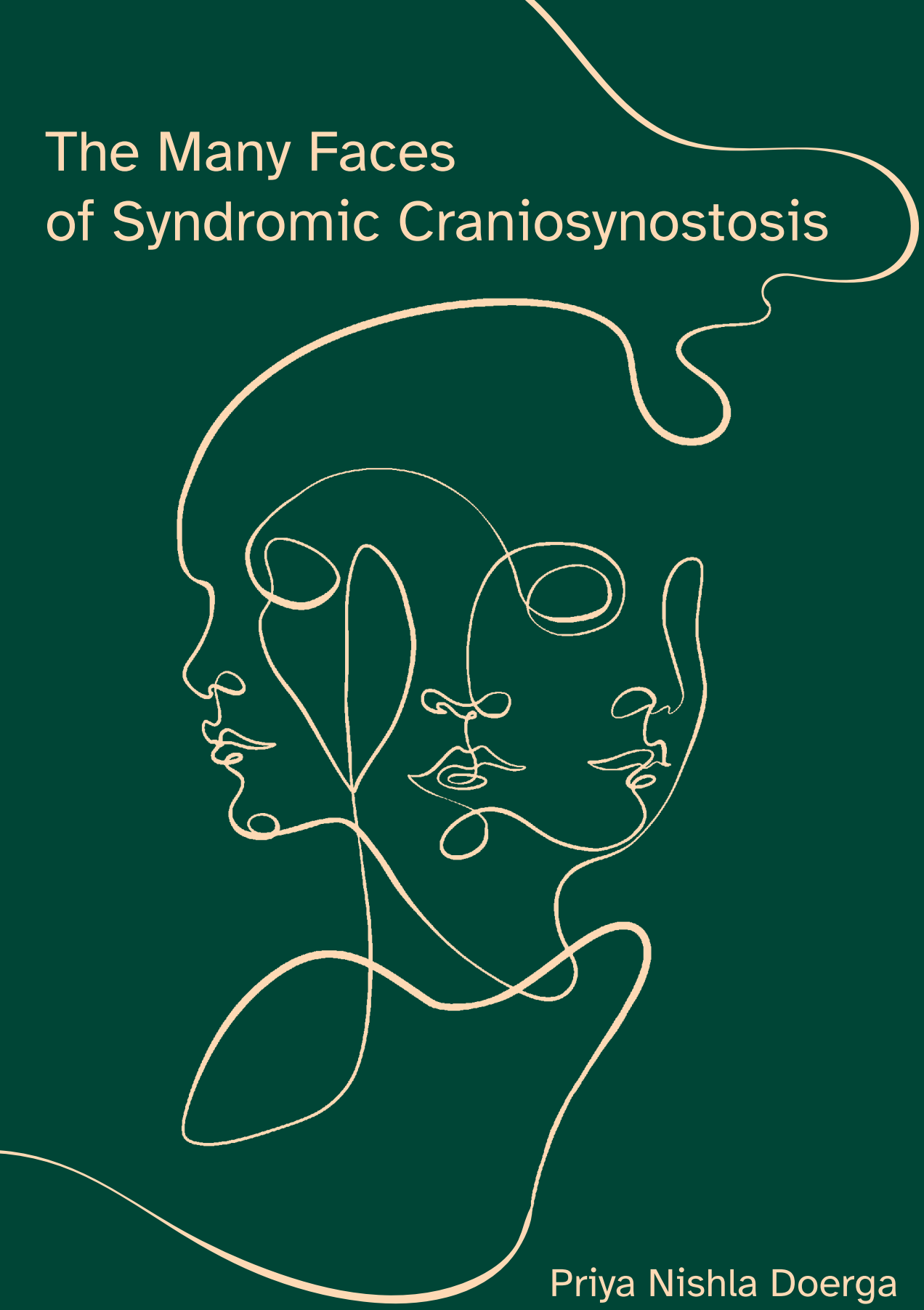
The Many Faces of Syndromic Craniosynostosis



Priya Nishla Doerga

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The Many Faces of Syndromic Craniosynostosis

De vele gezichten van syndromale craniosynostose

Thesis

to obtain the degree of Doctor from the

Erasmus University Rotterdam

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Erasmus University Rotterdam

Doctoral Committee:

Promotor:	prof.dr. I.M.J. Mathijssen
Other members:	prof.dr. C.M.F. Dirven prof.dr. G.J.V.M. van Osch prof.dr. S.G.F. Robben
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LIST OF ABBREVIATIONS

ASL	Arterial spin labeling
CBF	Cerebral blood flow
CMI	Chiari malformation type I
CSF	Cerebrospinal fluid
FGFR	Fibroblast growth factor
FOHR	Fronto-occipital horn ratio
FM	Foramen magnum
ICH	Intracranial hypertension
ICP	Intracranial pressure
ICV	Intracranial volume
OFC	Occipito-frontal circumference
OSA	Obstructive sleep apnea
sCS	Syndromic craniosynostosis
TH	Tonsillar herniation
VM	Ventriculomegaly

CHAPTER 1

GENERAL INTRODUCTION

General introduction

This thesis will discuss different aspects of how syndromic craniosynostosis (sCS) influences physiological processes that are important in intracranial pressure regulation, and will then focus on one syndrome specifically, Crouzon syndrome.

Craniosynostosis is the premature closure of skull sutures, it is often combined with skull base synchondroses, and leads to deformities of the skull and skull base.[1] In sCS premature closure of multiple sutures occurs in combination with other congenital anomalies, often a genetic cause can be identified. sCS is rare and has a prevalence of 0.9 per 10,000 live births.[2] Children with sCS have an increased risk for developing intracranial hypertension (ICH), which can lead to visual problems, headaches, developmental delay and neurological deficits.

The introduction will discuss a short description of what is known about sCS and how it relates to ICH, followed by what questions remain, and finally, how this thesis will aim to answer those questions.

What do we know?

Craniosynostosis syndromes

In patients with sCS closed skull sutures are often combined with facial dysmorphias such as hypertelorism, exorbitism, midface hypoplasia, a narrow and high palate, dental abnormalities, and abnormalities of hands and feet.[1]

In this thesis we will focus on the craniosynostosis syndromes that occur most often: Apert, Crouzon, Muenke and Saethre-Chotzen syndrome. Complex or multisutural craniosynostosis refers to cases where multiple sutures are involved, but a genetic cause is not (yet) detected. **Table 1** shows an overview of the different craniosynostosis syndromes.

Table 1
Overview of aspects of most common craniosynostosis syndromes

	Apert	Crouzon/Pfeiffer	Muenke	Saethre-Chotzen	Complex
Genetic mutation[3]	*FGFR2*, missense substitutions encoded by exon IIIa, disruptions of exon IIIc splicing caused by *Alu* insertion or exon deletion	Mostly *FGFR2*, IgIIIa (exon 8), IgIIIc (exon 10), intron sequence flanking IgIIIc	*FGFR3*, p.(Pro250Arg)	*TWIST1* mutation or deletion	Unknown
Prevalence[2]	*0.359 per 10.000*	*0.095 per 10.000*	*0.104 per 10.000*	*0.095 per 10.000*	*0.359 per 10.000*
Sutures	*Multisuture, often involving bilateral coronal sutures, often leading to the characteristic turribrachycephaly*	*Mostly pansynostosis, however, varies from pansynostosis to all sutures patent*	*Unilateral or bilateral coronal, macrocephaly with all sutures patent*	*Most often unicoronal or bicoronal, other sutures may be involved, all sutures can be patent*	*Two or more sutures*
Associated congenital anomalies [4-13]	Hypertelorism, shallow orbits with exorbitism, downslanting of palpebral fissure, midface hypoplasia, high arched palate, cleft palate, dental abnormalities, strabismus, ptosis of the upper eyelids, anisometropia, hearing loss (often conductive), multilevel airway obstruction, complex syndactyly of hands and feet, spinal fusions, a minority of patients has cardiac abnormalities, true gastrointestinal malformations, and anomalies of the genitourinary tract.	Hypertelorism, shallow orbits with exorbitism, midface hypoplasia, multilevel airway obstruction, atresia of auditory canals, conductive hearing deficit, strabismus, ptosis of the upper eyelids, acanthosis nigricans, elbow ankylosis and congenital heart disease.	Sensorineural hearing loss, high arched palate, strabismus, anisometropia, epicanthal fold changes, hypertelorism, fusion of carpal bones, fusion of tarsal bones, hypoplastic middle phalanges of hands and feet, epiphyseal coning, cutaneous syndactyly.	Brachydactyly, simple syndactyly, ptosis of upper eyelids, downslanting of palpebral fissure, lacrimal duct abnormalities, palatal anomalies, maxillary hypoplasia, external ear anomalies, conductive, mixed and profound sensorineural hearing loss, congenital heart malformation, short stature, skeletal anomalies.	Wide range of possible concurrent congenital anomalies.

Table 1
Overview of aspects of most common craniosynostosis syndromes - continuation

		Apert	Crouzon/Pfeiffer	Muenke	Saethre-Chotzen	Complex
OSA[11,21] †		70%, mild to severe	63.3%, mild to severe	75%, mild	60%, mild	68%, mild to severe
IQ *[22]		78.7 (13.3); 59-94	103.0 (20.1); 54-133	95.2 (16.4); 73-124	100.0 (26.6); 52-141	93.9 (22.0); 49-133
Cerebral anomalies	**CMI[23,24]**	8-11%	23-32%	7%	6%	23%
	Hydrocephalus	4-12%[5,14,19,20]	9-64%[14,16-18]	0%[14,15]	0%[14]	-
	Other[4,7,18,25]	Agenesis/thin of corpus callosum, defective septum pellucidum, mesial temporal abnormalities, ventriculomegaly (non-progressive), posterior fossa arachnoid cyst, limbic malformations, mega cisterna magna.	Agenesis of corpus callosum, ventriculomegaly (non-progressive), schizencephaly, septum peluccidum abnormalities.	Rare, case reports of hippocampal and bilateral medial temporal dysgenesis, ventricular dilation, a small cerebellum, porencephalic cyst of the occipital horn, and absence of the corpus callosum. Epilepsy and seizures have also been reported.	Rare	-

OSA: obstructive sleep apnea; IQ: intelligence quotient, CMI: Chiari malformation type I

† Prevalence in percentage, severity of OSA

*Mean (SD); range

Intracranial hypertension

Dynamics of intracranial hypertension in syndromic craniosynostosis

In this thesis we utilize the Monro-Kellie hypothesis, which states that intracranial volume consists of three compartments: first, brain volume; second, blood volume; and third, cerebral spinal fluid (CSF). These three compartments are contained within a non-compliant box, the cranial vault (see **Figure 1**). When one of the three compartments increases in volume, this will occur at the expense of the other compartments. Compliance occurs through CSF compartment shifting and autoregulation. When these means of compliance fall short, it can cause intracranial hypertension (ICH). ICH is dangerous because it can cause visual problems, developmental problems and neurological problems. In sCS compliance is assumed to be decreased due to a combination of factors that involve the cranial vault, and the three intracranial compartments.

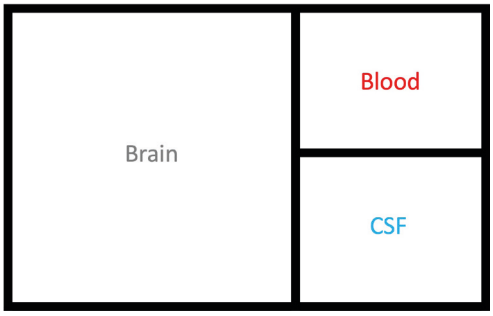

Figure 1. The Monro-Kellie Hypothesis with the skull depicted as a box, and three compartments: 1. Brain, 2. Blood, 3. Cerebrospinal Fluid (CBF)

Cranial vault and compartment 1: brain volume

Brain volume of patients with sCS has shown to be normal, when compared to controls.[24] What is most feared in craniosynostosis, is that the growing skull cannot accommodate the growing brain. When the skull cannot accommodate the brain, this can result in craniocerebral disproportion, which is an important factor in ICH.

When multiple sutures have prematurely closed, the risk of craniocerebral disproportion is great. This is exemplified in cases of cloverleaf skull deformity, in which synostoses of skull sutures and cranial base causing bitemporal bulging, and a cloverleaf shaped head.[26-28] Follow-up studies indicate that when sCS patients have a deviating skull growth curve, they can develop craniocerebral disproportion and ICH.[29]

Craniocerebral disproportion cannot be the only driving force in ICH in sCS patients however, since it has been shown that most sCS patients have a normal cranial vault volume[30,31] as well as a normal brain volume,[24] while still having a higher than normal prevalence of ICH. To find out what other factors are important in developing ICH in these children it is crucial to determine how sCS influences the other two intracranial compartments.

Compartment 2: blood volume

Blood outflow

Children with sCS have an abnormal cerebral venous anatomy varying from jugular foramen stenosis,[32,33] to aberrant dural veins and occipital collateral veins. This abnormal cerebral vein anatomy has shown to be the related to *FGFR2* and *TWIST* 1 mutations.[34]

The clinical importance of aberrant venous anatomy is underlined by the case described by Thompson et al.[35] that describes the death of a child with sCS after dissection of occipital collateral veins during vault remodeling. Drainage of venous cerebral blood was greatly dependent on these occipital collateral veins, their dissection led to an acute and fatal situation of ICH.

Studies have shown signs of abnormal venous anatomy in sCS patients, which could cause venous outflow obstruction and curb drainage capacity, like a smaller jugular foramen, aplastic or hypoplastic sinus transversus. Prominent emissary veins are often present, and are thought to function as a way to increase drainage capacity.[32] However, the exact physiological mechanisms are not clear yet.

Abnormal cerebral venous anatomy could have an effect on two compartments: the blood compartment and the CSF compartment. Abnormal venous anatomy may impair venous drainage, leading to venous hypertension and raised intracranial pressure. Venous hypertension may further increase intracranial pressure by reducing reabsorption of cerebrospinal fluid (CSF) at the level of the arachnoid villi.[36]

Blood inflow

In healthy individuals, an increase in blood inflow occurs during REM sleep, related to increased brain activity. During rapid eye movement (REM) sleep a general hypotonia occurs of all voluntary muscles, except for ocular muscles and the diaphragm. Amongst children with sCS obstructive sleep apnea (OSA) is highly prevalent, due to midface and/or mandibular hypoplasia causing obstructions in the upper airways.

In children with sCS and OSA, REM sleep worsens their airway obstruction because the muscles of the pharynx relax.[37] This causes an increase of the number of apneas during REM sleep.[38] The moments of apnea cause an accumulation of CO_2, which causes vasodilation in the brain. To maintain an adequate cerebral blood pressure, the cerebral blood flow is increased. Increased blood flow adds to the blood compartment of intracranial volume, and causes the intracranial pressure to rise.

Thus, while REM sleep already comes with a tendency for increased ICP in healthy individuals, in children with sCS and OSA this risk becomes even greater due to CO_2 induced vasodilation.

