant. As a likely consequence of intracranial hypertension, papilledema is a sign that the optic nerve head is affected, and that the main risk for craniosynostosis patients—optic nerve atrophy and irreversible visual loss—may follow. However, we are aware that the sensitivity of papilledema might be suboptimal, and therefore we perform additional examinations such as optical coherence tomography and intracranial pressure monitoring when intracranial hypertension is suspected but papilledema absent.[29-31] We recommend routine screening for intracranial hypertension after vault expansion: even when there are no signs or symptoms of intracranial hypertension, this should include assessment of symptoms (headaches, behavioral changes, frequent awakenings during the night), OFC measurement and fundoscopy.

CONCLUSION

Our preference for occipital expansion as the initial craniofacial procedure in Apert and Crouzon-Pfeiffer syndromes is supported by the greater increase it produces in intracranial volume (as evidenced by the OFC), which reduces the incidences of tonsillar herniation and papilledema.

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8 Discussion

This thesis was designed to study the pathophysiology of intracranial hypertension (ICH) in patients with syndromic and complex craniosynostosis, and its relation to additional abnormalities of the skull and brain. Patients with craniosynostosis have a high risk for developing ICH and following risk factors are thought to play an important role: a disproportion between the volume of the skull and brain, venous outflow obstruction, tonsillar herniation (TH)/ Chiari malformation type I (CMI), cerebrospinal fluid (CSF) excess due to its overproduction, reduced resorption or obstructed outflow, and obstructive sleep apnea (OSA). These factors highly interact in a dynamic and very complex process, which is still not fully understood. Most likely additional risk factors that are still unrecognized may interact in this complex process. For example, OSA was not yet discovered in the 80's. The pathophysiology may be based on the Monro-Kellie doctrine, which states that the intracranial volume (ICV) is a fixed volume of brain, CSF, and blood volumes. During the development of ICH, intracranial pressure (ICP) can be increased by an absolute or relative increased amount of one or more of these contents.

Craniocerebral disproportion can either be caused by a reduced skull volume or an increased brain volume, and has been thought to play a major role in developing increased ICP in patients with craniosynostosis syndromes. Most likely a mismatch between brain and skull volumes will cause ICH when skull sutures fuse prematurely, and the brain continues to grow. However, there is no clear evidence to support this hypothesis. Studies in children with syndromic and non-syndromic craniosynostosis, (age range 0-10 years old, and the majority younger than 5 years old) show that the ICV is the same for patients and controls, with the exception of a smaller ICV in patients with pansynostosis.[1, 2] In addition, in patients with Crouzon and Apert syndromes, the pre- and postoperative ICV may be larger compared to controls.[1, 3, 4] Another kind of craniocerebral disproportion is caused by overcrowding of the posterior fossa (PF), which is too small for the cerebellum, possibly due to a hypoplastic occipital bone. As a consequence, PF overcrowding may contribute to the development of CMI; when there is no more space left for the cerebellar tonsils within the PF they are pushed downwards into the spinal canal. However, it still remains not fully understood whether CMI is a consequence or cause of ICH.

CSF is produced by the epithelium of the choroid plexus, mainly located in the lateral ventricles. An increased amount of CSF, due to CSF overproduction by the choroid plexus, malabsorption by the arachnoid spaces, or a reduced outflow at the level of the foramen magnum (FM) can result in enlarged ventricles and increased ICP. During early development, fibroblast growth factors (*FGF*'s) and fibroblast growth factor receptors (*FGFR*'s) are expressed within the choroid plexus. Studies revealed that *FGF*'s have the ability to modulate gene expression within the epithelium of the choroid plexus, and be indirectly involved in the function of the choroid plexus.[5] *Fgfr1*, *2*, *3*, and *4* are also present in the early formation of the choroid plexus; whereas *fgfr1* and *fgfr4* are expressed only in the early stage, *fgfr2* expression is maintained during the total development of the choroid plexus. This suggests that *fgfr2* may play a role in its function. In addition, *fgfr3* is present within the nuclei of choroid plexus cells, and most likely plays a more indirect role in CSF secretion and production.[6]

Although CSF flow studies have not been performed in patients with craniosynostosis syndromes, most likely they have an altered CSF flow, due to their skull and brain abnormalities. With each cardiac systole, CSF oscillates in and out of the cranial vault, secondarily to the expansion of intracranial

blood vessels. CSF flow patterns and velocities differ between healthy controls and patients with CMI, probably due to anatomical differences. Differences in CSF flow patterns have also been detected between symptomatic and asymptomatic CMI patients.[7] In craniosynostosis patients, the CSF outflow may not only be disturbed by the presence of TH or CMI, but it may also be impaired by a reduced size of the FM, or a combination of both. A normal growth of the bone structures is necessary for a normal development of the FM in size and shape, which is needed to allow a sufficient flow of CSF between the cranial vault and the spinal canal. The FM is composed of the occipital bone and 4 intra-occipital synchondroses, which allow the FM to expand. Premature fusion of these synchondroses results in a reduced FM size and disturbance of the CSF flow putting the affected patients at risk for developing ICH. Particularly the combination of TH or CMI and a reduced FM size is expected to impair the CSF outflow.

Blood About 10% of the ICV is filled with blood. Adequate blood supply is required to perfuse the brain with oxygen, which is delivered by the intracranial arteries. As important as the blood supply is the venous outflow; when the outflow is impaired the inflow will automatically be disturbed as well. The entire venous outflow takes place over the jugular veins, which are running through the jugular foramina. An inborn anomaly or a developed obstruction of venous outflow might contribute to ICH. Patients with craniosynostosis syndromes have smaller jugular foramina on 3D CT scan than healthy controls. However, no significant difference in the size of the jugular foramina was found between patients with or without papilledema.[8] Rich et al., however, found a smaller jugular foramina size in syndromic craniosynostosis patients with ICH compared to those without ICH, and compared to patients with non-syndromic craniosynostosis, measured by subdural pressure measurements.[9]

Skull vault surgery in craniosynostosis patients mainly focuses on expansion of the cranial vault, to create a larger volume, which allows the brain to grow. Although clinical signs such as papilledema seem to resolve after skull vault expansion, it is particularly the CSF that fills up the new space rather than the brain.[10] Since craniosynostosis patients may develop ICH after skull surgery, a single vault expansion is not always a definite solution. Postoperative ICH is seen in a large proportion of syndromic craniosynostosis patients, and seems to increase with time.[11] Eighteen to 35% of Apert patients may develop ICH after primarily skull vault expansion,[12, 13], which is a similar frequency compared to 35-43% found in a cohort including patients with Crouzon-Pfeiffer, Apert, and Saethre-Chotzen syndromes together.[14] A study performed including only Saethre-Chotzen patients showed the development of ICH necessitating a second cranial vault expansion in 35% and 42% of patients at 1 year and 5 years of postsurgical follow up, respectively.[15] This suggests the presence of a genetic component.

Within craniosynostosis patients the presence of OSA is important because of the high prevalence and its role in increasing the ICP. During OSA the blood concentration of CO_2 rises (hypercapnia) and O_2 level decreases (hypoxia). Vasodilatation occurs as a consequence of hypercapnia, and blood inflow increases to compensate for hypoxia. While OSA is more severe during REM sleep than during nonREM sleep,[16] and ICP levels are also higher during REM sleep, in both syndromic and nonsyndromic craniosynostosis patients,[17] ICP, cerebral perfusion, and respiratory obstruction

seem to interact in a vicious cycle.[18] Almost 70% of the patients with syndromic craniosynostosis patients suffer from OSA. Midface hypoplasia has been thought to be the major cause of OSA, and is mainly seen in Apert and Crouzon-Pfeiffer syndromes.[19] However, patients with mild or no midface hypoplasia (e.g. patients with Muenke and Saethre-Chotzen syndromes as well as those with complex craniosynostosis), seem to develop OSA as often as patients with severe midface hypoplasia (e.g. Apert and Crouzon-Pfeiffer patients). Though the frequency may be similar, OSA is more severe in patients with Apert and Crouzon-Pfeiffer: their sleep studies show more severe abnormalities, they have a lower tendency to improvement, and they have a higher need of treatments compared to patients without midface hypoplasia.[20] Besides midface hypoplasia, OSA can be caused by adenotonsillar hypertrophy, pharyngeal collapse, mandibular hypoplasia, and other airway anomalies.

In summary, the pathophysiology of ICH is complex, and does not depend only on ICV, but other factors such as OSA, venous hypertension, and CSF excess may play an important role.

INTERPRETATION OF RESULTS

Intracranial hypertension

The first period of life is thought to be the most susceptible to develop a craniocerebral disproportion, because the brain grows mostly in the first years of life. Our results showed that the growth of the brain occurs mainly within the first 5 years of life, and continues up to 18 years. The total brain volume does not differ between 1-12 years old patients with syndromic and complex craniosynostosis patients and controls,[21] as previously shown in patients with Crouzon-Pfeiffer syndrome.[22] This indicates that the brain development in terms of size is not disturbed, and that the responsible gene mutation does not cause a different brain volume. Although data about the relationship between ICV and brain volume are lacking, previous studies showed that ICV is not reduced in patients with craniosynostosis, with the exception of those with pansynostosis.[23] In patients with Apert and Crouzon syndromes, ICV is even larger compared to healthy controls. The relation between ICV and ICH has been studied by epidural and subdural pressure measurements. Gault et al. measured ICP via an epidural transducer in children aged between 0 and 100 months. Patients with a pressure of 15mmHg or higher were classified as having ICH. In addition, patients with increased ICP had a reduced ICV ($p<0.005$), while patients with a reduced ICV did not have a significantly higher ICP compared to patients with a normal ICV.[24] Furthermore, Fok et al. performed overnight subdural pressure measurements during at least 12 hours in children between the age of 1.5 and 122 months, taking into account the age specific intracranial pressure (2mmHg in neonates, 5mmHg in 12months, 6-13mmHg in 7years, 15mmHg in older children). They found that 92.6% of the patients had ICH, but only 8% of them had a reduced ICV. [25] Therefore, ICV measurements alone cannot be used to predict the occurrence of ICH. When ICV is normal or enlarged, and brain volume is normal as well, the development of ICH seems to be caused by other factors such as OSA. The relation between occipito-frontal ratio (OFC), ICH and OSA has been evaluated. OFC can be used as a predictor of ICV since both are highly correlated within the total group of syndromic craniosynostosis patients, as well as for each individual syndrome. Measuring the

OFC during clinical practice is thus very useful in determining which patients are at risk for impaired skull growth.[26] In a prospective study, Spruijt et al. showed that the incidence of ICH decreases from 21% to 8%, within the first year after skull vault expansion. One year after skull vault surgery, lack in head growth and the presence of OSA are significantly related to the occurrence of ICH that increases again up to 21%. These findings suggest that skull vault surgery performed at a very young age might not be sufficient later in life, or that skull vault surgery does not treat the cause of ICH in these patients. In craniosynostosis patients, who receive surgery within the first year of life, skull growth may be impaired later in life, starting 1 year after skull vault expansion.[27] The postponement of skull vault later in life is, however, not an option because IQ is significantly lower in children with different types of craniosynostosis operated after 1 year of age compared to those operated before 1 year of age.[28, 29] In terms of surgical technique that is used to treat or prevent ICH, an occipital vault expansion has major advantages compared to the frontal approach. Occipital expansion allows for overcorrection, and small asymmetries are more tolerated at the occipital side than at the frontal side of the skull.[30] In addition, our data shows that an occipital vault expansion with the use of springs results in a lower percentage of papilledema and TH compared to a fronto-orbital advancement. This is most likely due to the increased ICV that is obtained by an occipital expansion, as shown by a higher increase in OFC. However, neither technique includes treatment of OSA.

CSF is one of the other components of the ICV that may play a role in disturbing ICP. Enlarged ventricles can develop due to an overproduction of CSF by the choroid plexus, caused by the FGFR2 expression in this area.[6] CSF outflow can be disturbed by a reduced size of the FM, especially in combination with the presence of TH or CMI, resulting in enlarged ventricles as well. However, although it is well known that CMI and ventriculomegaly are related to each other, it still remains unclear which causes the other. Within the group of craniosynostosis patients, ventricular volume was significantly larger in patients with Apert syndrome, and in patients with CMI. Patients with CMI included mostly patients with Crouzon-Pfeiffer syndrome; however the syndrome itself was not related to an increased ventricular volume.[21] It might be possible that a different underlying mechanism is responsible for the increased ventricular volume in the different syndromes; enlarged ventricles in combination with CMI may represent hydrocephalus, not simple ventriculomegaly. Unfortunately, follow-up MR studies, as well as ICP measurements were not included in the study, and thus not correlated to these data. Nevertheless, previous studies have already shown that non-progressive ventriculomegaly is more frequently found in both Apert and Crouzon-Pfeiffer syndromes compared to true hydrocephalus. Proudman et al. showed that 51% of the Crouzon patients had mild ventriculomegaly, and only 9% suffered from severe ventriculomegaly/ hydrocephalus.[31] In addition, Noetzel et al. found that only 2 of 12 Crouzon patients had hydrocephalus. Ventriculomegaly may represent a primary brain abnormality rather than a consequence from craniosynostosis,[32] but the precise pathomechanism remains not fully understood.

Based on our findings, it is unlikely that TH and CMI result from an overcrowded PF. We did not find differences in both cerebellar and PF volumes as well as volume ratio (cerebellum volume/ PF volume) between not-operated craniosynostosis patients, operated craniosynostosis patients and

control subjects. This means that an overcrowded PF was not seen in the different groups including patients before surgery. In addition, none of the craniosynostosis syndromes was associated with a reduced PF volume. Patients with Apert and Muenke syndromes showed a larger PF compared to controls, most likely due to the more common presence of mega cisterna magna in these patients. In addition, we detected TH and CMI in both not-operated and operated craniosynostosis patients, mostly after the age of 1.5 years. The majority of patients with CMI had Crouzon-Pfeiffer syndrome or complex craniosynostosis, and had a significantly higher CV/PFV ratio compared to controls (0.77 vs. 0.75; p= 0.008). This finding suggests that their posterior fossa is slightly overcrowded, but the range of their CV/PFV ratio did not exceed the range seen in the control group. Therefore, cerebellar and PF volumes, as well as the CV/PFV ratio cannot predict the occurrence of CMI in craniosynostosis patients.

We found that the FM is significantly smaller in patients with craniosynostosis syndromes compared to controls (p< 0.05). Surprisingly, this difference was seen in every craniosynostosis syndrome. Our finding is in agreement with another study that showed that Crouzon–Pfeiffer patients have a smaller FM compared to age matched controls.[33] In addition, we found that this size difference is already present at birth, when intra-occipital synchondroses (IOS) were mostly open. Similar to controls, the posterior IOS close before the anterior IOS. In Crouzon-Pfeiffer patients both anterior and posterior IOS fused prematurely (p< 0.01), while in Apert patients only the posterior IOS fused prematurely (p= 0.028). Premature fusion of the intra-occipital synchondroses was not seen in any other craniosynostosis syndrome, though these patients also had a reduced FM size. Therefore, a reduced FM size can partially be explained by a premature fusion of the synchondroses, and partially by hypoplasia of the occipital bone. Enlarged ventricular size, assessed by the fronto-occipital horn ratio (FOHR) was significantly associated with a reduced FM size; though this relation was very weak (R=0.04). A reduced FM may reduce CSF outflow and, hence, causes enlargement of the ventricles. A smaller FM size, however, could not be related to the presence of CMI (p= 0.36).