Compartment 3: cerebrospinal fluid

Hydrocephalus occurs more often in sCS patients in general and specifically in Apert and Crouzon patients.[24] One cause for hydrocephalus in sCS patients is a small overcrowded posterior fossa and/or a small foramen magnum (FM), which can result in increased resistance for the CSF outflow and absorption.[14,16,39-41] A recent imaging study has confirmed that FM size is smaller in Crouzon patients than in controls.[42] Posterior fossa size however, has shown to be similar to that of controls.[23]

There are two other theories for the etiology of hydrocephalus in sCS patients. First, is the theory of a CSF absorption problem, caused by the abnormal venous anatomy mentioned before, including aplastic or hypoplastic cerebral veins, which could impede venous drainage. This could cause increased venous pressure. CSF pressure is normally slightly greater than venous pressure of the superior sagittal sinus, to maintain a pressure gradient that drives reabsorption of CSF. An increased venous pressure caused by impeded venous outflow as a result of abnormal venous anatomy, could impede CSF absorption into the venous system.[14,43-45]

Meningeal lymphatic vessels clear fluid and waste from the glymphatic system to deep cervical lymph nodes.[46] A recent study by Ahn et al. [39] has shown in a rat model that CSF drainage is highly dependent on meningeal lymphatic vessels at the skull base using CSF contrast enhanced MRI and fluorescent imaging. This may be of great importance in sCS patients with jugular foramen stenosis, since the jugular foramen is one of the exit routes for the meningeal lymphatic vessels at the skull base. It may also be of importance in patients with CMI, since crowding of the posterior fossa might impede CSF absorption into the meningeal lymphatic vessels of the skull base.

Second, is the theory of CSF overproduction. *FGFR2* has been shown to be present in the choroid plexus.[47] Some speculate that changes in *FGFR2* could lead to an overproduction of CSF and hereby add to the third compartment. **Figure 2** depicts pathological processes in sCS.

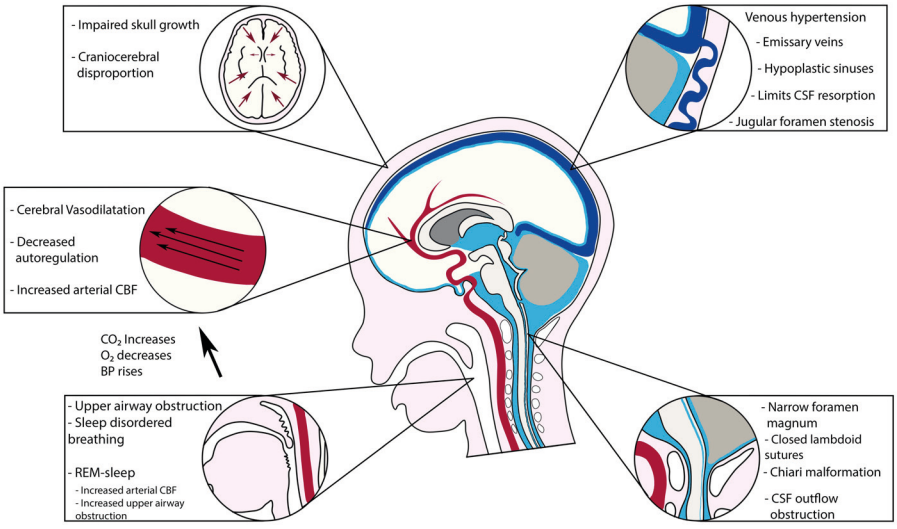

Figure 2. Pathophysiological processes concerning intracranial hypertension in children with syndromic craniosynostosis

Detection of intracranial hypertension

Clinically it can be difficult to recognize ICH in sCS children, because the symptoms can be ambiguous. The classic clinical signs of ICH which include headaches, vomiting, changes in vision and/or changes in behavior, and disturbed consciousness, are often absent or related to ophthalmologic anomalies or to the genetic mutation itself.[48,49]

The gold standard for diagnosing ICH is invasive intracranial pressure (ICP) measurement. Invasive ICP measurement in sCS patients is done overnight. Normal values of ICP in children are scant, and thus there is no consensus on cut-off points that indicate raised ICP at different ages in childhood. While invasive ICP measurement is the gold standard, it is an invasive procedure that requires hospital admission, and is associated with potential complications, such as hemorrhage, cerebral spinal fluid leak, and infection. Therefore, it is not routinely used as a screening method.

An indirect noninvasive method of screening for ICH is examination of the optic nerve for papilledema. Papilledema is defined as swelling of the optic disc, with marginal blurring and obscuration of retinal vessels. Since the optic nerve is an extension of the central nervous system, it is in direct contact with the subarachnoid space of the brain, and when ICH occurs, papilledema can be diagnosed. Since papilledema can be assessed through the eyes, non-invasive methods such as funduscopic examination, and optical coherence tomography (OCT) can be used for this assessment.

A study by Tuite et al. showed that presence of papilledema as shown by fundoscopy has a sensitivity of 100% in children older than 8 years old, but only 22% in children younger than 8 years old. In younger children, the absence of papilledema does not rule out ICH.[49] In that study the high prevalence of ICH in unisutural patients and low prevalence of ICH in sCS patients does not match other literature on ICH in craniosynostosis.[15,29,50-52] This study might be showing the results of an abnormal selection of patients, in particular the fact that it only included patients undergoing their first formal craniofacial assessments, with ages ranging from 2.5 months to 15 years, and excluding all patients with prior craniofacial surgery, ICP monitoring, or ventriculoperitoneal shunt insertion. This indicates that this might be a study population with many mild cases of craniosynostosis, and not a realistic representation of craniosynostosis patients, and of sCS patients in particular. While this study has never been repeated, its results are often referred to, to show the low sensitivity of papilledema in children below 8 years of age. The specificity of presence of papilledema however, is very high and has shown to be around 100%.[49,53,54]

What is important to keep in mind, is that papilledema remains a very important clinical sign, since the severity of papilledema says a lot about the prognosis for the patient's visual acuity. The severity of papilledema, in particular when pallor and cotton wool spots are present, is positively correlated with visual loss.[55] When papilledema is not present, in general there is little threat of vision loss. Therefore, screening for papilledema is still the first choice, given its feasibility and low risk. However, papilledema may be absent, even in presence of ICH. Therefore, when papilledema is absent, but other signs of ICH are present, an OCT or invasive ICP measurement should be considered to confirm presence of ICH.

OCT uses broad-band near infra-red-light sources and penetrates the tissue up to 3mm. Therefore, it can detect microstructural abnormalities of 1µm. OCT is often used to determine or follow up on ophthalmologic disorders such as maculopathies and glaucoma. In patients with ICH

OCT shows an increased retinal thickness and in particular an increased retinal nerve fiber layer.[56,57] OCT has shown a high sensitivity in detecting ICH in children, but a lower specificity.[53]While OCT can give an objective measurement of presence of papilledema, one of the challenges lies in lack of attention of the patient to obtain a representative image, particularly in those below 4 years old.[58] To handle this obstacle, recent studies by Swanson et al.[53,54] examining the reliability of OCT to detect ICH in sCS patients, have conducted OCT measurements and 1 minute ICP measurement while the patient was sedated, before a surgical procedure.

It is thought that papilledema develops at a slow rate in sCS patients, since ICH is not continuously present, but mostly present during episodes of REM-sleep. The higher sensitivity of OCT than fundoscopic assessment of papilledema might suggest that OCT can detect ICH at an earlier stage. However, the effects of sedation on OCT measurements and ICP measurements are not well established. Furthermore, in the studies by Swanson et al. ICP was measured for the duration of 1 minute during sedation, as opposed to measuring ICP during sleep. Increases in ICP during episodes of REM-sleep could therefore not be detected. Thus, while OCT is a promising technique to determine ICH, there is still a lot left to learn about the relation between OCT and ICP.

A deviating or stagnating head growth has been shown by Spruijt et al. to be an important indicator for raised intracranial pressure.[29] This study determined head growth by serial measurements of the occipitofrontal head circumference (OFC). A falling off of the OFC was present in 12 out of 13 patients with ICH and only in 7 out of 47 patients without ICH. ICH was determined by presence of papilledema through fundoscopy and OCT. Invasive intracranial pressure measurements were done when ICH was suspected, but papilledema was absent and retinal thickness was normal.

Other classic signs that suggest ICH are volcano sign and impressiones digitatae. Volcano sign is the term for an anterior bulge, a variably ossified protuberance at the site of the anterior fontanel.[59] An anterior bulge develops when ICH is present at the time of anterior fontanel closure. The brain takes advantage of the remaining compliance of the cranial vault at this site, causing a bulge. Presence of impressiones digitatae, or a copper beaten skull, are prominent depressions on the inner surface of the skull that correspond with the gyri of the brain, are suggestive for ICH especially when they are progressive.[49,60,61]

At our clinic, sCS patients receive fundoscopic examination at time of the first visit to the outpatient clinic, every 6 months between 1 to 4 years old, and afterwards annually until the age of 6 years old. Crouzon patients undergo two additional fundoscopic examinations at 1 year and 3 months, and 1 year and 9 months due to the high prevalence of ICH. After the age of 6, patients undergo fundoscopic examination only when there are signs of increased ICP, such as stagnating growth curve of head circumference, headaches, disturbed sleeping or behavioral changes. When papilledema is detected, fundoscopy should be repeated within 4-6 weeks, to confirm the finding.

What questions remain, and how will we try to answer them?

Our main question in this thesis is how does sCS relate to ICH? We explore questions about ICH in sCS by approaching them along the lines of the Monro-Kellie hypothesis, and first we look at the blood compartment.

In **Chapter 2** we address our first question: How does sCS influence cerebral blood outflow? In a pilot study we concentrated on blood outflow: we used ultrasound to determine differences between cerebral venous flow patterns of patients with craniosynostosis and controls.

Our next question follows in **Chapter 3**: how does sCS influence cerebral blood inflow? We address this question by examining arterial cerebral blood flow (CBF). Though many surgical interventions are aimed at maintaining or improving CBF, not much is known about how CBF in sCS patients is different from that of controls. In this study we used a non-invasive magnetic resonance imaging (MRI) technique called arterial spin labeling (ASL) to determine CBF in sCS patients and compared it to control subjects.

Subsequently, in **Chapter 4** and **Chapter 5** we examine treatment methods and clinical outcome of sCS patients. **Chapter 4** addresses the brain compartment and the CSF compartment by trying to answer the question: does CMI influence neurological assessments in sCS children? Some craniosynostosis centers advocate surgery once CMI is determined to prevent the neurological effects.[62] However, information about neurological effects of CMI in sCS patients is scant. In this chapter we therefore aimed to determine what the effect of CMI is on neurology in sCS patients, and to determine how neurological assessment could be used to determine symptomatic CMI.

Chapter 5 focuses on the blood compartment by addressing the question: how does surgical treatment of upper airway obstructions effect OSA? Since OSA adds to the ICH dynamic by increasing blood inflow, treating patients with OSA is an essential part of the treatment algorithm of sCS patients. One part of this treatment method is to surgically optimize the upper airways. In this study we evaluate the effect of this surgical intervention on the anatomy of the upper airways and on OSA severity.

In **Chapter 6** we focus on Crouzon syndrome and the CSF compartment. We address the question: how do ventriculomegaly and tonsillar herniation develop over time in Crouzon patients? Crouzon patients have a diverse phenotype varying from very mild to very severe, can suffer from all known ICH risk factors, and clinical outcome is difficult to predict. Crouzon patients therefore generally receive a closer follow-up than patients with other craniosynostosis syndromes. Crouzon patients have the highest prevalence of ICH, which, among other things, is related to the development of hydrocephalus.

Lastly, in **Chapter 7** we review the literature to see if we can answer our question on how sCS relates to ICH. We attempt to answer this question by examining studies on ICH in sCS patients, and by categorizing the literature into different Monro-Kellie compartments. We also attempt to answer the question: to what degree are problems in sCS patients caused by intrinsic genetic makeup or by ICH?

Chapters

2. Pilot case-control study of intracranial venous physiology in craniosynostosis
3. Cerebral blood flow in children with syndromic craniosynostosis compared to control subjects
4. Neurologic assessment of children with syndromic and complex craniosynostosis
5. Upper airway endoscopy to optimize obstructive sleep apnea treatment in Apert and Crouzon syndromes

6. The Course and Interaction of Ventriculomegaly and Cerebellar Tonsillar Herniation in Crouzon Syndrome over Time
7. What we know about intracranial hypertension in children with syndromic craniosynostosis

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CHAPTER 2

PILOT STUDY OF INTRACRANIAL VENOUS PHYSIOLOGY IN CRANIOSYNOSTOSIS

Martijn J. Cornelissen, Robbin de Goederen, Priya Doerga, Iris Cuperus, Marie-Lise van Veelen, Maarten Lequin, Paul Govaert, Irene M. J. Mathijssen, Jeroen Dudink, Robert C. Tasker

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Abstract

OBJECTIVE In addition to craniocerebral disproportion, other factors, such as Chiari malformation type I, obstructive sleep apnea, and venous outflow obstruction, are considered to have a role in the occurrence of intracranial hypertension in craniosynostosis. This pilot study examined cerebral venous flow velocity to better characterize the complex intracranial venous physiology of craniosynostosis.

METHODS The authors performed a prospective cohort study of craniosynostosis patients (n = 34) referred to a single national (tertiary) craniofacial unit. Controls (n = 28) consisted of children who were referred to the unit's outpatient clinic and did not have craniosynostosis. Transfontanelle ultrasound scans with venous Doppler flow velocity assessment were performed at the first outpatient clinic visit and after each surgery, if applicable. Mean venous blood flow velocities of the internal cerebral vein (ICVv) and the superior sagittal sinus (SSSv) were recorded and blood flow waveform was scored.

RESULTS Preoperatively, SSSv was decreased in craniosynostosis patients compared with controls (7.57 vs 11.31 cm/sec, p = 0.009). ICVv did not differ significantly between patients and controls. Postoperatively, SSSv increased significantly (7.99 vs 10.66 cm/sec, p = 0.023). Blood flow waveform analyses did not differ significantly between patients and controls.

CONCLUSIONS Premature closure of cranial sutures was associated with decreased SSSv but not ICVv; indicating an effect on the superficial rather than deep venous drainage. Further Doppler ultrasound studies are needed to test the hypothesis that at an early stage of craniosynostosis pathology SSSv, but not pulsatility, is abnormal, and that abnormality in both SSSv and the superficial venous waveform reflect a more advanced stage of evolution in suture closure.

Introduction

Craniosynostosis occurs in approximately 1 in 1500 births and results in abnormal shape of the cranium and increased risk of intracranial hypertension (ICHT).[1] In published series, the prevalence of ICHT ranges from 1% to 85%, and it is particularly high in syndromic cases of craniosynostosis.[2-5] Historically, the development of ICHT in craniosynostosis was attributed solely to skull growth restriction (i.e., craniocerebral disproportion).[6] Now, however, the accumulated evidence suggests that other factors may also be relevant,[7-11] including: cranial vault venous outflow obstruction, ventriculomegaly (or hydrocephalus if progressive), tonsillar herniation or presence of Chiari malformation type I, and obstructive sleep apnea (OSA). These pathophysiological features are rarely seen in single-suture craniosynostosis patients, and so we have to conclude that they are unlikely to account for the development of ICHT in such patients. In our previous work we have recognized a discrepancy in the rate of ICHT by suture involvement that is not readily explained by any of the mechanisms outlined above. For example, in cases of metopic suture synostosis, the rate of ICHT is low (1%–2%), irrespective of relatively small intracranial volume after surgery.[2,12] The opposite is true in sagittal suture synostosis; that is, despite a relatively larger intracranial volume, ICHT is found in 6%–10% of patients.[13,14]

In this context, clinical researchers have focused on cerebral venous drainage in craniosynostosis, albeit with few definitive studies. We know that there is an interaction between superior sagittal sinus (SSS) pressure (PSSS) and intracranial pressure (ICP). For example, as early as 1984, Sainte-Rose et al. suggested that a rise in PSSS due to obstruction resulted in a rise in ICP.[11]19 We also know that the mean venous blood flow velocity of the SSS (SSSv), measured using Doppler ultrasound in single-suture cases of craniosynostosis, differs from the norm.15 Last, we know that cranial venous drainage is different in craniosynostosis patients.[8,10] Taking all of the above evidence together, we conclude that abnormality in cerebral venous dynamics is an important physiological feature of single-suture craniosynostosis. However, understanding the interaction between cerebral venous blood flow, cerebrospinal fluid (CSF) drainage, and ICP also requires consideration of anatomy. For example, the superficial venous drainage system, as reflected in the SSS, drains blood from the lateral aspects of the anterior portion of the cerebral hemispheres and collects CSF from the arachnoid granulations. The internal cerebral vein (ICV) is a component of the deep venous drainage system, and on each side of the brain it takes blood from the choroid plexus and thalamic and caudate nuclei. Therefore, in the current pilot investigation we have used Doppler ultrasound to examine cerebral venous flow velocity in the superficial and deep cerebral venous drainage systems to better characterize the complex intracranial venous physiology of craniosynostosis. Comparing both venous drainage systems enables us to examine the effect of craniosynostosis on the deep and superficial venous drainage system and, therefore, to evaluate the effect of corrective surgery on venous drainage and to identify possible targets to prevent ICHT.

Methods

This study was approved by our institution's medical ethics committee. Informed consent was obtained from all participants. Participants with syndromic and nonsyndromic craniosynostosis were recruited from craniosynostosis patients presenting to the Dutch craniofacial center in 2016. The healthy control group was also recruited at our center and comprised patients referred for nonsynostotic occipital plagiocephaly, metopic ridging, or nonsyndromic cleft lip.

Patient Management

Craniosynostosis patients were treated according to our center's previously published treatment protocol.14 Briefly, this meant that fronto-orbital advancement and remodeling was performed between 9 and 12 months of age for the following indications: metopic synostosis, unicoronal synostosis, Saethre-Chotzen's syndrome, and Muenke's syndrome. Sagittal synostosis patients were treated with springs, which were inserted at 5–6 months of age and removed approximately 12 weeks later. Patients with lambdoid synostosis, Apert's syndrome, or Crouzon's syndrome were treated with posterior decompression with the use of springs at around 5–6 months of age (with the springs removed 12 weeks later).

Doppler Ultrasound Procedure and Analyses

Prospective, transfontanelle ultrasound scans with Doppler studies were performed using an Esaote MyLab Twice ultrasound scanner. Scans were carried out at the first outpatient clinic visit and follow-up evaluation after each surgery. Controls underwent only 1 ultrasound study at the time of presentation to the outpatient clinic. During the ultrasound procedure, patients were positioned either supine or with the head of the bed elevated to a maximum of 30°. Studies were carried out when a child was quiet and at rest. Data from agitated or crying children were excluded because of the influence of heart rate variability and raised intrathoracic pressure on measurement of SSSv and mean venous blood flow velocity of the ICV (ICVv).

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

All ultrasound and Doppler data were obtained by one of two observers (M.J.C. or P.D.) and digitally stored. (The interobserver agreement for mean ICVv and mean SSSv, as assessed by intraclass correlation coefficient, was > 0.95.) The ICV blood flow waveform produced by spectral analysis using image-processing software (Esaote MyLab) was scored using a previously described categorization (**Table 1**).11 Two observers (M.J.C. and R.d.G.) scored the waveform independently. Instances of disagreement between the scorers was resolved by open evaluation and agreed consensus. The evaluators' kappa statistics were 0.89 and 0.73 for the ICV and SSS waveforms, respectively.

Statistical Analyses

The sample size for our pilot study was based on previous guidelines16 and our center's medical ethics committee's recommendations. The statistical analyses assumed normal distribution for ICVv and SSSv data. A multivariate analysis of variance (MANOVA) test was performed to assess the effect of craniosynostosis on SSSv and ICVv. The chi square test was used for assessment of waveform categorical data. Finally, in the comparisons of pre- to postoperative change, we used the preoperative data along with the data from after the last (or most recent) operation. Post hoc nonparametric testing (Kruskal-Wallis or Wilcoxon signed-rank test) was performed when appropriate.

Table 1

Blood flow waveform categories as described by Ikeda et al. [15]

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

Results

We recruited 34 craniosynostosis patients, including 14 patients with sagittal synostosis, 11 with metopic synostosis, 2 with unicoronal synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 3 with Muenke's syndrome, and 2 with Crouzon's syndrome. Postoperatively, we were able to obtain ultrasound scans in 22 (65%) of these 34 patients (8 with sagittal suture synostosis, 9 with metopic synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 2 with Muenke's syndrome, and 1 with Crouzon's syndrome). The control group comprised 28 patients (24 with nonsynostotic occipital plagiocephaly or metopic ridging, 2 with cleft lip, and 2 unaffected twin siblings of craniosynostosis patients).

None of the patients with craniosynostosis had papilledema at the time of initial assessment. One patient with Muenke's syndrome developed papilledema after the preoperative ultrasound study, and for this reason she underwent posterior cranial vault decompression. Additionally, 1 patient with Crouzon's syndrome developed papilledema after the first ultrasound. At the time of the postoperative ultrasound study the papilledema was resolving in both cases but had not completely disappeared. None of the other patients had papilledema at the postoperative assessment.

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

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

* OFC in standard deviations compared to the national normal values.

Preoperative ICVv and SSSv

Table 2 summarizes the initial findings in the 3 study groups (patients with nonsyndromic or syndromic craniosynostosis and controls). The age distribution differed significantly between groups (Kruskal-Wallis test, $p < 0.001$). Post hoc testing showed no significant difference with regard to age at ultrasound between the syndromic and nonsyndromic craniosynostosis groups (Mann-Whitney U-test, $p = 0.24$), but it did show a significant difference between the nonsyndromic group and controls (Mann-Whitney U-test, $p = 0.001$). There was no significant between-groups difference in occipitofrontal head circumference (OFC) (ANOVA, $p = 0.20$).

We performed a MANOVA analysis to test whether there were significant differences with regard to venous flow velocity between craniosynostosis patients and controls, correcting for age at ultrasound and OFC. This analysis showed significantly lower venous blood flow velocity in the SSSv in craniosynostosis patients compared with controls (Table 3). Age at ultrasound and OFC were not significant contributors to this effect. Additional testing did not show statistically significant differences between nonsyndromic and syndromic craniosynostosis patients after correction for age at ultrasound and OFC.

Table 3
MANOVA correcting for age at time of ultrasound and OFC.

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

df = degree of freedom.
Velocities are presented in centimeters/second. Design: Intercept + age at ultrasound + OFC + craniosynostosis.
Adjusted $R^2 = 0.25$.
* Statistically significant.

Venous Blood Flow Waveform

Preoperative cerebral venous blood flow waveform scores are shown in Table 4. The chi-square test did not show any significant differences in distribution among the different groups for the 2 measurements.

Postoperative Blood Flow Velocity

Preoperative and postoperative cerebral venous blood flow velocities of the SSS were gained in 15 patients: 4 patients with scaphocephaly, 6 with trigonocephaly, 1 with lambdoid synostosis, 1 with Crouzon's syndrome, 1 with Saethre-Chotzen's syndrome, and 2 with Muenke's syndrome. A related-samples Wilcoxon signed-rank test showed a significant increase in SSSv postoperatively (median 7.25 cm/sec [IQR 6.75–8.95 cm/sec] vs 10.20 cm/sec [IQR 8.95–12.20 cm/sec], p = 0.023) The ICVv remained unchanged (median 9.90 cm/sec [IQR 7.95–10.98 cm/sec] vs 10.15 cm/sec [IQR 8.00 11.35 cm/sec], p = 0.68). Fig. 1 shows patient-specific pre- to postoperative change of the SSSv.

Table 4

Distribution of preoperative blood flow waveform grades in patients with nonsyndromic or syndromic craniosynostosis and controls.

Variable	Nonsyndromic craniosynostosis	Syndromic craniosynostosis	Controls
ICV			
Grade 0	5	0	3
Grade 1	17	5	23
Grade 2	0	0	0
Grade 3	0	0	0
Total	22	5	26
SSS			
Grade 0	7	1	5
Grade 1	12	4	19
Grade 2	4	1	2
Grade 3	0	0	0
Total	23	6	26

Values are numbers of patients. The preoperative venous blood flow waveform grades are based on the scoring system described in Table 1. No significant differences were found for ICV (p = 0.77) or SSS waveform (p = 0.62) using the chi-square test.

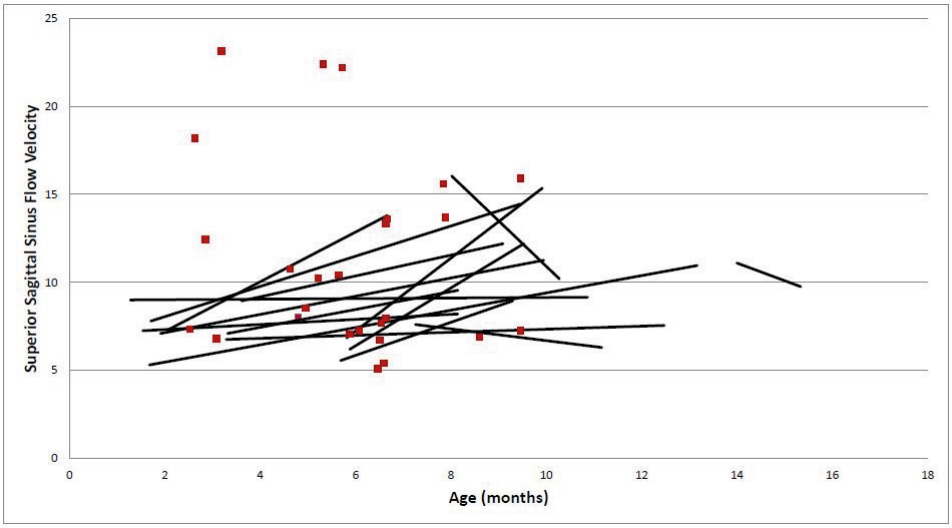

Figure 1: Preoperative to postoperative change in superior sagittal sinus flow velocity of the patients. Each black line indicates the data from 1 patient. The red squares represent point data from controls. See text for details.

Discussion

This study assessed cerebral venous blood flow velocity and blood flow waveform in patients with craniosynostosis compared with controls using Doppler ultrasound. Before surgery, patients with craniosynostosis showed lower SSSv compared with controls, that increased postoperatively. There was no difference in ICVv at any time, and blood flow waveform characteristics were similar in both cases and controls.

Previous studies have reported on the interaction between hydrocephalus and hydrodynamic and hemodynamic pressures (i.e., raised ICP and PSSS) in various patient groups.[11,16-18] For example, in children with achondroplasia and hydrocephalus, cine phase-contrast MRI shows reduced SSSv.[16] Hirabuki et al. hypothesized that the reduced cerebral venous blood flow, as indicated by reduced SSSv, was the result of venous outflow obstruction.[16] In our current findings, we have taken measurements from both the superficial and deep cerebral venous drainage systems as a test of the anatomy before and after any potential point of venous constriction or compression. The resulting data indicate that premature closure of cranial sutures may, in itself, be related to decreased SSSv and thus reduced cerebral venous drainage from the superficial system, i.e., at a point proximate to the confluence of the straight sinus and SSS. In contrast to these observations, Mursch et al. found higher SSSv in craniosynostosis patients;[17] it should, however, be noted that their measurements were made at the site of venous constriction/compression. Of interest, de Souza and Pinto showed that the diameter of the SSS is related to sagittal suture growth.[19] These findings, together with our own, strengthen the hypothesis that cerebral venous outflow obstruction due to venous constriction or compression

is caused by the presence of a synostotic suture. Consistent with this idea is our observation that decreased SSSv is also found in single-suture craniosynostosis patients (**Table 2**); until now, cerebral venous hypertension has been considered an attribute of syndromic craniosynostosis.[8,10] In fact, we think that this physiology may be important in the etiology of ICHT in unisutural craniosynostosis patients, particularly as OSA, Chiari malformation type I, and hydrocephalus are not found in this patient group. Furthermore, the postoperative increase in SSSv may also reflect that venous obstruction/compression caused by the synostotic suture has been relieved and resistance into venous outflow in the superficial drainage system has been lowered. Since we only performed postoperative analyses in 15 patients, these findings should be confirmed in a larger study.

In regard to the characteristics of the cerebral venous waveform in craniosynostosis, Mursch et al. previously reported that such patients had different SSS pulsatility measurements (i.e., pulsatility index and resistance index).[17] We could not reproduce these findings when using a system of scoring venous blood flow waveform profiles. Taken together with the above discussion of SSSv, this observation suggests that we may have been seeing patients early in the course of uncorrected natural history; that is, at an early stage of pathology when there is premature suture fusion with an effect on SSSv but pulsatility remains unchanged. The state in which craniosynostosis influences both SSSv and SSS waveform pulsatility most likely represents a more severe or later stage.

There are some limitations in this study that need to be considered. First, we have little comparative data. Even though the cranial venous outflow of patients with craniosynostosis has been a subject of research over the past decade, we have only one quantitative study of SSSv, until now. The present study was designed as a pilot project to explore potential effects of craniosynostosis on the superficial and deep cerebral venous drainage systems, and we hope that our findings will stimulate research in other clinical centers. Second, in accordance with our institution's medical research ethics advice for pilot studies, we could only recruit up to 15 patients in each diagnostic group, which, at this preliminary stage, limits the generalization of our findings. Third, postoperative analyses were limited by the presence of closure of the anterior fontanelle—the radiological "window" for examining the SSS and ICV. We have no control over this limitation, but in the future dynamic cerebral MR venography may provide useful information. Fourth, flow velocity is not equal to flow volume. In this study we showed that there is a lower flow velocity in the SSS, but it is not yet proven that this also means a lower flow volume. However, we do believe a lower flow velocity is more likely to represent a lower flow volume in this case, especially given the flow velocity increase postoperatively. Last, technical components of Doppler ultrasound studies have the potential to add to variability, e.g., angle of insonation, patient activity, and positioning. We have limited these potential technical effects by standardizing our approach and excluding data that are inadequate (e.g., because patients were restless or moving).