The presence of moderate/severe OSA is significantly related to the presence of ICH.[27] The risk for developing OSA is almost 70% in patients with syndromic craniosynostosis,[20] and is caused by either an obstruction at the level of the rhinopharynx, oropharynx, or hypopharynx (including midface hypoplasia, hypertrophic adenotonsils, narrow nasal cavity, collapse of the pharyngeal walls, and mandibular hypoplasia). Untreated OSA can lead to major physical and functional impairment, including disturbed cognitive functions and delayed development.[34] Endoscopy of the nose, uvulopalatine plane, tongue base, hypopharynx, and larynx in patients with Apert and Crouzon-Pfeiffer syndromes showed a multilevel obstruction in 82% of the patients with OSA. Moreover, after midface advancement the Bachar's severity index (a score for severity and level of obstruction as evaluated by upper airway endoscopy)[35] decreases in 88% of the patients, and OSA disappeared in all patients. However, residual obstruction is still seen in all patients, mostly at the level of the tongue and the uvulopalatine plane.[36]

Taken this all together (**table 1**), skull vault surgery resolves ICH. However, when OSA is not well under control, ICP may rise again and ICH will relapse. The age at vault expansion surgery is important. Surgery at a very young age may decrease the restricting effect of synostosis on the growing brain,

which possibly leads to adverse developmental effects. However, the ossification rate is high during young age and, hence, early surgery may result in a high recurrence rate. Therefore, it is preferable to perform surgery at a later age, although this should not be delayed for patients with ICH.[37] While it is of great interest to compare the diverse treatment protocols of the different institutes, results about the outcome of patients who are treated at different ages are lacking.

Table 1: Overview of possible contributors to intracranial hypertension per craniosynostosis syndrome.

	Apert	Crouzon-Pfeiffer	Muenke	Saethre-Chotzen	Complex
Brain volume	Normal	Normal	Normal	Normal	Normal
Ventricles	Enlarged	Normal	Normal	Normal	Normal
Posterior fossa	Enlarged	Normal	Enlarged	Normal	Normal
Cerebellum	Normal	Normal	Enlarged	Normal	Normal
Tonsillar herniation	26%	61%	47%	17%	52%
Foramen magnum	Reduced	Reduced	Reduced	Reduced	Reduced
OSA	Severe	Severe	Mild	Mild	Mild

Hence, we can distinguish major contributors to ICH such as OFC/ICV over time and OSA from minor contributors including ventricular volume, posterior fossa overcrowding, and FM size. Next to this mechanic concept, it is also possible that the genetic mutation responsible for the different syndromes may predetermine a certain predisposition towards impaired brain development. Patients with Apert or Crouzon-Pfeiffer syndromes due to a mutation in *FGFR2* have the most severe phenotype, followed by those with mutations in *TWIST1*, while the mildest phenotype is seen in craniosynostosis patients with *FGFR3* involvement.

Brain and cognition

Previous studies have shown that cognitive and behavior functions may be impaired in children with nonsyndromic and syndromic craniosynostosis. Maliepaard et al. studied a group of 82 syndromic craniosynostosis patients, and found the intelligence quotient (IQ) to be within the normal range (96.6±21.6). In addition, patients with Apert syndrome were the only ones with a lower IQ than the normal population (76.7±13.3).[38] Similar findings have been found by Da Costa et al., who studied a small cohort of children aged between 7 and 16 years old with nonsyndromic (n=18) and syndromic craniosynostosis (n=13). In their study, the majority (77%) of children with syndromic craniosynostosis had a normal intelligence. Additionally, IQ was significantly lower in children with syndromic craniosynostosis than in nonsyndromic craniosynostosis (83.1±21.9 versus 104.7±15.8).[39] Renier et al. showed that the percentage of craniosynostosis patients (including scaphocephaly, trigonocephaly, plagiocephaly, brachycephaly, complex craniosynostosis, Apert, and Crouzon syndromes) with a normal cognitive outcome is higher among those who had surgery before one year of age compared to patients who were treated at an older age. However, no further details are mentioned about the

IQ level.[29] In contrast, other studies showed that postoperative developmental quotient (DQ)/ IQ in patients with nonsyndromic frontal plagiocephaly did not change depending on the age at cranial vault surgery. Surgery after the age of 1 year did, however, correlated with a higher prevalence of raised ICP.[40] Maliepaard et al. found that 16% of the people within the normal population has an IQ <85, while this proportion is much higher in the craniosynostosis group; namely 67% in Apert patients, 22% in Crouzon-Pfeiffer patients, 39% in Muenke patients, 21% in Saethre-Chotzen patients, and 30% in patients with complex craniosynostosis.[38] For the affected patients, an IQ below 80 means inability to work and live independently. In general, the main predictor of long-term cognitive outcome is the initial developmental stage. It remains unknown whether cognitive outcome is related to the brain abnormalities detected on CT or MR, including (non-progressive) ventriculomegaly, agenesis or thinning of the corpus callosum, agenesis of the septum pellucidum, paucity of the antero-mesial temporal white matter, medial temporal lobe hypoplasia, pyramidal hypoplasia, venous malformations, and CMI.

Diffusion tensor imaging (DTI) is an MRI technique that can be used to investigate white matter microstructure within the brain. By measuring the diffusion of water molecules in a biological tissue such as the brain, quantitative information of the structure can be obtained. This information reflects the spatial orientation of microstructures, such as white matter fibers. Commonly used diffusion properties for studying white matter integrity include: fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). DTI has particularly been used in patients with hydrocephalus or dementia, while there is only limited literature about the application of DTI to study children with congenital abnormalities, such as craniosynostosis. Our study showed that it is challenging to perform DTI-fiber tractography in patients with craniosynostosis syndromes. This was caused by partial volume effects due to an anisotropic voxel size we used, and due to the deformed brain structures and abnormal ventricular shape and size. To provide reliable fiber tracts, adaption of standard fiber tracking protocols was essential. FA of the mean white matter in syndromic craniosynostosis patients was equal to that in controls (0.44 versus 0.45±0.02, p= .536), indicating that these patients have a normal organization of white matter tracts. However, MD, RD and AD were increased (p< 0.001). This suggests abnormal microstructural tissue properties of the investigated white matter tracts. No craniosynostosis syndrome-specific difference in DTI properties was seen for any of the fiber tracts studied in this work. We found that cingulated gyrus and corticospinal tracts were mostly affected.

Unfortunately, there are only a few DTI studies on children with craniosynostosis, and only 1 of them focused on syndromic craniosynostosis. Using a single region of interest (ROI) approach, Florisson et al. showed lower FA values in the mean white matter of craniosynostosis patients compared to controls, which is in contrast to our study. This difference can be explained by the different technique and software that was used. The use of a single ROI is less reliable than performing fiber tractography, and might overestimate the FA of the single structure. However, both studies showed higher mean white matter diffusivity values in patients with craniosynostosis syndromes (globally and for the individual craniosynostosis syndromes).[41] A recent study performed at day of life 12, 25, and 42 in rabbits with

naturally occurring coronal suture synostosis showed a significant lower FA in the corpus callosum, cingulum and fibriae in animals with bicoronal suture synostosis compared to wild types. In addition, ADC and RD were higher in craniosynostosis rabbits compared to wild types at day of life 25 and 42. Remarkably, when craniosynostosis rabbits underwent suturectomy at day of life 1, they had similar FA, ADC and RD values compared to wild types. This indicates that white matter microstructural changes due to craniosynostosis are reversible after suturectomy.[42] In our patient population all patients were treated by skull vault surgery within the first year of life, and we found postsurgical changes in DTI scalars. Based on the results of the rabbit model by Bonfield et al., our patients were treated too late or insufficiently, or other factors such as sleep apnea may cause the changes in DTI scalars.[43] Patients with OSA have intermittent hypoxia during sleep. Hypoxia decreases the O_2 supply to brain tissue causing a failure of energy delivery and, subsequently, cell depolarization and derangement of the ionic balance.[44-48] If this process is prolonged, it can lead to cytotoxic and neurotoxic edema with reduced extracellular/extra-axonal volume, which can be easily measured using DTI-FT.[49, 50] In addition, clinical studies revealed that mild-severe OSA (AH>15) in adults may injure different brain structures, in particular cerebellar and limbic regions, as well as interconnecting fibers,[51-53] such as corpus callosum, cingulum bundle, fornix, internal capsule, cerebellar peduncles, and corticospinal tracts.[52] Injury to these brain structures may be responsible for short-term memory and planning deficits, and increased mood and anxiety symptoms seen in these patients.[54-56]

Within our group of patients, we did not find more severe changes in DTI scalars in patients with high (e.g. Apert and Crouzon syndromes) compared to low (e.g. Muenke or Saethre-Chotzen syndromes) risk to develop OSA. However, the presence and severity of OSA was not considered in our study. Therefore, the role of OSA as well as the type of genetic mutation and the presence of ICH cannot be excluded as potential causes of changes in DTI scalars of white matter structures. Hence, it is crucial to study white matter micro-architecture in very young, untreated craniosynostosis patients who did not develop yet any episodes of ICH. This is the only approach that may allow us to understand the timing of secondary white matter injuries and distinguish them from intrinsic (primary) causes, like the genetic mutation.