Therefore, considering the results of the present study and the above limitations, our hypothesis is that cerebral venous drainage and outflow has a role in the etiology of ICHT, even in single-suture craniosynostosis patients. This finding should be confirmed in future studies, which should also explore potential differences between the different types of craniosynostosis. It would

also be interesting to test whether patients with an affected suture in the midline (i.e., metopic or sagittal synostosis) show a more profound effect of suture closure on SSSv compared with the other subtypes of craniosynostosis. In addition, the effect of surgery should be evaluated, especially the possible hierarchy in severity (i.e., closed suture with decreased SSSv vs decreased SSSv with abnormal venous waveform).

Conclusions

This pilot study of cerebral venous outflow patterns in craniosynostosis patients shows that premature closure of cranial sutures is associated with decreased SSSv, but not ICVv—that is, an effect on the superficial venous drainage rather than deep venous drainage. Further Doppler ultrasound studies are needed, not only to confirm the current findings, but also to test the hypothesis that at an early stage of craniosynostosis pathology SSSv is abnormal while pulsatility is normal, and that abnormalities in both SSSv and the superficial venous waveform reflect a more advanced stage of evolution in suture closure.

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CHAPTER 3

CEREBRAL BLOOD FLOW IN CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS: COHORT ARTERIAL SPIN LABELING STUDIES

Priya N. Doerga, Maarten H. Lequin, Marjolein H. G. Dremmen, Bianca K. den Ottelander, Katya A. L. Mauff, Matthias W. Wagner, Juan A. Hernandez-Tamames, Sarah L. Versnel, Koen F M. Joosten, Marie-Lise C. van Veelen, Robert C. Tasker, Irene M. J. Mathijssen

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Abstract

OBJECTIVE In comparison with the general population, children with syndromic craniosynostosis (sCS) have abnormal cerebral venous anatomy and are more likely to develop intracranial hypertension. To date, little is known about the postnatal development change in cerebral blood flow (CBF) in sCS. The aim of this study was to determine CBF in patients with sCS, and compare findings with control subjects.

METHODS A prospective cohort study of patients with sCS using MRI and arterial spin labeling (ASL) determined regional CBF patterns in comparison with a convenience sample of control subjects with identical MRI/ASL assessments in whom the imaging showed no cerebral/neurological pathology. Patients with SCS and control subjects were stratified into four age categories and compared using CBF measurements from four brain lobes, the cerebellum, supratentorial cortex, and white matter. In a subgroup of patients with sCS the authors also compared longitudinal pre- to postoperative CBF changes.

RESULTS Seventy-six patients with sCS (35 female [46.1%] and 41 male [53.9%]), with a mean age of 4.5 years (range 0.2–19.2 years), were compared with 86 control subjects (38 female [44.2%] and 48 male [55.8%]), with a mean age of 6.4 years (range 0.1–17.8 years). Untreated sCS patients < 1 year old had lower CBF than control subjects. In older age categories, CBF normalized to values observed in controls. Graphical analyses of CBF by age showed that the normally expected peak in CBF during childhood, noted at 4 years of age in control subjects, occurred at 5–6 years of age in patients with sCS. Patients with longitudinal pre- to postoperative CBF measurements showed significant increases in CBF after surgery.

CONCLUSIONS Untreated patients with sCS < 1 year old have lower CBF than control subjects. Following vault expansion, and with age, CBF in these patients normalizes to that of control subjects, but the usual physiological peak in CBF in childhood occurs later than expected.

Introduction

Syndromic craniosynostosis (sCS) is a congenital disorder in which several skull sutures close prematurely, causing facial, calvarial, and skull base anomalies.[1] This disorder occurs in 0.9 per 10,000 live births,[2] and is associated with additional congenital anomalies and intracranial hypertension (ICH).[3,4] In these children ICH is mainly seen in the first 6 years of life, and can ultimately lead to vision loss.[5] Hence, many craniofacial surgical treatment centers recommend a cranial vault expansion before 1 year of age for all children with sCS to prevent ICH.[6-8] The reasoning here is that physical constraint such as delayed skull growth and progressive expansion of CSF ventricles are important factors in the development of ICH. However, it is also possible that the problem is physiological and related to alteration in cerebral blood flow (CBF) development and dynamics.

To date, only limited research has been conducted on characterizing the developmental progression of CBF in children with sCS, in part because the technical needs for assessment have been invasive or required using radiation, contrast media, and nuclear medicine.[9-11] Such research focused on how vault expansion affects CBF, with no comparison to data from control subjects.[12-14] Now, newer and validated techniques for CBF assessment using MRI with arterial spin labeling (ASL) mean that measurements can be made without using contrast agents and radiation exposure. Therefore, in this study we aimed to determine CBF in patients with sCS, and compare the findings to normal values from healthy children 0–18 years old. Our research questions were: 1) does CBF in untreated patients with sCS differ from that of control subjects; 2) does CBF in patients with sCS following vault expansion differ from that of control subjects; and 3) does CBF improve in sCS patients with serial CBF measurements pre- to postsurgical vault expansion?

Methods

The Ethics Committee of the Erasmus Medical Center approved this prospective imaging study in patients with sCS. In our national sCS center (Erasmus Medical Center), all patients are managed according to a clinical protocol that since 2012 has included MRI with an ASL sequence, after referral (usually < 1 year of age) and when 4 years old. Patients with Crouzon syndrome undergo additional MRI when they are 2 years of age because of their high risk of developing Chiari malformation type I. Patients with sCS were included as a consecutive sample starting from 2012. Children < 7 years old generally undergo deep sedation or anesthesia during the MRI procedure, which includes using propofol and sevoflurane.

The data used to represent control information for sCS comparisons were generated as a convenience sample[15] from subjects undergoing MRI for clinical reasons, but the following conditions were met: 1) the subjects were found to have no neurological pathology of the head and neck area; 2) the subjects were free of any neurological or psychological morbidity on follow-up; and 3) the subjects' MRI data were of sufficient quality to be used for research. Indications for MRI with ASL sequence in these control subjects were to follow up on extracranial pathology such as rhabdomyosarcoma, epithelioma, and facial port-wine stain, and to exclude intracranial pathology in cases of abnormal headaches, behavioral disorders, and brief minor neurological deficit without sequelae.

MRI Data

MRI was performed on a 1.5-T unit (General Electric Healthcare), including pseudocontinuous ASL sequences, with the following imaging parameters: TR 4604 msec, TE 10.7 msec, voxel size 3.75

× 3.75 × 4.0 mm, field of view 24.0, postlabeling delay (PLD) for children < 2 years 1025 msec, PLD for children > 2 years 1500 msec. Data processing was performed using the software program Advantage Workstation Server (General Electric Healthcare). Quantitative perfusion maps were generated based on a tissue relaxation time of 1.5 seconds and lambda of 0.9. Equilibrium magnetization of blood was estimated from the data.

ASL images were coregistered with T2- and T1-weighted MR images. Measurement of CBF was performed by manually placing regions of interest (ROIs) on T2- and T1- weighted images, after which the corresponding location and CBF value on the ASL image were extrapolated. We manually placed ROIs, because automated programs perform ROI placement with lower accuracy in patients with sCS, because of their distorted brain anatomy.[16] A measurement protocol based solely on anatomical landmarks was constructed with 47 ROIs distributed over frontal, parietal, temporal, and occipital lobes, and the cerebellum. Each ROI was placed on three consecutive slices in which the structure of interest was visible. We then averaged the three values. If a structure was not visible on all three slices, the average was calculated using slices on which it was visible. The evaluator was not blinded to whether a subject was a control subject or sCS patient. True blinding of the evaluator was impossible, because the abnormal head shape is visible on MR images. However, the evaluator closely followed the measurement protocol based solely on anatomical landmarks, minimizing the need for individual interpretations, and thereby minimizing the potential bias of not blinding the evaluator.

Table 1
Characteristics in syndromic craniosynostosis patients and controls

	sCS patients			
	Total (n = 76)	**Untreated (n = 36)**	**Treated (n = 40)**	**Controls (n = 86)**
Mean age (range), years	4.5 (0.20 - 19.18)	1.5 (0.20 - 10.67)	7.24 (1.15 - 19.18)	6.37 (0.1 - 17.78)
Females, n (%)	35 (46.1%)	18 (50%)	17 (42.5%)	38 (44.2%)
Males, n (%)	41 (53.9%)	18 (50%)	23 (57.5%)	48 (55.8%)
Syndrome, n (%)				
Apert	14 (18.4%)	4	10	
Crouzon	23 (30.3%)	11	12	
Muenke	8 (10.5%)	2	6	
Saethre-Chotzen	3 (3.9%)	3	0	
Complex	18 (23.7%)	8	10	
Carpenter	2 (2.6%)	2	0	
Unicoronal synostosis	6 (7.9%)	4	2	
Unknown craniosynostosis syndrome	2 (2.6%)	2	0	
Age categories				
I (< 1 yr)	27	27	0	8
II (1 < 3 yrs)	7	4	3	17
III (3 < 8 yrs)	29	4	25	34
IV (≥ 8 yrs)	13	1	12	27

Values represent absolute numbers

Statistical Analyses

Statistical analyses were performed using IBM SPSS statistical program (version 24, IBM Corp.) and R software (R Foundation for Statistical Computing). To determine the reproducibility of the measurement protocol, average-measures 2-way mixed intraclass correlation coefficients tested intra- and interrater reliability. P.N.D. performed all ASL measurements. Intrarater reliability was

tested (P.N.D.) by repeating ASL measurements in a subset of 10 control subjects. Interrater reliability was tested (B.K.D.O.) by performing ASL measurements in a subset of 10 control subjects.

Cross-Sectional Measurements: sCS Patients Compared to Controls

Differences in CBF of cross-sectional measurements between untreated patients, treated patients, and control subjects were examined in supratentorial and infratentorial brain areas, including data from the frontal, parietal, occipital, and temporal lobes, and cerebellum. In supratentorial areas, cortex and white matter were separately assessed. Multivariate analysis of covariance (MANCOVA) determined possible differences as a multiple model and, as such, determined whether or not factors (such as patients vs controls) influenced the relationship between responses (such as CBF of brain lobes and cerebellum). Analyses of covariance (ANCOVAs) determined possible differences as univariate models and, as such, assessed the influence of factors on a single response at a time. Variables that we considered for the MANCOVA model were age, sex, and sedation technique (sevoflurane, propofol, combination of sevoflurane and propofol, or awake). We first ran a full model with all covariates for each age category and included covariates that had a p value < 0.10 in the final model. Only age had p values below 0.10.

We stratified age into four categories as used in previous studies:[17] category I (0 to < 1 year old), category II (1 to < 3 years old), category III (3 to < 8 years old), and category IV (8 years and older). In these categories, we were able to make the following comparisons: category I, comparing untreated patients to controls; category II, comparing untreated and treated patients to controls; and categories III and IV, comparing treated patients to control subjects. The p values of MANCOVAs and ANCOVAs within age categories were adjusted for multiple testing with a Bonferroni correction. The level of significance was set at 0.05. The p values were not further adjusted between age categories. There were two reasons we chose age stratification. The first reason was to facilitate comparisons to other literature on the subject. The second was that a regression model, while more sensitive, could have introduced bias by grouping all sCS patients together, because younger patients were more often untreated and older patients were more often treated.

Age-related progression of CBF for controls, untreated, and treated patients was graphically assessed. Predicted mean CBF profiles for each group were obtained via linear regression using B splines of age. These mean profiles, together with 95% confidence interval (CI) bands for the control group, were then used to visualize further differences in the progression of CBF patterns over time between the controls and the treated and untreated patients.

Longitudinal Measurements

Age-related progression of CBF in patients with longitudinal pre- to postoperative measurements was graphically assessed. Patient-specific line graphs for individuals with longitudinal data were compared to the mean CBF profile and 95% CI bands for controls to determine differences in age-related progression of CBF. The McNemar chi-square test determined longitudinal differences in proportions of patients below 95% CI bands pre- and postoperatively.

Table 2 CBF data of patients with hydrocephalus, VP drains, and papilledema

		Lobe						
Variable	**No. of Pts**	**Frontal**	**Parietal**	**Occipital**	**Temporal**	**Cerebellum**	**Cortical matter**	**White matter**
Age category I	**27**							
Est. mean (±3SD)		47.66 (4.21-91.12)	51.15 (9.58-92.73)	53.99 (-2.55-110.53)	58.15 (3.44-112.85)	68.38 (25.34-111.42)	64.60 (7.45-121.76)	34.69 (-0.26-69.65)
Hydrocephalus	3	34.66	43.36	33.78	35.02	46.69	47.67	20.57
		47.38	53.16	53.14	56.10	49.94	60.51	35.05
		51.14	61.52	57.11	56.70	58.10	69.07	38.74
VP-drain	1	68.31	67.76	65.99	82.43	79.96	78.26	59.03
Papilledema	4	33.81	39.27	47.46	45.21	49.94	51.31	23.62
		44.36	44.50	47.87	50.35	72.31	55.91	36.72
		47.38	52.63	57.11	56.10	73.02	60.51	38.74
		50.22	53.16	67.56	59.66	81.01	66.47	40.74
Age category II	**7**							
Est. mean (± 3SD)		58.12 (11.95-104,28)	61.59 (20.35-102.83)	60.59 (18.47-102.66)	70.98 (21.62-120.34)	55.73(16.25-95.22)	78.61 (17.74-139.49)	40.90 (18.94-62.87)
Hydrocephalus	0	-	-	-	-	-	-	-
VP-drain	0	-	-	-	-	-	-	-
Papilledema	1	56.23	62.49	61.32	68.37	60.43	79.81	38.15
Age category III	**29**							
Est. mean (± 3SD)		70.91 (40.09-101.74)	75.57 (44.75-106.39)	80.56 (38.53-122.60)	83.05 (43.16-122.94)	65.56 (17.15-113.97)	99.80 (54.60-145.00)	44.22 (27.14-61.30)
Hydrocephalus	2	71.58	82.79	71.49	83.35	65.19	99.62	47.72
		80.53	87.16	82.09	95.19	66.19	110.39	52.61
VP-drain	0	-	-	-	-	-	-	-
Papilledema	2	56.23	62.49	61.32	68.37	58.93	79.81	38.15
		75.45	76.38	85.55	95.01	60.43	110.42	46.09
Age category IV	**13**							
Est. mean (± 3SD)		61.84 (7.45-116.23)	67.26 (4.75-129.76)	62.38 (5.40-119.76)	73.48 (3.65-143.30)	62.33 (11.29-113.37)	87.06 (14.83-159.29)	38.16 (3.99-72.32)
Hydrocephalus	4	35.78	37.97	31.66	41.66	42.14	54.59	22.95
		43.14	59.37	56.56	61.53	47.80	73.47	24.47
		52.41	64.14	56.56	63.05	60.57	74.61	32.84
		71.56	66.23	58.17	81.96	64.91	94.12	39.85
VP-drain	0	-	-	-	-	-	-	-
Papilledema	0	-	-	-	-	-	-	-

Pts: patients, VP-drain: ventriculoperitoneal drain, Values represent the CBF in ml/100 g/min (standard deviation)

Results

Table 1 summarizes the demographic data of 76 patients with sCS and 86 control subjects. This study included patients with Apert, Crouzon, Muenke, and Saethre Chotzen syndromes. Complex craniosynostosis refers to patients in whom the genetic cause is unknown but expected because multiple sutures are involved. Nine patients had hydrocephalus, 1 patient had a ventriculoperitoneal (VP) drain, and 7 patients had papilledema. Exploratory analysis showed that CBF data of these patients were within ± 3 standard deviations (SDs) of the estimated mean of sCS patients' brain regions and brain structures, and hence were not outliers (Table 2).

Intrarater reliability tests for ROI ASL measurements resulted in an intraclass correlation coefficient of 0.99 (95% CI 0.93–0.99). Interrater reliability tests for ROI ASL measurements resulted in an interclass correlation coefficient of 0.91 (95% CI 0.57–0.98).

Patients With sCS Compared to Controls

Overall, we found no significant differences in CBF between males and females in their white matter (controls: mean difference 0.76 ml/100 g/min, 95% CI −5.30 to 3.78, p = 0.74; sCS patients: mean difference 1.42 ml/100 g/min, 95% CI −6.06 to 3.22, p = 0.54) or cortical matter (controls: mean difference 4.03 ml/100 g/min, 95% CI −3.97 to 12.04, p = 0.32; sCS patients: mean difference 1.27 ml/100 g/min, 95% CI −12.20 to 9.66, p = 0.82). Hence, in the following presentation of results the data by sex have been grouped.

Table 3 summarizes the CBF differences between control subjects and sCS patients in age categories I–IV. In age category I, by univariate analysis (ANCOVA), CBF is significantly lower in untreated sCS patients for all brain lobes, cortical matter, and white matter. On multivariate analysis (MANCOVA) of supratentorial and infratentorial areas, as well as supratentorial cortex and white matter, significant differences remained between untreated sCS patients and controls. In age category II, multivariate analyses failed to identify any significant differences. In age categories III and IV these absolute CBF differences between sCS patients and controls are smaller. The apparent discrepancy in age categories III and IV between the MANCOVA and ANCOVA may be due, in part, to the greater power of MANCOVA, but possibly also implies a multivariate response pattern.

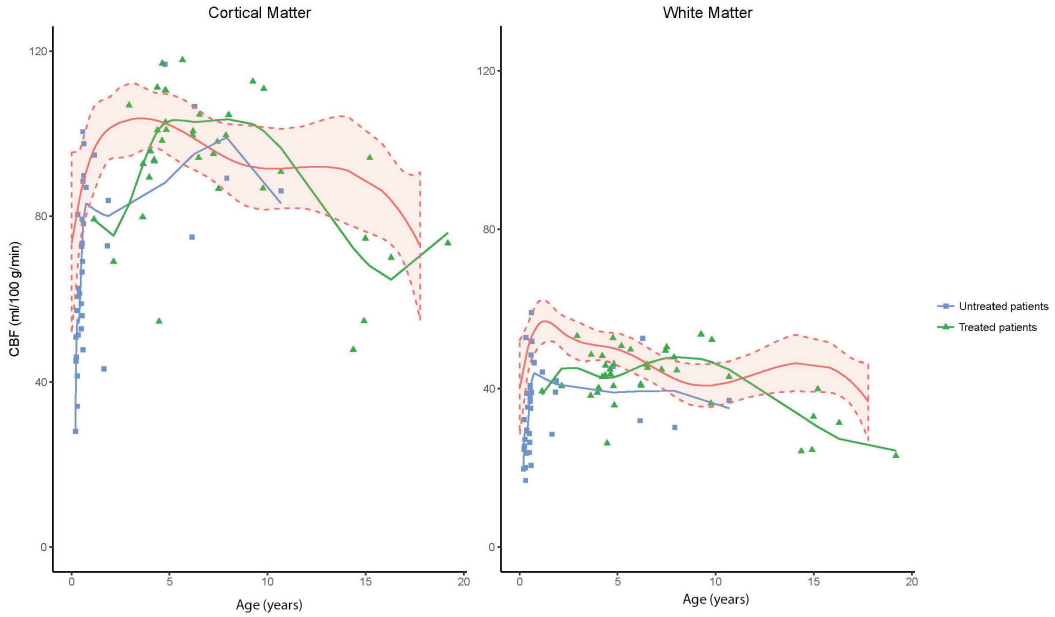

Figure 1. Distribution of CBF for the supratentorial cortex and white matter in untreated and treated sCS patients by age at measurement, plotted against the distribution of control subject CBF data by age (mean and 95% CI represented by red line and pink shading, respectively).

Figure 1 depicts CBF of the supratentorial cortex and white matter as a function of age for untreated sCS patients, against the background (mean and 95% CI) generated from control data for brain lobes and the cerebellum. **Figure 2** shows the distribution of data for brain lobes and the cerebellum. In controls all four brain lobes and supratentorial cortical matter show an increasing CBF in the first year of life, with a peak around the age of 4 years, after which there is declining CBF through childhood to an adult level. The cerebellum and supratentorial white matter similarly show a similar age-related pattern with the peak at 1 year of age. On inspection of these graphs it is also evident that the data points from sCS patients do not follow the distribution of data observed in controls. For example, even though all four brain lobes and supratentorial cortex of sCS patients show a similar developmental progression in CBF with age to that of controls, they have a lower CBF at the outset of postnatal CBF development and the peak appears to occur at a later age, at approximately 5–6 years. The cerebellum and supratentorial white matter in sCS compared with control subject data also show a similar developmental profile of CBF. The observation of early lower CBF at the outset of postnatal development in sCS patients is supported by significant CBF differences in age category I (**Table 3**, **Figure 3**).

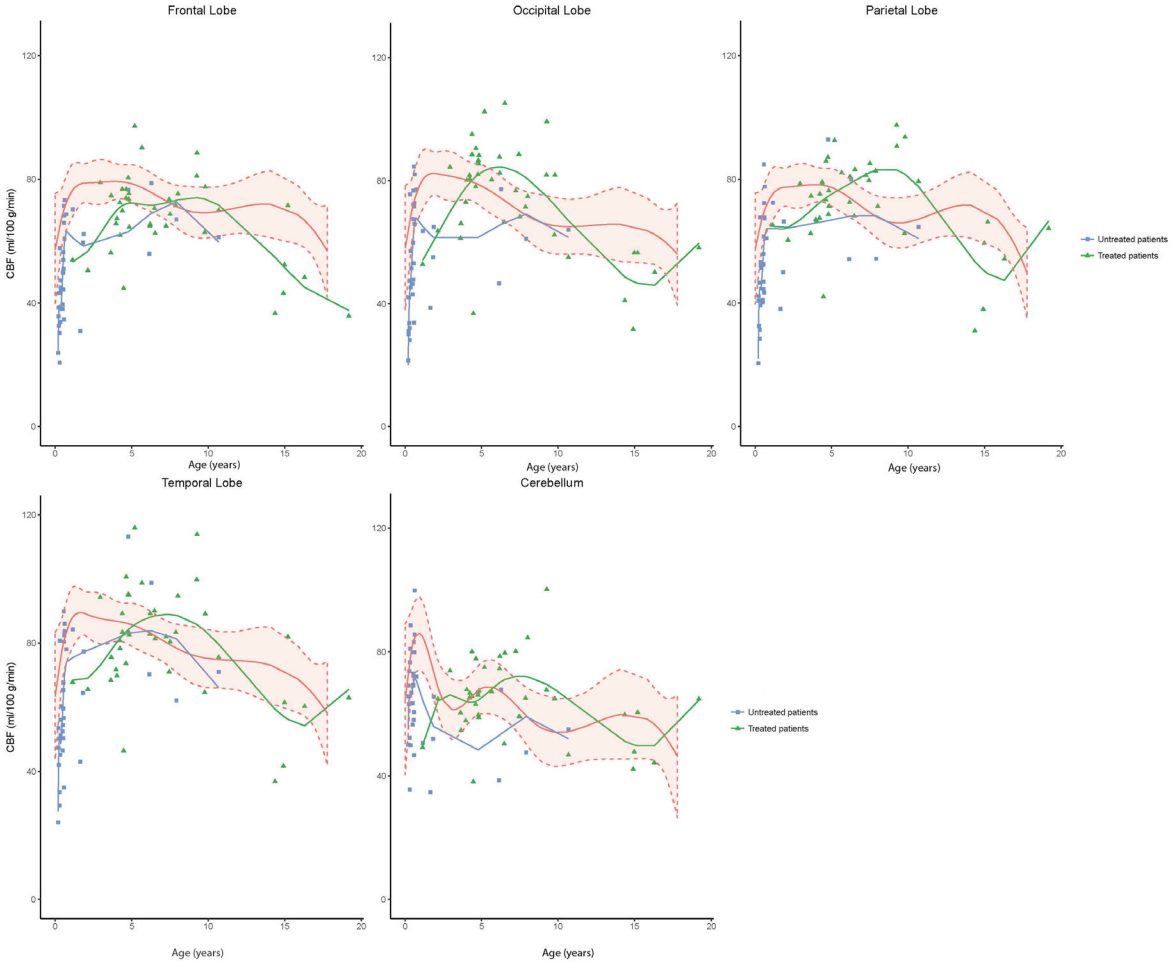

Figure 2. Distribution of CBF for supratentorial and infratentorial areas in untreated and treated sCS patients by age at measurement, plotted against the distribution of control subject CBF data by age (mean and 95% CI represented by red line and pink shading, respectively). Figure is available in color online only.

Table 3
Mean CBF in control subjects and syndromic craniosynostosis patients in age categories I to IV

	Controls		Patients		ANCOVA	MANCOVA
Age category	Mean	SE	Mean	SE	P-value	P-value
Category I (<1 yrs)*						
Supratentorial and infratentorial areas						**<0.004**
Frontal lobe	67.338	4.429	47.663	2.409	**<0.001**	
Parietal lobe	66.090	4.466	51.154	2.430	**0.006**	
Occipital lobe	67.606	5.196	53.992	2.827	**0.028**	
Temporal lobe	74.635	5.318	58.146	2.893	**0.010**	
Cerebellum	75.519	5.906	68.380	3.213	0.296	
Supratentorial: cortex and white matter						**0.006**
Cortex	83.578	5.317	64.603	2.892	**0.004**	
White matter	48.857	3.634	34.691	1.977	**0.002**	
Category II (1 to <3 yrs)						
Supratentorial and infratentorial areas						0.097
Frontal lobe	76.629	4.108	58.117	6.403	**0.024**	
Parietal lobe	76.171	4.053	61.590	6.317	0.066	
Occipital lobe	82.319	4.052	60.563	6.315	**0.009**	
Temporal lobe	88.620	4.300	70.977	6.702	**0.038**	
Cerebellum	75.811	6.773	55.734	10.555	0.124	
Supratentorial: cortex and white matter						0.067
Cortex	99.858	4.723	78.614	7.361	**0.024**	
White matter	54.232	2.857	40.903	4.453	**0.020**	
Category III (3 to <8 yrs)						
Supratentorial and infratentorial areas						**0.020**
Frontal lobe	77.427	2.205	70.913	2.574	0.060	
Parietal lobe	75.559	2.290	75.570	2.674	0.998	
Occipital lobe	76.234	2.809	80.561	3.279	0.322	
Temporal lobe	84.247	2.592	83.048	3.025	0.765	
Cerebellum	64.229	2.419	65.558	2.823	0.723	
Supratentorial: cortex and white matter						**0.005**
Cortex	100.060	2.916	99.800	3.404	0.954	
White matter	49.072	1.351	44.221	1.577	**0.023**	
Category IV (≥8 yrs)						
Supratentorial and infratentorial areas						**0.002**
Frontal lobe	68.952	2.269	61.842	3.404	0.091	
Parietal lobe	66.389	2.668	67.256	4.003	0.858	
Occipital lobe	65.813	2.690	62.378	4.035	0.483	
Temporal lobe	72.875	2.974	73.478	4.461	0.911	
Cerebellum	56.977	2.295	62.329	3.443	0.204	
Supratentorial: cortex and white matter						0.066
Cortex	89.650	3.126	87.059	4.689	0.648	
White matter	42.802	1.532	38.155	2.297	0.101	

Values represent the CBF in ml/100 g/min. Boldface type indicates statistical significance
* Age category I = untreated patients; age category II = untreated and treated patients; age categories III and IV = treated patients.

Longitudinal Data

On general inspection of CBF data in sCS patients (**Table 3**, **Figures 1–3**), it appeared that the CBF of treated sCS patients > 5 years old was higher than that of untreated sCS patients. Therefore, in a further analysis, we reviewed 12 patients with sCS who underwent serial MRI with ASL before and after vault expansion. The mean age at preoperative MRI was 0.6 years (range 0.2–1.8 years), and the mean age at postoperative examination was 2.4 years (range 0.9–3.8 years). **Figures 4** and **5** summarize the serial ASL measurements in these sCS patients overlaid on normative data by age (mean and 95% CI) in our control subjects. The number of patients whose CBF was below the 95% CI of control subjects preoperatively versus postoperatively for the frontal lobe changed from 10/12 to 6/12 ($p = 0.125$), for the parietal lobe from 10/12 to 4/12 ($p = 0.070$), for the occipital lobe from 10/12 to 3/12 ($p = 0.065$), for the temporal lobe from 12/12 to 5/12 ($p = 0.016$), for the cerebellum from 7/12 to 5/12 ($p = 0.774$), for the cortical matter from 10/12 to 3/12 ($p = 0.065$), and for white matter from 11/12 to 7/12 ($p = 0.219$).

Discussion

In this study of CBF in children with sCS we have identified three main features when findings are compared with control subject data. First, patients with untreated sCS < 1 year old have lower than expected CBF. Second, with surgical vault expansion, and age progression, CBF in sCS patients eventually falls within the range of control subject data. Third, the expected early childhood peak in CBF occurs around the age of 5–6 years in patients with sCS, which is later than that observed in controls.