CONCLUSION

After interpretation of our results and the available literature, restricted growth of the skull within the first year after birth seems to be less important than previously thought. The skull volume is not reduced, and the brain volume is not increased in patients with craniosynostosis syndromes. Skull vault expansion can temporarily reduce ICP, but it will rise again if the primary cause is not managed or additional pathophysiological processes such as OSA interfere. Several years after skull vault surgery, ICH is related to both OSA and a stagnating OFC, causing a disproportion between skull vault and brain. A detailed knowledge about the underlying problems in children with craniosynostosis syndromes is paramount to offer them very specific treatment. Future studies are needed to detect patient specific risk profiles and, hence, optimize the treatment.

Limitations

The main limitation of the presented studies is the cross-sectional nature. The pathophysiology of increased ICP is a dynamic and multi-factorial process that needs longitudinal data to be studied in an optimal way. In addition, syndromic and complex craniosynostosis are rare diseases. High-quality conventional and advanced (e.g. DTI) imaging data sets of control subjects are difficult to find, challenging the selection of age and gender matched controls. Therefore, we had to apply more complex statistical models that, however, reduced the statistical power. Lastly, all patients included in our studies have been treated according to our departmental protocol for patients with craniosynostosis syndromes and our results are not applicable to patients who have been treated with other protocols. Since different treatment and follow-up protocols are used among the different institutes, it is of great importance to compare the outcome of the patients. Unfortunately, it is difficult to compare data between different clinics, because detailed and accurate clinical data are usually missing. It would be beneficial for data comparison to standardize measurement methods for e.g. ICH and cognitive functions, as well as the content and frequency of follow-up examinations. An international collaboration between institutes treating patients with craniosynostosis is highly needed to achieve this goal and should be initiated in European countries.

Future perspectives

The development of ICH within patients with syndromic and complex craniosynostosis is a complex and dynamic process. For full understanding, longitudinal data need to be studied in a model that incorporates all possible predictors of increased ICP including OFC, OSA, ventricular size, brain size, ICV, presence of TH or CMI, vascular abnormalities including stenosis of the jugular veins, and closing of the skull sutures and skull base synchondroses. As example, the study of the relationship between CMI and ventriculomegaly will need longitudinal MR data to understand which one is the causative factor. In addition, the volume ratio between ICV, brain, and ventricular volume needs to be followed over time to understand the timing and causes of occurring disproportion between these measurements. Finally, all these measurements need to be correlated with the presence of ICH.

The knowledge about the presence of white matter injury and its relation to cognitive outcome is limited. The comparison of DTI scalars between not-operated craniosynostosis patients with a non-deformed brain and normal ICP and healthy controls may elucidate the influence of genetic mutations rather than environmental factors. In addition, the effect of OSA on white matter micro-architecture needs also to be assessed comparing white matter DTI scalars of craniosynostosis patients with and without OSA.

Arterial spin labeling (ASL) is an MRI modality that can be used to study perfusion of the entire brain, which comes closest to measure neural activity. Thereby, ASL uses magnetically labeled water molecules within the arterial blood, while the perfusion is visualized on MR images. It would be interesting to know whether closure of the skull sutures results in a reduced perfusion of the brain, in the entire brain, specific systems of the brain, and beneath the involved skull suture. In addition, the effect of OSA on brain perfusion should be studied as well.

In terms of the surgical treatment of ICH, it would be interesting to compare the outcomes between patients who underwent an occipital vault expansion and those who underwent surgery that includes treatment of OSA as well, like a monobloc procedure. When OSA is the cause of the ICH, treating OSA should be preferred. Therefore, surgical and non-surgical interventions/ treatment should be included in this study model as well, including tonsillectomy, cranial vault surgery, VP-shunt, and medical drugs. Furthermore, information about neurological and functional disabilities and their relation to specific brain or skull abnormalities or to the genetic mutation will add to the development of patient specific risk profiles, and thus to the treatment of the individual patient.

Clinical recommendations:

An international collaboration between the different institutes treating patients with craniosynostosis is needed to compare the different treatment protocols, and find out how treatment can be optimized. First, the data collection needs to be comparable.

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9

Summary

This thesis was designed to study the pathophysiology of intracranial hypertension and its relation to additional abnormalities of skull and brain in patients with syndromic and complex craniosynostosis. Within this patient population there is a high risk for developing increased intracranial pressure (ICP), due to a disproportion of the skull and brain, venous hypertension, tonsillar herniation/ Chiari I malformation (CMI), enlarged ventricular size, and obstructive sleep apnea syndrome (OSA).

Chapter 1 gives an introduction of the pathophysiology of intracranial hypertension, and of the patient population that is involved. Studies included in this thesis contain different radiological techniques, including 3D Magnetic Resonance Imaging (MRI) to perform volumetric measurements of the brain, ventricles, cerebellum and posterior fossa. In addition, Diffusion Tensor Imaging (DTI) MRI was used to study white matter integrity of corpus callosum, cingulated gyrus, fornix, corticospinal tracts, and medial cerebellar peduncle. 3D computer tomography (CT) scans were studied to evaluate bony and cartilage structures such as the size of the foramen magnum (FM) and the closure timing of its intra-occipital synchondroses. The intracranial volume (ICV) was also measured in 3D CT scans, and then related to the occipital-frontal circumference (OFC), a routine measurement performed at the outpatient clinic to study skull growth. This relation shows the reliability of the OFC in predicting intracranial volume. Lastly, to determine which surgical treatment is superior above the other, different outcome measures including the prevalence of papilledema, the presence of CMI, and visual acuity were compared between patients (Apert and Crouzon-Pfeiffer syndromes) who underwent a fronto-orbital advancement and those who underwent an occipital vault expansion.

MAIN FINDINGS

Chapter 2:

- Patients with craniosynostosis syndromes have a normal brain volume.
- Patients with Apert syndrome have an increased ventricular volume.
- Patients with CMI (most commonly found in Crouzon-Pfeiffer syndrome) have an increased ventricular volume.

Chapter 3:

- Neither volumes of the cerebellum and posterior fossa, nor their volume ratio (CV/PFV) can predict which craniosynostosis syndrome is more prone for developing CMI than others.
- Treatment of intracranial hypertension should focus on the skull vault and other contributors to it, such as OSA and venous hypertension.

Chapter 4:

- Performing DTI–fiber tractography in patients with craniosynostosis is difficult due to partial volume effects caused by deformed brain structures and anisotropic voxel size.
- Patients with craniosynostosis syndromes have a normal fiber organization.
- Patients with craniosynostosis syndromes have increased diffusivity parameters suggesting abnormal microstructural tissue properties of the investigated white matter tracts.

Chapter 5:

- The foramen magnum is smaller in syndromic and complex craniosynostosis patients than in controls.
- This difference can only partially be explained by premature fusion of the intra-occipital synchondroses.
- This difference is already present at birth; therefore hypoplasia of the occipital bones is likely to contribute as well.

Chapter 6:

- OFC is a significant predictor of the ICV in patients with syndromic and complex craniosynostosis.
- Measuring the OFC during clinical practice is useful in determining which patients are at risk for impaired skull growth.