A key factor in determining the indication and timing of cranial vault expansion in sCS patients is the presence of ICH, or the impending propensity to develop it. Recent discussions have also focused on the way in which abnormal venous anatomy during the first year of life may also impact the development of ICH.[18,19] Thus, to better understand the effects of these cranial vault and vascular changes in relation to the postnatal development of CBF in sCS, we sought to use a novel noninvasive MRI technique for assessing CBF, namely ASL.[20] Previous studies have shown that the ASL-derived estimation of CBF provides data that are comparable to CBF values using other techniques, e.g., FDG-PET, SPECT scanning, and dynamic susceptibility contrast MRI.[9-11] A recent study by Carsin-Vu et al.[21] used ASL to examine CBF in healthy subjects ranging from 0 to 18 years old, and supports the results we found in our controls. That study similarly found an increasing CBF with a peak at 3–4 years and a decline until adolescence, and found no differences between patients based on sex or anesthesia. One difference was a lower mean CBF in their pediatric population than in ours. Their low CBF values could be the result of using a relatively long PLD of 1800 msec, which is recommended in adults. For children a PLD of 1500 msec is recommended, as used in our study.[22]

Previous work using PET scanning in 10 single-suture nonsyndromic craniosynostosis patients showed generalized lower CBF before surgery, which was most pronounced in the frontal lobe and occipital lobe.[12] We have extended and confirmed these observations with more complete characterization of CBF in 27 patients with sCS in the first year of life. We also describe a generalized reduction in CBF to all brain lobes, especially the frontal lobe. However, the posterior fossa findings were different; we did not observe any differences in cerebellar CBF between untreated sCS patients and controls, which could be due to a homeostatic mechanism that protects the cerebellum.[23]

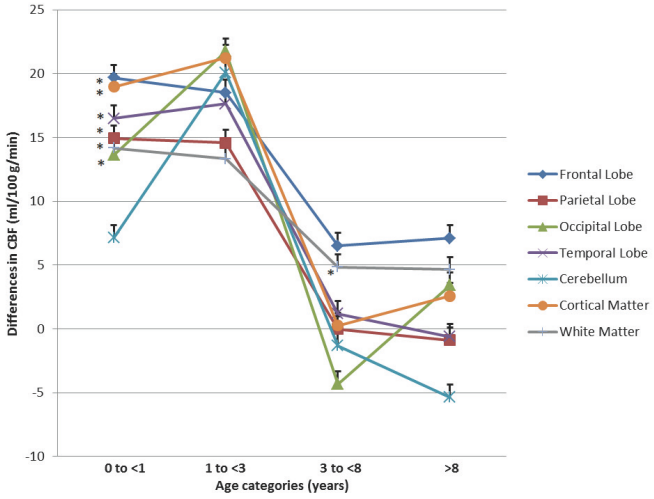

Figure 3. Mean (and standard error) differences in CBF between control subjects and patients with sCS by age category (years).
*Statistical significance in MANCOVA and ANCOVA testing. Figure is available in color online only.

The potential effect of surgical vault expansion on improving CBF in sCS also warrants further discussion. In our study it is difficult to determine whether the apparent normalization of CBF is due to surgical intervention, or whether it is a natural consequence of age and development. In the limited series of longitudinal pre- and postoperative CBF measurements, this study could not show statistically significant changes, possibly due to the small number of patients. However, this limited series did show abnormally low CBF before surgery that was higher, and more likely to be within the 95% CI of controls, after surgery. This finding is of interest because other serial studies focusing on cerebral perfusion[12,14,24-26]4,8,9,24,30 and cerebral venous blood flow19 in craniosynostosis have also shown improvements after surgical treatment; the interval between pre and postoperative measurements varies from 7 days to 4 months in these studies. The only studies on CBF changes with surgery have concentrated on evolution in the tissue underneath the closed suture.[14,24,25] We now provide global and regional data on CBF before and after surgery.

The pressure-volume curve for brain tissue and the contents of the cranium implies that any increase in brain, blood, or CSF will lead to an increase in intracranial pressure (ICP) once compensatory mechanisms of changes in blood and CSF fail. In sCS, total intracranial volume could be restrictive because the cranial sutures are fused, although this is not prevalent in the first year of life.[27,28] The impact of increased CSF space/volume observed in our study is not large, as shown by the exploratory findings in sCS patients with hydrocephalus. However, the common finding of elevated ICP in sCS might thus be caused by abnormal venous outflow. Enlarging the skull may potentially normalize CBF not only because it improves blood outflow, but also because it enlarges total intracranial volume, which shifts the pressure-volume curve to the left, reflecting better compliance to shifts in ICP.

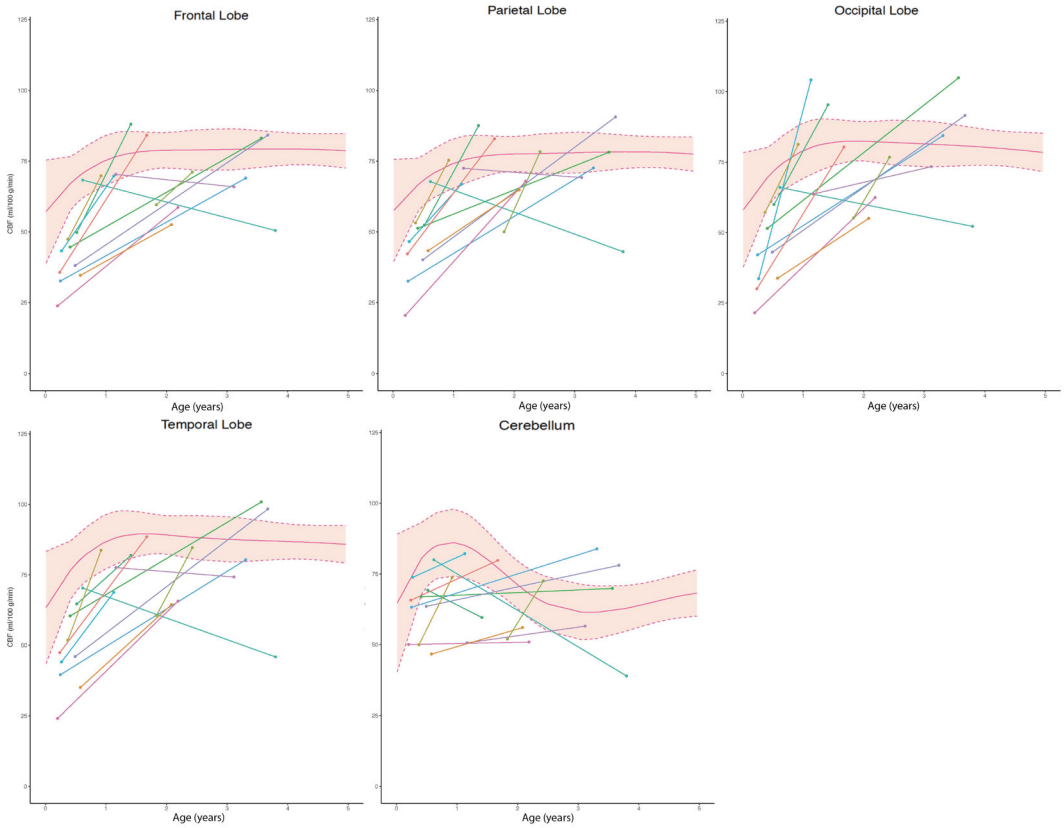

Figure 4. Longitudinal preoperative to postoperative measurements of CBF in sCS patients against the distribution of control subject CBF data by age (mean and 95% CI represented by red line and pink shading, respectively). Figure is available in color online only.

After the age of 3 years, CBF in surgically treated sCS patients appears similar to the level observed in control subjects. However, the distribution in CBF by age is different in children with sCS, with the physiological peak in CBF occurring at approximately 5–6 years of age. This finding is a new observation and it may offer part of the explanation for the problem of ICH in sCS patients. For example, the age of 5–6 years is the time at which sCS patients often develop ICH, and it is possible that this peak in CBF is not compensated by abnormal venous anatomy.[18] We now wonder whether, in such sCS patients, the timing of the peak in a CBF maturational profile is a vulnerable period because of the limit set by outflow, i.e., “outgrowing” drainage capacity.

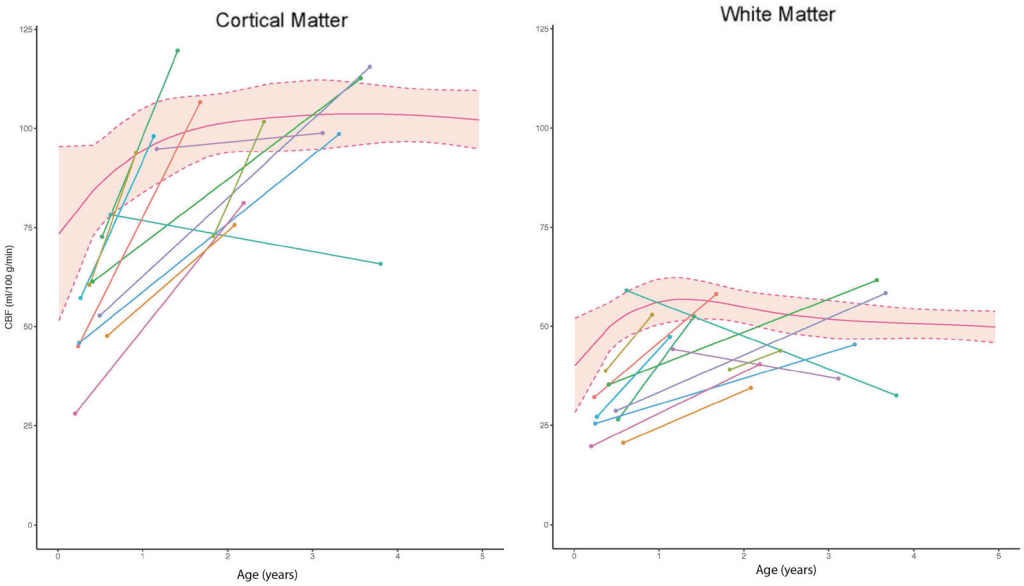

Figure 5. Longitudinal preoperative to postoperative measurements of CBF (gray matter, white matter) in sCS patients against the distribution of control subject CBF data by age (mean and 95% CI represented by red line and pink shading, respectively).

Our study does have two main limitations, which concern control subject selection and the ASL technique. First, in the matter of control subject selection, age matching would have been our preferred method to obtain control data, but this approach was not possible because of ethical constraints in subjecting healthy young children to the anesthesia required for undergoing MRI examination, solely for research purposes. Hence, we settled for a convenience sample in which a clinical investigation was being performed but there was no evidence of imaging or clinical neuropathology and morbidity, aiming for at least 8 control subjects per age category, based on other cerebral perfusion literature.[17,21] However, we have been able to use data from nearly 90 control subjects ranging from infants to adults, and while our results in controls are supported by recent literature,[21] we cannot avoid the fact that children included as controls in this study had a reason for undergoing imaging of the head and neck area, and therefore might not be assumed to be perfectly normal.

Second, in regard to the ASL measurements and estimation of CBF, there are two limitations that need to be considered. The sensitivity of ASL is reduced in white matter, because CBF is lower and the arterial transit time is longer than that of gray matter.[29] However, through higher field strength and use of a pseudocontinuous ASL technique, we have addressed this challenge; the narrow 95% CI for white matter indicates that our methodology has resulted in an accurate estimate of CBF in white matter. Next, in regard to our estimation of CBF, the findings may have been affected by a so-called partial volume effect. The partial volume effect relates to the fact that the voxel size in ASL is several times larger than the voxel size available from T1-weighted acquisitions. Hence, most of the voxels measured in ASL contain a combination of tissues and/or CSF,[29] which may be more pronounced when there is slow development or atrophy of cortical matter. In order to limit the partial volume effect, we chose to measure a series of ROIs in three consecutive slices on which the structure of interest was visible, and average the resulting CBF measurements.

Conclusions

This case cohort study shows that CBF of untreated children < 1 year old with sCS is lower than that of controls. After surgical vault expansion in children with sCS, and with age, the expected childhood peak in CBF occurs about 1 year later than that noted in control subjects. After surgery, and with age, children with sCS eventually attain CBF levels similar to those of control subjects.

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CHAPTER 4

UPPER AIRWAY ENDOSCOPY TO OPTIMIZE OBSTRUCTIVE SLEEP APNEA TREATMENT IN APERT AND CROUZON SYNDROMES

Priya N. Doerga, Bart Spruijt, Irene M.J. Mathijssen, Eppo B. Wolvius, Koen F.M. Joosten, Marc P. van der Schroeff

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Abstract

INTRODUCTION: Obstructive sleep apnea (OSA) is highly prevalent in children with Apert and Crouzon syndromes. Although often related to midface hypoplasia, it is a multi-level problem for which routine midface advancement might be a suboptimal treatment choice. We therefore wished to: 1.) use upper airway endoscopy to examine the level of obstruction in children with OSA; 2.) determine the relationship between endoscopic assessment and OSA severity; and 3.) evaluate the effect of surgery on endoscopic assessment and OSA severity.

METHODS: Prospective observational cohort study of patients considered for midface advancement, underwent upper airway endoscopy. Endoscopy findings were scored according to the system of Bachar, based on level (nose, uvulopalatine plane, tongue base, hypopharynx and larynx); and severity (no, partial or complete obstruction). Polysomnography was used to diagnose OSA.

RESULTS: We included 22 children (Apert N = 10, Crouzon N = 12), 17 had OSA, 14 of whom had multilevel obstruction and 3 single-level obstruction. The endoscopy findings were correlated with OSA severity: R = 0.56, P = 0.01. Midface advancement (N = 8) reduced Bachar's severity index in 7 of 8 patients, and OSA in all patients.

CONCLUSIONS: OSA in children with Apert or Crouzon syndrome is often a multi-level problem. Upper airway endoscopy is essential to optimizing OSA treatment.

Introduction

Obstructive sleep apnea (OSA) is highly prevalent in children with Apert and Crouzon syndromes.[1] Characterized by an upper airway obstruction that disrupts normal ventilation, it leads to a variety of symptoms, the commonest of which are apnea, snoring, and difficulty in breathing during sleep.[2] The gold standard for diagnosing it is polysomnography. OSA can result in major neuropsychological and cognitive impairment, failure to thrive, feeding difficulties, recurrent infections and behavioral deficits.[3,4] It also contributes to the development of intracranial hypertension.[5,6]

The cause of OSA in children with Apert or Crouzon syndrome is often related to midface hypoplasia, which is common in these patients.[7-9] Other anatomical abnormalities include nasal septum deviation, choanal atresia, hypertrophy of adenoid and/or tonsils, palatal deformities, mandibular hypoplasia, and tracheal cartilage anomalies.[10-13]

Children with Apert or Crouzon syndrome who have midface hypoplasia and who suffer from OSA, usually receive midface advancement with distraction (e.g., monobloc procedure, LeFort III or facial bipartition). However, as OSA is often a multi-level problem in these children,[14] treating it with midface advancement without further examination of its cause might lead to undertreatment or even mistreatment.