Chapter 7:

- Within patients with Apert and Crouzon-Pfeiffer syndromes an occipital vault expansion results in a greater increase in ICV, reduces the incidences of tonsillar herniation and papilledema compared to those who underwent a frontoorbital advancement.
- Occipital vault expansion should be the initial craniofacial procedure in patients with Apert and Crouzon-Pfeiffer syndromes.

Craniocerebral disproportion refers to a mismatch between brain and ICV of the skull, including brain, blood and cerebrospinal fluid. A mismatch can either be caused by a reduced skull growth, or by increased ICV. Earlier studies showed that ICV is normal or even enlarged in craniosynostosis patients. Therefore it seems that the compensatory skull growth is sufficient for normal brain growth. Only 1 study was performed in Crouzon-Pfeiffer that measured brain volume, indicating it was equal to controls. **Chapter 2** of this thesis described that the brain volume in the most distinct craniosynostosis syndromes including Apert, Crouzon-Pfeiffer, Muenke, and Seathre-Chotzen and in complex craniosynostosis patients is equal to control subjects, between the range of 1 – 12 years. This indicates that brain volume is not affected by the genetic mutations, and also not reduced by potentially restricted skull growth. The brain grows mostly within the first 5 years of life, and age has a significant influence on brain volume. Therefore, this period is of most interest for developing a mismatch between brain and skull. In addition, we found that a CMI was found in 14% of our patients, including 8% in Apert, 32% in Crouzon-Pfeiffer, and 7% in Muenke syndrome. Ventricular volume was not related to age. Enlarged ventricular volume was particularly found in Apert patients and in patients with CMI, which was most commonly found in Crouzon-Pfeiffer patients (32%). Corrected for the presence of CMI, the diagnosis of Crouzon-Pfeiffer was not associated to an enlarged ventricular volume. This means that enlarged ventricular size is more specific for CMI than for Crouzon-Pfeiffer syndrome.

Data about cerebellar and posterior fossa volumes in syndromic and complex craniosynostosis patients were lacking. **Chapter 3** compares cerebellar and posterior fossa volumes (CV and PFV, respectively), including their ratio (CV/PFV) of craniosynostosis patients to that of controls. The posterior

fossa is bordered by the cerebellar tentorium, tentorial insura, dural walls of the jugular foramen, clivus, FM and exoccipital bones, and includes the brainstem (pons, medulla oblongata and inferior part of the midbrain), the 4th ventricle, 2 cisterns with their outlets, and the cerebellum. The cerebellar volume includes the two cerebellar hemispheres, vermis, but not the 4th ventricle. This study demonstrates that cerebellar and posterior fossa volumes are not predictive for developing CMI, nor is their ratio. We found that both volumes are normal or even larger in craniosynostosis patients; patients with Apert and Muenke syndrome had a larger posterior fossa compared to controls, whereas the cerebellum was also larger in Muenke patients. Moreover, the volume ratio did not exceed that in controls, in none of the syndromes. In Apert syndrome this ratio was even smaller than controls; indicating that the cerebellum was located in a relatively large posterior fossa. Although craniosynostosis patients with CMI had a higher CV/PFV ratio than controls, the difference was very small, and the range of the CV/PFV ratio felt within that of controls. Therefore, the involvement of posterior fossa overcrowding is assumed to play a minor role in causing CMI. Hence, treatment of increased ICP should be less focused at the posterior fossa.

Besides structural and dynamical abnormalities of the brain and skull, patients with craniosynostosis syndromes are prone for having disturbances of the white matter of the brain. White matter integrity can be studied with the use of diffusion tensor imaging (DTI). DTI measures the direction of water molecules along a certain white matter tract, as explained in **chapter 4**. This can be done by placing a single region of interest (ROI), or with the use of fiber tractography (FT). The latter technique should give more objective and more complete information about the white matter tract since it measures diffusion parameters over the whole tract rather than at a certain location in the tract. We experienced that DTI-FT is difficult to perform in patients with skull and brain deformities. Therefore, standard protocols were adapted to include reliably measurements. Fractional anisotropy (FA) appears to be equal between controls and craniosynostosis patients, however diffusivity properties are higher in craniosynostosis patients, indicating myelin loss and axonal injury. Since only operated craniosynostosis patients were included in our study, we cannot distinguish between a primary cause of the genetic mutation and a secondary cause by the skull and brain deformity itself. Although we corrected for ventricular size, and did not found a relation between DTI parameters and ventricular size, we can not predict the effect of ventriculomegaly on white matter for a certain amount of time.

The human skull is caudally bordered by the FM. The FM is formed by occipital bones which are connected to each other via 4 cartilage structures called intra-occipital synchondroses. It enables CSF, which is produced in the choroid plexus and transported via the third and fourth ventricle, to exit the skull and to enter the spinal sac. In **chapter 5a**, we studied FM size in Crouzon-Pfeiffer patients and the closure of its intra-occipital synchondroses; the anterior and posterior intra-occipital synchondroses, AIOS and PIOS respectively. These synchondroses are the cartilaginous joints that allow the FM to expand, which is necessary to develop a sufficient CSF passage between the cranial cavity and the spinal sac. This study revealed that the FM is smaller in Crouzon-Pfeiffer patients than in healthy controls. Therefore we wondered whether this was specific for Crouzon-Pfeiffer patients, and may be involved in developing intracranial hypertension. Consequently, we studied FM size in the other craniosynostosis syndromes as well, see **chapter 5b**. We found that FM size is smaller in different craniosynostosis

syndromes; Apert, Crouzon-pfeiffer, Muenke, Saethre-Chotzen syndromes, as well as in complex craniosynostosis. Moreover, in Crouzon-Pfeiffer patients both AIOS and PIOS close prematurely, while in Apert patients only PIOS fuse prematurely. Remarkably this size difference is already present at birth, which indicates that prematurely fusion of intra-occipital synchondroses is not the only cause. Due to the genetic mutation, hypoplasia of the occipital bones is likely to be involved as well.

During follow-up, craniosynostosis patients are frequently seen at the outpatient clinic to study general health, the presence of papilledema by fundoscopy, and head circumference, indicators for the presence of increased ICP. Evaluating long-term follow-up measurements of head circumference, i.e. occipito-frontal circumference (OFC) gives information about skull growth. Until now it was unclear whether head circumference measurement gave reliable information about skull growth and ICV, and consequently whether patients were developing craniocerebral disproportion. It seems that in healthy controls this relation is high (r= 0.98). In **chapter 6** we described that in our craniosynostosis patients, this relation is also high for the most distinct syndromes together (r= 0.91). Moreover, the correlation was high per craniosynostosis syndrome, for operated and not-operated patients separately, and even for patients with a turricephalic skull shape. Therefore, we can conclude that head circumference measurement is a reliable predictor for ICV, which makes it a rapid and accurate method to monitor skull growth during follow-up at the outpatient clinic.

Until 2005, a fronto-orbital advancement was preferred as first surgical procedure for vault expansion in patients with different craniosynostosis syndromes (including those with the involvement of both coronal sutures and lambdoid sutures). However, following a presentation of professor Hayward, the protocol in our hospital changed by performing an occipital vault expansion as first surgical procedure in patients with Apert and Crouzon-Pfeiffer syndromes, in whom coronal sutures are mostly involved. In **Chapter 7** we described that an occipital expansion indeed results in a greater increase of ICV, and reduces the incidences of tonsillar herniation and papilledema, after 5 years of follow-up. Other advantages of an occipital expansion compared to frontoorbital advancement are: lower risk of device infection, shorter surgery time, and less blood loss during surgery.

Taken all these results together we can conclude that restricted growth of the skull directly after birth seems to be less important than previously thought. In addition, brain volume is normal in craniosynostosis patients. Skull vault surgery can temporarily reduce ICP, however ICP will rise again whenever the actual cause is not treated well, or whenever other pathophysiological processes interfere, such as OSA. After skull vault surgery, skull growth may become restricted. Therefore, both OSA and a stagnating OFC are related to developing intracranial hypertension. In case OSA treatment would be sufficient, cranial vault expansion may be overtreatment of the patient. Future studies need to reveal patient specific risk profiles, to evaluate individual problems, and consequently optimize individual treatment. Hence, we recommend an international collaboration between different institutes to compare their treatment protocols, and discover the advantages and disadvantages of each protocol.