In children with Apert or Crouzon syndrome we therefore wished 1.) to use upper airway endoscopy to examine the level (or levels) and degree of obstruction in children with OSA; 2.) to determine whether obstructions seen in the endoscopic assessment relate to the OSA severity; and 3.) to evaluate the effect of surgery - i.e., midface advancement - on the endoscopic features and OSA severity.

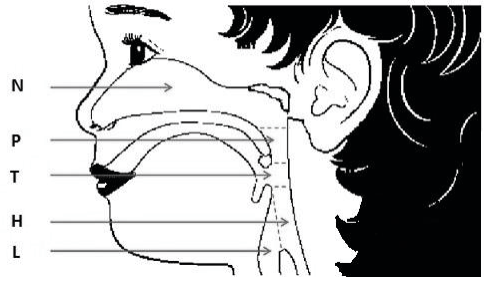

Figure 1. Levels of the upper respiratory tract used by Bachar et al. N: nose and nasopharynx, P: uvulopalatine plane, T: tongue base, H: hypopharynx, L: larynx.

Methods

Patients

In January 2006 a prospective observational cohort study started at the Dutch Craniofacial Center, Erasmus University Medical Center e Sophia Children's Hospital, Rotterdam, The Netherlands. On the basis of genetic analysis, this included children with Apert or Crouzon syndrome, who underwent upper airway endoscopy between January 2006 and February 2015. All children who

were scheduled for midface advancement were eligible for upper airway endoscopy. There were two indications for midface advancement: 1) an absolute indication (moderate/severe OSA, and/or severe exorbitism); and 2) a relative indication (midface retrusion with malocclusion, exorbitism, lagophthalmus, or psychosocial problems). If a child had an absolute indication, midface advancement was performed irrespective of age. In children with relative indications we prefer to perform midface advancement between 7 and 9 years of age or after the age of 17 years. The Ethics Committee of the Erasmus MC (MEC-2005-273) approved the study.

Airway assessment procedure

Airway endoscopy (nasal, pharyngeal, laryngeal, tracheal, and bronchial endoscopy) was performed in children who were considered for midface advancement. The endoscopy was performed in the operation room, under general anesthesia before the surgical procedure started. Pre-operative endoscopy used both a rigid endoscope (in order to exclude concomitant lower airway pathology, e.g., subglottic pathology) and a flexible endoscope (for assessment of the upper airway). In patients who had moderate/severe OSA before surgery, we usually used follow-up endoscopy to evaluate the effect of surgery. This involved the flexible endoscope only.

We chose to score the findings of the upper airway endoscopy according to the system of,[15] which is used in adults with OSA since it also includes the nose in its classification. As **Figure 1** shows, this system divides the upper respiratory tract into the following: nose and nasopharynx (N; one level, hereafter referred to as nose); uvulopalatine plane (P); tongue base (T); hypopharynx (H) and larynx (L). The system scores both the level and the severity of the obstruction, scoring no obstruction as 0, partial obstructions as 1, and complete obstruction as 2. The obstruction is noted as the first letter of the level, and is combined with a number indicating its severity. In this way, N1T2 would refer to a partial obstruction of the nose and complete obstruction of the tongue base. The scores for the different levels are then summed up to a single score (e.g., N1T2 sums up to 3): Bachar's severity index.

In addition to the Bachar system, we scored the findings of the upper airway endoscopy according to the VOTE system, which is widely used in adults with OSA.[16] This system divides the upper respiratory tract into velum (V), oropharynx and tonsils (O), tongue base (T) and epiglottis (E), but does not include the nose and nasopharynx. While both systems assess the upper airway similarly, starting from the uvulopalatine plane (velum), their distributions of the levels differ. As in Bachar's severity index, the scores for the level and severity of the obstruction are summed up to a single score, the VOTE-index.

Polysomnography

All patients underwent polysomnography in the hospital. Follow-up polysomnography was performed after midface advancement had been completed. During polysomnography a variety of cardiorespiratory and neurophysiologic variables were assessed and also videotaped. The main cardiorespiratory variables we assessed included: nasal airflow (thermistor), chest and abdominal wall motion, arterial oxygen-hemoglobin saturation using pulse oximetry (pO2), transcutaneous pxO2, snoring, and electrocardiogram. Data were analyzed using Shell. BrainRT Software Suite

Version 2.0 (O.S.G. Bvba Rumst, Belgium). Results of polysomnography were suitable for analysis if it provided a total sleep time (TST) of at least 360 min, i.e., data free of artifacts. Summary statistics and events were scored according to the 2012 update of the American Academy of Sleep Medicine (AASM) rules for scoring respiratory events.[17] Obstructive events were defined as a reduction in nasal airflow of ≥90% (apnea) or 30-90% (hypopnea) for the length of at least two breaths, in the presence of thoracic and abdominal breathing movement. A hypopnea was only included if it was associated with a subsequent desaturation of at least 3% from baseline or with an arousal. A mixed apnea is a combination of an obstructive and a central apnea (same criteria as obstructive apnea, only without presence of thoracic and abdominal breathing movement).

The obstructive apnea-hypopnea index (oAHI) was defined as the number of obstructive apneas, mixed apneas and obstructive hypopneas with desaturation indexed by the total sleep time; OSA was defined as an oAHI _1 per hour. Patients were subdivided into no OSA (oAHI <1), mild OSA (oAHI ≥1 and <5), moderate OSA (oAHI≥5 and <25) or severe OSA (oAHI ≥25).[18-20]

Statistical analysis

A Spearman correlation was used to assess the correlation between the upper airway endoscopy findings and OSA severity. A P value of <0.05 was considered statistically significant.

Results

We included 22 patients (12 boys), including cases of Apert (N = 10), Crouzon (N = 12). Mean age at time of endoscopy was 7.1 years. The baseline patient characteristics are presented in **Table 1**.

Seventeen (77.3%) of the 22 patients had OSA: 6 with Apert syndrome and 11 with Crouzon syndrome. **Table 2** gives an overview of the level (or levels) and magnitude of the obstructions according to Bachar, and also of OSA severity. Three of the patients with OSA, had a single-level obstruction, and 14 had a multilevel obstruction. All but one patient with a multilevel obstruction had an obstruction at the level of the nose. It should be noted that all patients, also those without OSA, had at least a partial obstruction at one of the levels (i.e., Bachar's severity index ≥1). **Figure 2** shows examples of an obstruction at the level of the uvulopalatine plane and the tongue base. Upper airway endoscopy findings were significantly positively correlated with OSA severity for Bachar's severity index (R = 0.56, P = 0.01; see **Table 3**), but not for the VOTE index (R = 0.29, P = 0.17).

Table 1
Patiënt characteristics

	N=22
Diagnosis	
Apert	10
Crouzon	12
Age at endoscopy (years)[a]	7.1 (0.2 – 20.0)
Male (%)	12 (54.6)
OSA (%)	17 (77.3)

Values represent absolute numbers
[a] Mean (range)

To evaluate the effect of surgery, 8 patients underwent upper airway assessment before and after midface advancement. In 2 patients, midface advancement was combined with mandibular advancement on the basis of the findings during upper airway assessment (mandibular distraction [N = 1, see **Figure 3**], and bilateral sagittal split osteotomy [N = 1]). For each patient, **Table 4** shows the upper airway endoscopy findings (Bachar's severity index) and OSA severity before and after midface advancement. Midface advancement reduced the Bachar's severity index in 7 of 8 patients and, OSA in all patients. The post-operative correlation between Bachar's severity index and OSA severity was not significant (P = 0.37). Despite this decrease in Bachar's severity index, there were residual obstructions at multiple levels, mainly those of the nose, tongue base, and uvulopalatine plane.

Table 2
Overview of the level (or levels) and magnitude of the obstructions (Bachar et al.), and of OSA severity

#	OSA	Diagnosis	N	P	T	H	L	SI
Single-level								
1	no	Apert	1	0	0	0	0	1
2	no	Crouzon	1	0	0	0	0	1
3	no	Apert	0	0	0	2	0	2
4	mild	Crouzon	1	0	0	0	0	1
5	mild	Crouzon	1	0	0	0	0	1
6	mild	Apert	0	2	0	0	0	2
Multi-level								
7	no	Apert	1	0	2	0	0	3
8	no	Apert	1	1	1	0	0	3
9	mild	Crouzon	1	1	0	0	0	2
10	mild	Crouzon	1	0	1	0	0	2
11	mild	Crouzon	1	1	0	0	0	2
12	mild	Apert	1	1	1	0	0	3
13	mild	Crouzon	1	0	2	0	0	3
14	mild	Crouzon	1	1	2	0	0	4
15	moderate	Apert	1	0	2	0	0	3
16	moderate	Apert	1	0	2	2	0	5
17	moderate	Crouzon	2	1	1	1	0	5
18	severe	Crouzon	0	1	1	0	0	2
19	severe	Crouzon[a]	2	0	1	0	0	3
20	severe	Apert[b]	1	1	1	1	0	4
21	severe	Crouzon	2	0	0	0	2	4
22	severe	Apert	2	1	1	1	1	6

N: nose/nasopharynx; P: uvulopalatine plane; T: tongue base; H: hypopharynx; L: larynx; 1: partial obstruction or flutter; 2: complete obstruction.
SI: Bachar's severity index
[a]Patient with tracheal cannula due to severe OSA
[b]Due to severe OSA, one patient would later receive a tracheal cannula

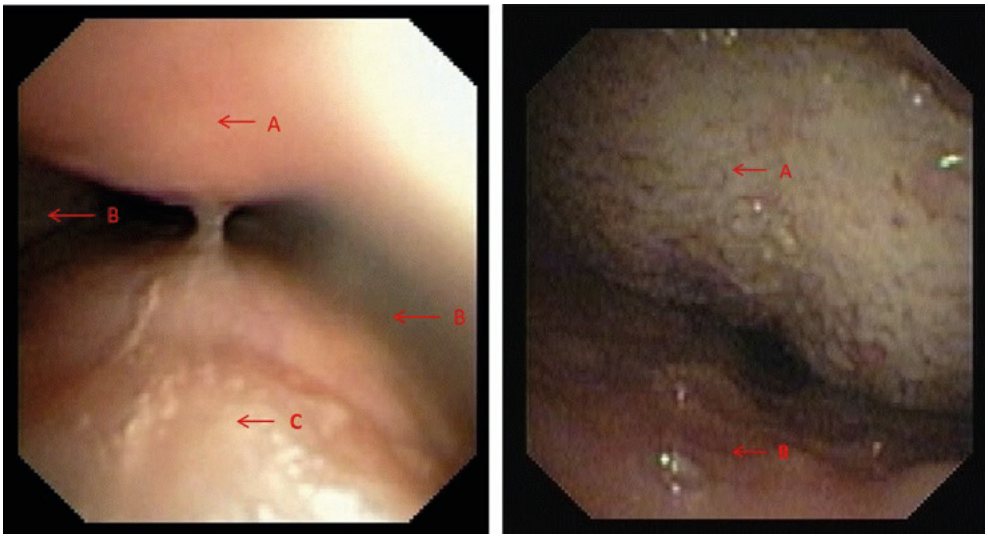

Figure 2. Endoscopic footage of obstructions at the level of the uvulopalatine plane and tongue base. a) Obstruction at the level of the uvulopalatine plane; A: soft palate; B: lateral walls of the pharynx; C: posterior wall of the pharynx. b) Obstruction at the level of the tongue base; A: tongue; B: posterior wall of the pharynx.

Discussion

This study about upper airway endoscopy in children with Apert or Crouzon syndrome has three key findings: 1.) OSA is often caused by multilevel obstructions; 2.) endoscopy assessment is significantly positively correlated with OSA severity; and 3.) midface advancement, combined with mandibular advancement if indicated, reduces the upper airway obstruction, thereby leading to a reduction of OSA.

We confirmed the findings of previous authors[14] that, although midface hypoplasia is often present, the cause of upper airway obstruction in these patients is multilevel. This demonstrates the importance of performing upper airway endoscopy before surgical intervention for OSA. Although midface advancement is one treatment modality for children whose midface hypoplasia is accompanied by severe OSA, it may not successfully relieve the symptoms of airway obstruction if the levels of obstruction are not first identified with upper airway endoscopy.

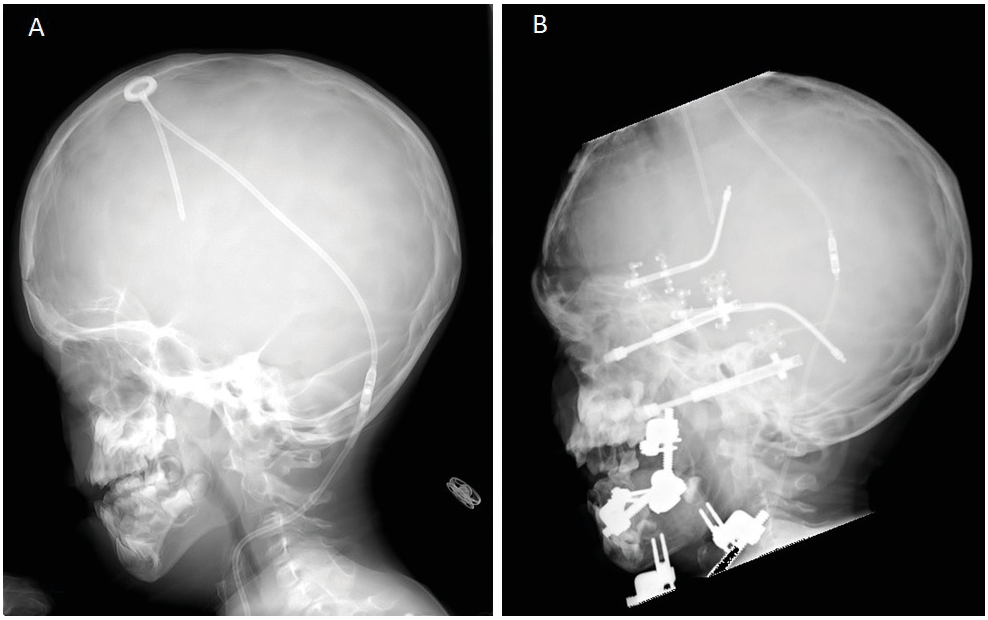

Figure 3. X-ray of a patient with midface and mandibular hypoplasia: A) pre-operatively; B) monobloc and mandibular advancement, during distraction. It should be noted that this patient had previously received a ventriculoperitoneal shunt at another hospital. Ventriculoperitoneal shunts reduce the driving force of skull growth. For this reason, we are reluctant to use shunts in young patients with craniosynostosis, and prefer skull expansion.