10 Nederlandse samenvatting

Dit proefschrift beschrijft de pathofysiologie van intracraniële hypertensie en haar relatie tot afwijkingen van de schedel en de hersenen in patiënten met een syndromale of complexe craniosynostose. Binnen deze patiëntenpopulatie is er een hoog risico voor het ontwikkelen van verhoogde intracraniële druk, de volgende factoren spelen daarbij een rol: een wanverhouding tussen schedel en hersenen, de aanwezigheid van veneuze hypertensie, het hebben van een tonsillaire herniatie/ Chiari I malformatie (CMI), vergrootte ventrikels, en obstructief slaapapneu (OSA).

Hoofdstuk 1 geeft een introductie over de pathofysiologie van intracraniële hypertensie en over de patiëntenpopulatie. Voor de studies in dit proefschrift zijn verschillende radiologische technieken gebruikt, waaronder 3D Magnetic Resonance Imaging (MRI) om volumes van de hersenen, ventrikels, cerebellum en fossa posterior te meten. Daarnaast werd Diffusion Tensor Imaging (DTI) MRI gebruikt om de integriteit van verschillende witte stof banen in de hersenen te meten, zoals die van het corpus callosum, cingulum, fornix, corticospinale banen en mediale cerebellaire baan. 3D computer tomografie (CT) scans werden gebruikt om bot en kraakbeen structuren te evalueren, zoals de grootte van het foramen magnum (FM) en het moment van sluiten van de intra-occipitale synchrondroses. Het intracraniële volume (ICV) werd ook gemeten in 3D CT-scans, en gerelateerd an de occipitale-frontale omtrek (OFC), een routine-meting uitgevoerd op de polikliniek ter follow-up van de schedelgroei. Er kon worden aangetoond dat de OFC een hoog voorspellende waarde heeft voor het bepalen van het ICV. Tenslotte, om te bepalen welke chirurgische behandeling superieur is boven de ander, werden resultaten zoals de prevalentie van papiloedeem, de aanwezigheid van CMI en de visus vergeleken tussen patiënten (Apert en Crouzon-Pfeiffer syndroom) die een fronto-orbitale schedelverruiming hebben ondergaan met hen die een occipitale schedelverruiming ondergingen.

BELANGRIJKSTE BEVINDINGEN

Hoofdstuk 2:

- Patiënten met craniosynostose syndromen hebben een normaal hersenvolume.
- Patiënten met Apert syndroom hebben een vergroot ventrikelvolume.
- Patiënten met een CMI (het meest gevonden in Crouzon-Pfeiffer syndroom) hebben een vergroot ventrikelvolume.

Hoofdstuk 3:

- Noch het volume van het cerebellum en/of de fossa posterior, noch hun volume verhouding (CV/ PFV) kunnen voorspellen welk craniosynostose syndroom een verhoogd risico heeft op het ontwikkelen van een CMI.
- De behandeling van intracraniële hypertensie moet zich niet zozeer richten op de fossa posterior, maar meer op het totale schedelvolume en andere bijdragende factoren, zoals OSA en veneuze hypertensie.

Hoofdstuk 4:

- Het uitvoeren van DTI-fibertractografie bij patiënten met craniosynostose is complex, dit is te wijten aan 'partial volume effects', welke veroorzaakt worden door de deformiteit van de verschillende hersenstructuren en het gebruik van een anisotrope voxelgrootte.
- Patiënten met craniosynostose syndromen hebben een normale organisatie van de onderzochte witte stof banen.
- Patiënten met craniosynostose syndromen hebben verhoogde diffusiviteit parameters, wat suggereert dat er een abnormale microstructuur aanwezig is van de onderzochte witte stof banen.

Hoofdstuk 5:

- Het foramen magnum is kleiner in syndromale en complexe craniosynostose patiënten dan in de controle groep.
- Dit verschil kan slechts ten dele worden verklaard door voortijdige sluiten van de intra-occipitale synchrondrosen.
- Dit verschil is al aanwezig bij de geboorte; daarom is het zeer waarschijnlijk dat hypoplasie van het occipitale bot hieraan een bijdrage levert.

Hoofdstuk 6:

- OFC is een belangrijke voorspeller van het ICV bij patiënten met syndromale en complexe craniosynostose.
- Het meten van de OFC tijdens de klinische praktijk is nuttig bij het bepalen welke patiënten een verhoogd risico hebben op een verminderde schedelgroei.

Hoofdstuk 7:

- Binnen de groep patiënten met Apert en Crouzon-Pfeiffer syndroom resulteert een occipitale schedel expansie in een grotere toename van het ICV, een lager percentage tonsillare herniatie en minder papilledema in vergelijking met hen die een fronto-orbitale schedelverruiming ondergingen.
- Een occipitale schedel expansie, ter voorkoming van het ontwikkelen van intracraniële hypertensie, moet de initiële craniofaciale procedure zijn in de behandeling van patiënten met Apert en Crouzon-Pfeiffer syndroom.

Craniocerebrale disproportie verwijst naar een disbalans tussen hersen- en schedel volume, inclusief hersenen, bloed en liquor. Een dergelijke disbalans kan ofwel veroorzaakt worden door een verminderde groei van de schedel of door een verhoogd intracranieel volume. Eerdere studies toonden aan dat het ICV normaal tot zelfs vergroot is in craniosynostose patiënten. De schedelgroei lijkt dus voldoende voor een normale groei van de hersenen. Er is slechts 1 studie in de literatuur, uitgevoerd in Crouzon-Pfeiffer patiënten, waar het hersenvolume werd gemeten; deze studie geeft

aan dat het hersenvolume gelijk is tussen Crouzon-Pfeiffer patiënten en controles. In **hoofdstuk 2** van dit proefschrift wordt beschreven dat het hersenvolume in de meest voorkomende craniosynostose syndromen waaronder Apert, Crouzon-Pfeiffer, Muenke en Saethre-Chotzen syndroom, en in complexe craniosynostose patiënten gelijk is aan controles, tussen de range van 1-12 jaar. Dit geeft aan dat het hersenvolume niet wordt beïnvloed door de genetische mutaties en evenmin lijkt er een beperkende schedelgroei te zijn. De hersenen groeien met name binnen de eerste 5 levensjaren, waarbij leeftijd een significant effect heeft op het hersenvolume. Deze periode is daarom het meest kwetsbaar voor het ontwikkelen van een disbalans tussen hersen- en schedelvolume. In 14% van onze patiënten werd een CMI gevonden, waarvan 8% in Apert, 32% in Crouzon-Pfeiffer en 7% in Muenke syndroom. Het ventrikelvolume was niet gerelateerd aan de leeftijd. Een vergroot ventrikelvolume werd vooral gevonden in Apert patiënten en in patiënten met een CMI, welke het vaakst werd gezien in Crouzon-Pfeiffer patiënten (32%). Gecorrigeerd voor het hebben van een CMI, werd de diagnose Crouzon-Pfeiffer niet geassocieerd met een vergroot ventrikelvolume. Dit betekent dat het hebben van vergrootte ventrikels meer specifiek is voor het hebben van een CMI dan voor de diagnose Crouzon-Pfeiffer syndroom.

Tot op heden was er weinig bekend over het volume van het cerebellum en de fossa posterior in syndromale en complexe craniosynostose patiënten. **Hoofdstuk 3** toont de verschillende volumes, en vergelijkt deze tussen craniosynostose patiënten en controles. Naast de volumes wordt ook de verhouding tussen deze volumes (CV/ PFV) vergeleken tussen beide groepen. De fossa posterior wordt begrensd door het tentorium van het cerebellum, de dura bekleding van het foramen jugularis, de clivus, het FM en het occipitale bot, en het omvat de hersenstam (pons, medulla oblongata en het inferieure deel van het mesencephalon), de 4e ventrikel, 2 cisternen, en het cerebellum. Het volume van het cerebellum omvat de twee cerebellaire hemisferen, de vermis, exclusief de 4e ventrikel. Deze studie toont aan dat noch volumes van het cerebellum en fossa posterior, noch hun volume ratio, voorspellend zijn voor de ontwikkeling van CMI. Beide volumes werden normaal of zelfs groter bevonden in craniosynostose patiënten; patiënten met Apert en Muenke syndroom hadden een grotere fossa posterior in vergelijking met controles. Het cerebellum was ook groter in Muenke patiënten. In geen van de verschillende craniosynostose syndromen overschreed de volume ratio die van controles. In Apert syndroom was deze volume ratio zelfs lager kleiner dan in controles; wat aangeeft dat het cerebellum in een relatief grote fossa posterior gelegen was.

Hoewel craniosynostose patiënten met CMI een hogere CV/ PFV ratio laten zien dan controles, was dit verschil zeer klein en de range van de CV/ PFV ratio viel binnen die van de controle groep. Een disbalans tussen cerebellum en fossa posterior lijkt een kleinere rol spelen bij het veroorzaken van CMI dan eerder verondersteld. De behandeling van intracraniële hypertensie zal minder op de fossa posterior gericht moeten zijn.

Naast structurele en dynamische afwijkingen van de hersenen en schedel, kunnen patiënten met craniosynostose syndromen afwijkingen hebben aan de witte stof banen van de hersenen. Integriteit van de witte stof kan worden bestudeerd met behulp van 'Diffusion Tensor Imaging' (DTI). DTI meet de richting van watermoleculen in een bepaalde witte stof baan, zoals uitgelegd staat in **hoofdstuk 4**.

Dit kan op verschillende manieren, bijvoorbeeld door het plaatsen van een enkele 'region of interest' (ROI) of met behulp van fibertractografie (FT). De laatste techniek is een objectievere maat en geeft volledigere informatie over de witte stof baan in vergelijking met de informatie die wordt verkregen door enkel een lokale ROI te plaatsen. DTI-FT is complex in de uitvoering binnen patiënten met schedel- en hersenendeformiteiten. Daarom werden standaardprotocollen aangepast om betrouwbare metingen te bewerkstelligen. Fractionele anisotropie (FA) was gelijk tussen craniosynostose patiënten en controles, maar diffusie parameters waren hoger in craniosynostose patiënten dan in controles, wat duidt op myeline verlies en axonale schade. Gezien het feit dat enkel geopereerde craniosynostose patiënten in ons onderzoek geincludeerd waren, kunnen we geen onderscheid maken tussen een primaire oorzaak (door de genetische mutatie) en een secundaire oorzaak (door de schedel- en hersendeformiteit zelf). Hoewel er statistisch gecorrigeerd werd voor ventrikel grootte en er geen relatie aangetoond kon worden tussen DTI parameters en ventrikel grootte, kunnen we het lange termijneffect van ventriculomegalie op de integriteit van de witte stof niet voorspellen.

De schedel wordt caudaal begrensd door het FM. Het FM wordt gevormd door het occipitale bot, welke is verbonden via 4 kraakbeenstructuren, genaamd: intra-occipitale synchrondrosen. Het FM zorgt ervoor dat liquor, geproduceerd in de choroid plexus en getransporteerd via de derde en vierde ventrikel, de schedel kan verlaten richting het spinale kanaal. **In hoofdstuk 5a**, bestudeerden we de grootte van het FM in Crouzon-Pfeiffer patiënten en ook de sluiting van de voorste en achterste intra-occipitale synchrondrosen. Deze synchrondrosen zijn de kraakbenige structuren waardoor het FM kan uitzetten in diameter, dit is nodig om voldoende doorgang te ontwikkelen voor de liquor afvloed. De studie toonde aan dat het FM kleiner is in Crouzon-Pfeiffer patiënten dan in gezonde controles. Er werd verondersteld dat dit specifiek voor Crouzon-Pfeiffer patiënten zou zijn, en deze bevinding mogelijk betrokken kan zijn in de ontwikkeling van intracraniële hypertensie. Als gevolg daarvan werd het FM ook in de andere craniosynostose syndromen bestudeerd, zie **hoofdstuk 5b**. In vergelijking met controles, blijkt het FM kleiner te zijn in de verschillende craniosynostose syndromen; Apert, Crouzon-pfeiffer, Muenke, Sæthre-Chotzen syndroom, evenals in complexe craniosynostose. In Crouzon-Pfeiffer patiënten kan dit worden toegeschreven aan het voortijdig sluiten van zowel de voorste als de achterste intra-occipitaal synchondrosen. Terwijl in Apert patiënten alleen de achterste intra-occipitale synchondrosen voortijdig sluiten. Opmerkelijk is dat dit verschil in grootte al aanwezig is bij de geboorte, wat aangeeft dat een kleiner FM niet geheel toe te schrijven is aan het voortijdig sluiten van intra-occipitale synchrondrosen. Hypoplasie van de occipitale bot, als gevolg van de genetische mutatie speelt waarschijnlijk ook een rol.

Tijdens de follow-up worden craniosynostose patiënten gezien op de polikliniek waarbij er gekeken wordt naar de algemene gezondheid, de aanwezigheid van papilledema door middel van fundoscopie en wordt de schedelomtrek gemeten; dit zijn indicatoren voor de aanwezigheid van intracraniële hypertensie. Evaluatie van lange termijn follow-up metingen van de schedelomtrek, geeft informatie over de schedelgroei. Tot nu toe was het onduidelijk of de schedelomtrek betrouwbare informatie gaf over de groei van de schedel en het ICV, en als gevolg daarvan een disbalans ontwikkelden tussen schedel- en hersenvolume. Binnen controles is de correlatie tussen

OFC en ICV hoog (r= 0.98). In **hoofdstuk 6** wordt beschreven dat deze relatie ook hoog is in onze craniosynostose patiënten, voor de verschillende syndromen tezamen (r= 0.91). Tevens is de correlatie hoog per craniosynostose syndroom, voor geopereerde en voor niet-geopereerde patiënten, en zelfs voor patiënten met een turricephalie. We kunnen dan ook concluderen dat de schedelomtrek een betrouwbare voorspeller is voor het ICV, en dus een snelle en nauwkeurige methode is om de schedelgroei tijdens de follow-up op de polikliniek te controleren.

Tot 2005 had een fronto-orbitale schedel verruimming de voorkeur in de behandeling van patiënten met verschillende craniosynostose syndromen (waaronder die met de betrokkenheid van zowel coronanaden als lambdoïdnaden). Echter, na een presentatie van professor Hayward, is het protocol in ons ziekenhuis veranderd; er werd gekozen om een occipitale schedelexpansie als eerste chirurgische ingreep in te voeren bij patiënten met Apert en Crouzon-Pfeiffer syndroom, in wie voornamelijk coronanaden zijn aangedaan. In **hoofdstuk 7** beschrijven we dat een occipitale schedelexpansie resulteert in een grotere toename van intracranieel volume en een verminderde incidentie van tonsillaire herniatie en papiloedeem, na follow-up van 5 jaar. Andere voordelen van een occipitale schedelexpansie, ten opzichte van fronto-orbitale expansie, zijn: een lager risico op infectie van distractoren, een kortere operatie tijd en minder bloedverlies perioperatief.

Alle resultaten samen genomen, kunnen we concluderen dat de beperkte groei van de schedel direct na de geboorte minder belangrijk lijkt dan eerder gedacht. Het hersenvolume is normaal in craniosynostose patiënten. Schedel verruimende chirurgie kan intracraniële druk tijdelijk verlagen, maar deze zal weer stijgen wanneer de werkelijke oorzaak niet goed behandeld wordt of wanneer andere pathofysiologische processen, zoals OSA, interfereren. Zelfs na een schedelexpansie kan de schedelgroei beperkt raken. Daardoor zijn zowel OSA en een stagnerende groeicurve van de schedel gerelateerd aan de ontwikkeling van intracraniële hypertensie. Mocht de behandeling van OSA voldoende zijn, dan wordt een schedelexpansie gezien als overbehandeling van de patiënt. Toekomstige studies moeten patiënt specifieke risicoprofielen in kaart brengen, om de individuele behandeling te optimaliseren. Daarom pleiten we voor een internationale samenwerking tussen verschillende instituten om de behandelingsprotocollen met elkaar te vergelijken, en de voor- en nadelen van elk protocol te achterhalen.

11

Appendices

List of publications
PhD portfolio
Dankwoord
Curriculum Vitae

LIST OF PUBLICATIONS

Brain and ventricular volume in patients with syndromic and complex craniosynostosis.
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PHD PORTFOLIO

Name PhD student:	Bianca Francisca Maria Rijken
Erasmus MC department:	Plastic and Reconstructive surgery, and Hand surgery
PhD period:	September 2011 – April 2016
Promotor:	Prof. dr. I.M.J. Mathijssen
Co-promotor:	Dr. M.H. Lequin

PHD TRAINING	YEAR	ECTS
COURSES		
General academic skills		
Basiscursus Regelgeving en Organisatie (BROK), *Erasmus University Medical Center, Rotterdam*	2011	0.3
Biomedical English writing and communication, *Erasmus University Medical Center, Rotterdam*	2012	4
Scientific integrity course, *Erasmus University Medical Center, Rotterdam*	2014	0.3
Research skills		
Introduction to Clinical Research (NIHES PhD), *Erasmus University Medical Center, Rotterdam*	2012	0.7
Biostatistics for Clinicians (NIHES PhD) *Erasmus University Medical Center, Rotterdam*	2012	0.7
In-depth courses		
Microsurgery training *Skillslab, Erasmus University Medical Center, Rotterdam*	2011-2015	13
Workshops		
Nerve reconstruction *Skillslab, Erasmus University Medical Center, Rotterdam*	2012/2014	0.4
Tendon reconstruction *Skillslab, Erasmus University Medical Center, Rotterdam*	2013	0.2
Local transposition flaps *Skillslab, Erasmus University Medical Center, Rotterdam*	2013	0.2

Presentations

International conferences

Syndromic and complex craniosynostosis: A morphometric study of the foramen magnum.		
European Society of *Pediatric Neurosurgery (ESPN), Amsterdam*	2012	1
Syndromic and complex craniosynostosis: Volumetric analysis of the fossa posterior and cerebellum.		
European Society of Pediatric Radiology (ESPR), Athene, Greece	2012	1
Crouzon syndrome: Foramen magnum size and closing of the intra occipital synchondroses.		
International Society of CranioFacial Surgery (ISCFS), Jackson Hole, USA	2013	1
Consensus Conference on Pediatric Neurosurgery (CPN)/ ESPN, Rome, Italy	2013	1
Syndromic craniosynostosis and Chiari I malformation: Is the posterior fossa overcrowded?		
International Society of CranioFacial Surgery (ISCFS), Jackson Hole, USA	2013	1
CPN/ ESPN, Rome, Italy	2013	1
DTI-tractography in children with craniosynostosis syndromes.		
ESPR, Amsterdam	2014	1
Craniosynostosis syndromes: Foramen magnum, ventriculomegaly and Chiari I malformation		
ISCFS, Tokyo, Japan	2015	1
Occipitofrontal circumference predicts intracranial volume in cranio-synostosis syndromes		
ISCFS, Tokyo, Japan	2015	1

National conferences

Syndromale en complexe craniosynostose: Volume meting van het cerebellum en achterste schedelgroeve.		
Nederlandse Vereniging voor Schisis en Aangezichtsafwijkingen (NVSCA), Maastricht	2012	1
Nederlandse Vereniging voor Plastische Chirurgie (NVPC), Groningen	2012	1
Crouzon syndrome: Foramen magnum size and closing of the intra-occipital synchondroses.		
NVSCA, Gent	2013	1
Crouzon syndroom: de grootte van het achterhoofdsgat en de betrokken-heid van de intra-occipitale synchondrosen.		
NVPC, Amsterdam	2014	1

Poster presentations

Are there any volumetric differences of the fossa posterior and cerebellum in Crouzon patients with and without a chiari malformation type I?		
ESPN, Amsterdam & ESPR, Athens, Greece	2012	1
Syndromic and complex craniosynostosis: A morphometric study of the foramen magnum.		
ESPR, Athens, Greece	2012	1
Syndromic and complex craniosynostosis: Volumetric analysis of the fossa posterior and cerebellum.		
ESPN, Amsterdam	2012	1
Diffusion tensor imaging and fiber tractography in children with craniosynostosis syndromes.		
ISCFS, Tokyo, Japan	2015	1

Conference attendance

NVPC conference (6 times)	2011-2014	1.8
4th International Skullbase Course, Erasmus MC, Rotterdam.	2012	0.3
NVSCA conference (3 times)	2012-2014	0.9
Esser Course (5 times)	2012-2014	1.5
CSN/ ESPN conference (2 times)	2012-2013	0.6
Kortjakje 'Zondagsschool voor plastische chirurgie' (2 times)	2012-2013	0.6
ESPR conference (2 times)	2012/2014	0.6
ISCFS conference (2 times)	2013/2015	0.6

TEACHING AND LECTURING

Lecturing

Tutor of first year medical students		
Erasmus University Medical Center	2012	1
Suture techniques- course for medical students		
Erasmus University Medical Center, Rotterdam	2012-2013	2
Lectures for medical students (hand surgery and craniofacial surgery)		
Erasmus University Medical Center, Rotterdam	2012-2014	2
Coach at 'International Course in Microsurgery'		
Skillslab, Erasmus University Medical Center, Rotterdam	2012-2015	2

Supervising medical students

Supervising research projects second and third year medical students (NM, MB)		
Erasmus University Medical Center, Rotterdam	2013-2014	5
Supervising medical thesis of third year medical students (YL, BdO),		
Erasmus University Medical Center, Rotterdam	2013/ 2014	10

Other

Organizing Annual social program of the department of Plastic, Reconstructive, and Hand surgery		
Erasmus University Medical Center, Rotterdam	2012-2013	1
Organizing 20th Esser Course: To the base of the Thumb		
Erasmus University Medical Center, Rotterdam	2013	2
Developing OpenClinica Database (for craniofacial research)		
Erasmus University Medical Center, Rotterdam	2013	4
Organizing 24th Esser Course: Ins and Outs of Nose reconstruction		
Erasmus University Medical Center, Rotterdam	2014	2
Organizing NVSCA Conference		
Erasmus University Medical Center, Rotterdam	2014	2

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CURRICULUM VITAE

Bianca Francisca Maria Rijken was born on the 15th of April 1986, in Bergen op Zoom, the Netherlands. She followed secondary school at 'Gymnasium 't Juvenaat Heilig Hart', in Bergen op Zoom and graduated in 2004. In that year she started medical school at the Erasmus University Medical Center in Rotterdam. From the second year of medical school Bianca participated in different research projects at the department of Plastic and Reconstructive surgery and the department of Neurosurgery. During the 4th year of her study, Bianca was selected to participate in the Neuroscience research master at the Erasmus University Medical Center (supervisors: Dr. S.K. Koekkoek, Prof. dr. C.I. de Zeeuw). She received her Master degree in Neuroscience in 2010 and graduated from medical school in 2011.

In 2010 Bianca got involved in doing research concerning patients with syndromic and complex craniosynostosis, at the department of Plastic, Reconstructive and Hand surgery, Erasmus University Medical center, while in September 2011 she started to work as a fulltime PhD-student (supervisors: Dr. M.H. Lequin, department of Radiology, Prof. dr. I.M.J. Mathijssen, department of Plastic, Reconstructive and Hand surgery). Within this research period, Bianca also worked as a resident plastic surgery not in training from September 2014 until December 2014 (Prof. dr S.E.R. Hovius, Head of the department of Plastic, Reconstructive and Hand surgery, Erasmus University Medical Center).

In May 2015, Bianca started her residency at Maasstadziekenhuis Rotterdam (Drs. R.A. Klaassen), and she will continue her residency at the department of plastic and reconstructive surgery at the Erasmus University Medical Center starting from February 2017.