Table 3
Correlation between the upper airway endoscopy findings (Bachar's severity index) and OSA severity

Severity index → OSA	1	2	3	4	5	6
- no	2	1	2	-	-	-
- mild	2	4	2	1	-	-
- moderate	-	-	1	-	2	-
- severe	-	1	1	2	-	1

Values represent absolute patient numbers

We also found that the severity score determined using the system by Bachar et al. correlates with the degree of OSA. This positive correlation was not significant for the VOTE system, which does not include a score for obstructions at the nose/nasopharynx level. The nasal/nasopharyngeal level was the commonest location of upper airway obstructions. In many patients this was due to a nasal septum deviation, for which surgical correction is postponed until the age of 18. The reason for postponement is to avoid the risk of interfering with processes of facial growth: as the cartilaginous nasal septum is the dominant growth center and has poor wound healing capacity before the age of 18, recurrent deviations may otherwise result.[21] Intranasal obstructions are therefore a potential cause of persistent mild OSA after midface advancement, although it should be noted that children might react to this by switching to mouth breathing.

Table 4
The effect of midface advancement: upper airway endoscopy (Bachar et al.) and OSA severity before and after surgery

Patient		Pre-operative				Post-operative		
		Obstruction	SI	OSA	Surgery	Obstruction	SI	OSA
1	Crouzon	N1T1	2	mild	Monobloc	N1T1	2	no
2	Apert	N2P1T1H1L1	6	severe	Monobloc	N1P1T1H1L1	5	mild
3	Crouzon	N2P1T1H1	5	moderate	Monobloc	N1P1T1H1	4	no
4	Crouzon	P1T1	2	severe	Monobloc	P1	1	moderate
5	Apert	N1T2H2	5	moderate	Monobloc + mandibular distraction	N1T1	2	mild
6	Apert	N1T2	3	moderate	Le Fort II + BSSO	T1	1	no
7[a]	Crouzon	N2T1	3	severe	Monobloc	N1T1	2	mild
8[a]	Apert	N1P1T1H1	4	severe	Monobloc	N1	1	Moderate

Obstruction: N: nose/nasopharynx; P: uvulopalatine plane; T: tongue base; H: hypopharynx; 1: partial obstruction or flutter; 2: complete obstruction.
SI: Bachar's severity index
BSSO: bilateral sagittal split osteotomy
[a] Patient with tracheal cannula due to severe OSA

Bachar's severity index decreased in patients who were assessed before and after midface advancement; this was due to a decrease in the number of levels affected and/or by a reduction of its severity. Over the course of the overall study, we have come to recognize the importance of obstructions at the level of the tongue, which were present in all patients before midface advancement. In the early years of this study, such an obstruction was not necessarily treated. Over the years, however, our policy on this has changed, partly due to the two children who had had a complete obstruction at tongue base level. On basis of the findings during endoscopy, these two children subsequently underwent therapy: not only advancement of the midface, but also of the mandible. In both cases, surgery reduced the Bachar's severity index and substantially reduced their OSA. If midface advancement alone had been performed, this is unlikely to have been the case. After surgery however, endoscopy in both these patients showed a residual partial obstruction on the tongue base. This was because their degree of mandibular advancement was adjusted to that of the midface, and thus to the position of the eyes to avoid creating enophthalmus. In cases where there is no OSA or only mild OSA, it should be remembered that it is important to treat the patients' symptoms, and not solely the findings of the endoscopy.

Residual obstructions after midface advancement were present in all patients, not only at the level of the nose, but also frequently at the tongue base and uvulopalatine plane. This highlights the need to determine before subsequent surgery whether mandibular advancement is indicated in the same setting as midface advancement. It is also recommended that another endoscopy should be performed at the age of 18 years, when the final correction of the midface

is performed. If a partial obstruction of the tongue base is present, bimaxillary advancement should be considered rather than only a Le Fort I procedure.

Despite the above findings, some issues in this prospective study should be considered. For example, the report with the findings of the upper airway assessment might be subject to interobserver variability, although this effect seems limited since the endoscopies were performed by experienced pediatric otolaryngologists. Similarly, the otolaryngologists performing the endoscopies were not blinded to the OSA status of the patient. Finally, the system by Bachar does not make it possible to differentiate between a severe partial obstruction and a mild partial obstruction: all are scored as '1'. This is highlighted by a patient who had an N1T1 obstruction that did not change after surgery, despite a decrease in his OSA. A fact that is further supported by the correlation between the findings of the endoscopy with OSA severity, which was significant before midface advancement, but not afterward.

This study in children with Apert and Crouzon syndromes highlights the importance of upper airway endoscopy in subjects suffering from OSA. As obstructions are usually present at multiple levels in the upper airway, midface hypoplasia is often not the only cause of OSA. Since upper airway endoscopy can guide and optimize treatment of OSA in patients with Apert and Crouzon syndromes, it does not do justice to anatomical and functional disorders to perform midface advancement as a matter of routine.

Conclusion

OSA in children with Apert or Crouzon syndrome is often a multi-level problem. Upper airway endoscopy is essential to guiding and optimizing OSA treatment in these patients.

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CHAPTER 5

THE COURSE AND INTERACTION OF VENTRICULOMEGALY AND CEREBELLAR TONSILLAR HERNIATION IN CROUZON SYNDROME OVER TIME

Priya N. Doerga, Catherine A. de Planque, Nicole S. Erler, Marie-Lise C. van Veelen, Irene M.J. Mathijssen

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Abstract

BACKGROUND: Children with Crouzon syndrome have a higher incidence of cerebellar tonsillar herniation (TH) and ventriculomegaly than the general population, or children with other craniosynostosis syndromes.

OBJECTIVE: This retrospective cohort study aimed to determine how ventriculomegaly and TH develop and progress over time, and determine associations between ventriculomegaly and TH in Crouzon patients, treated according to our center's protocol.

METHODS: Fronto-occipital horn ratio (FOHR) and TH were determined over time using brain-imaging. These data were used to fit a mixed-model to determine associations between them, and with clinical variables, head-circumference, and lambdoid suture synostosis.

RESULTS: Sixty-three Crouzon patients were included in this study. Preoperatively, 28% had ventriculomegaly, and 11% had TH ≥ +5 mm. Postoperatively ventriculomegaly increased to 49%. Over time and with treatment, FOHR declined and stabilized around 5 years of age. TH ≥ +5 mm increased to 46% during follow-up. FOHR and TH were associated: expected FOHR with a TH of either 0 mm versus +8.6 mm at 0 years: 0.44 versus 0.49, and at 5 years: 0.34 versus 0.38; 10% increase of FOHR was associated with 1.6 mm increase in TH. Increased head-circumference was associated with increased FOHR. Lambdoid suture synostosis was associated with +6.9 mm TH increase.

CONCLUSIONS: In Crouzon patients, FOHR was large at onset and decreased and stabilized with treatment and time. FOHR was associated with head-circumference and TH. TH was strongly associated with lambdoid suture synostosis and FOHR. Increased head-circumference was associated with an increased FOHR, and closed lambdoid sutures before 1 year of age were associated with a +6.92 mm increase in tonsil position.

Introduction

Crouzon syndrome is a type of syndromic craniosynostosis, with a prevalence of 0.1 per 10,000 live births.[1] There is a lot of overlap between patients with Crouzon and Pfeiffer syndrome, both in phenotype and genetic mutations; we therefore consider them to be a homogenous group of varying severity of the same genetic defect, and refer to them all as Crouzon patients. Crouzon syndrome is characterized by mutations in genes for fibroblast growth factor receptors type 1, 2, and 3.[2] Clinically, they often present with multiple suture synostosis, exorbitism, and midface hypoplasia. Crouzon syndrome has a wide spectrum of disease severity, ranging from a mild phenotype to a severe phenotype requiring multiple surgeries to treat intracranial hypertension (ICH), or conditions that cause ICH such as ventriculomegaly or obstructive sleep apnea (OSA).[3-7] Detecting and treating ICH is important because it can cause visual impairment and is thought to affect neurocognitive development.[8]

The wide range of severity and unpredictability of the outcome of surgical treatments in Crouzon syndrome can make treating the individual Crouzon patient difficult. Unexpected problems that can occur are worsening of exorbitism, progressive expansion of ventricles after skull vault expansion, and recurrence of ICH soon after initial treatment.[7] This makes it difficult to decide which treatment is necessary at which moment. Repeat surgeries are related to hydrocephalus, cerebellar tonsillar herniation (TH), and their connection to ICH. Many theories have been postulated about the pathogenesis of TH and how it relates to ventriculomegaly.[9,10] Although there is no consensus about the sequence in which ventriculomegaly and TH occur, presence of either one is generally taken as a sign indicating a need for a closer follow-up.[7,11,12] This study has three main aims: (1) to determine how ventriculomegaly and TH develop and progress over time, (2) to determine how ventriculomegaly and TH relate to one another, (3) to determine which clinical traits, if any, are associated with TH or ventriculomegaly.

Methods

The medical ethics committee of the Erasmus MC approved this study (MEC2017-1143). This retrospective study gives an overview of children with Crouzon syndrome treated at the Erasmus MC in Rotterdam, the Netherlands, Sophia Children's Hospital, the national referral hospital for patients with syndromic craniosynostosis. It serves an approximately 3.6 million national pediatric population.[13] Patients were included sequentially from June 1994 to October 2019, DNA analysis confirmed Crouzon syndrome.

As part of our clinical protocol,[4] we perform surgical vault expansion before 1 year of age. First choice is occipital expansion with springs, scheduled around the age of 5–6 months. If ventriculomegaly develops before this age, vault expansion is scheduled earlier. When hydrocephalus appears after vault expansion, a shunt or endoscopic third ventriculostomy (ETV) will be considered. If initial ventricular enlargement following a cranial vault expansion is not progressive, an expectant policy is followed. If ICH
occurs, a second vault expansion is preferred over shunting. In general, a shunt is avoided before or shortly after cranial vault expansion to prevent skull growth reduction.

Brain Imaging

As per clinical protocol,[4] magnetic resonance imaging (MRI) exams were obtained at first presentation (usually before 1 year old), at 2 and 4 years old, and additionally when clinically indicated. All MRI data were acquired using a 1.5 Tesla MR Unit (General Electric Healthcare,

Milwaukee, Wisc.). Images were aligned in sagittal and coronal planes using Philips 3D-modeling in Intellispace software, to ensure measurements were done consistently and in the correct plane.

Computed tomography (CT) scans were acquired using a multidetector CT-scanner (Siemens, Erlangen, Germany). Scan protocol parameters were set to obtain image quality required for clinical interpretation. Patients underwent at least one CT-scan during follow-up before surgery, to determine which cranial sutures were closed. Additional CT-scans were done only when clinically indicated, to minimize radiation exposure.

Fronto-occipital horn ratio (FOHR) was used as parameter for ventricle size. FOHR is calculated as (frontal horn width + occipital horn width)/biparietal diameter*2, and gives a ratio of ventricle size that can be interpreted independent of age.[14,15] An FOHR ≥ 0.4 was considered ventriculomegaly. FOHR was determined on MRI or CT-scans. Children with hydrocephalus underwent VP-shunt/ETV.

The tonsil position was determined as the position of the lowest cerebellar tonsil in mm above (referred to as negative numbers) the foramen magnum (FM) or below the FM (TH, referred to as positive numbers; eg, tonsil position of 5 mm or more past the FM: TH ≥ +5 mm), and measured as a continuous variable. Increases in tonsil position referred to increasing downward movement of the cerebellar tonsils. Additionally, TH was divided into two categories: TH < +5 mm and TH ≥ +5 mm below FM.

Presence of abnormal venous anatomy was determined using MRI or CT-scans with angiography. We determined presence of occipital and mastoid emissary veins (0 = normal drainage pattern, 1 = abnormal emissary veins).

Clinical Measurements

Head-circumference was measured using the occipitofrontal circumference, which has shown to be a reliable indicator for intracranial volume.[16] Fundoscopy was performed to screen for ICH as determined by presence of papilledema. Patients were screened preoperatively, at the ages of 2, 4, and 6 years. Polysomnography was used to screen for the presence of OSA, using clinical in-house assessments, and ambulatory sleep studies. Obstructive apnea-hypopnea index (oAHI) was calculated as the number of obstructive and mixed apneas, or obstructive hypopneas with desaturation/arousal, divided by the total sleep duration of one night. The oAHI was used to classify patients in two categories: (1) no/mild (oAHI < 5), and (2) moderate/severe OSA (oAHI ≥ 5). Only head circumference and early lambdoid suture closure were different on preliminary analysis between children with and without TH ≥ 5 mm and children with and without FOHR ≥ 0.4, and were used for further statistical analysis. Information about the timing and types of surgeries was collected.

Statistical Analysis

Relevant characteristics of the study population are summarized using mean and range, or when appropriate median an interquartile range (IQR), for continuous variables and counts and proportions for categorical variables. To give an overview of the data, we created a heatmap, in which patients were categorized into four groups based on the moment TH ≥ +5 mm developed: (1) patients who developed TH ≥ +5 mm before first vault expansion, (2) patients who had no TH ≥ +5 mm on first MRI, and later developed it, (3) patients who underwent first MRI at a late age and had TH ≥ +5 mm, and (4) patients without TH ≥ +5 mm. For each of these groups, the heatmap shows the frequency of patients with FOHR ≥ 0.4, lambdoid suture synostosis before 1 year of age, papilledema, venous emissary veins, and moderate/severe OSA.

To investigate the association between FOHR and tonsil position, head-circumference, and lambdoid suture synostosis before 1 year of age, we fitted a mixed-model assuming FOHR to follow a beta distribution conditional on the covariates. To allow for nonlinear trajectories over time, we included the children's age using natural cubic splines with three degrees of freedom. Because this leads to difficulties in interpreting the effects of age directly, the effect of age is displayed in figures to facilitate interpretation. Correlation between repeated measurements of the same child was taken into account by including a random (patient specific) intercept. An analogous model, but assuming a normal distribution, was fitted to investigate the association between tonsil position and FOHR, head-circumference, and lambdoid suture synostosis at the age of less than 1 year. Because FOHR, tonsil position, and head-circumference were measured at different time points, values of the independent variables had to be imputed at the time points the dependent variable was observed. To this end, we estimated both mixed-models in the Bayesian framework, which allowed us to simultaneously impute the missing observations by specifying additional mixed-models for each of the independent variables.

Specifically, the model for FOHR was estimated jointly with random intercept linear mixed-models (with natural cubic splines for age) to impute head-circumference and TH, and the model for TH was fitted jointly with a random intercept beta mixed-model for FOHR and a linear random intercept model for head-circumference (both with a natural cubic spline for age). We assumed vague priors for all parameters. Results of the Bayesian models are presented as posterior mean and 95% credible intervals (CI).

Results

Patient Characteristics

Sixty-three Crouzon patients were included in this study, patient characteristics are presented in **Table 1**, and genetic changes are shown in **Table 2**. Median age at presentation was 0.9 (IQR 0.2–3.0) years; median follow-up at study conclusion was 10.2 (IQR 4.3–15.7) years.

Ventriculomegaly and TH Development and Progress over Time

Figure 1 shows factors TH ≥ +5 mm and FOHR ≥ 0.4 preoperatively and postoperatively in the 63 children, categorized by the moment at which TH ≥ +5 mm occurred. In patients with both ventriculomegaly and TH ≥ +5 mm (n = 18), TH ≥ +5 mm was detected before ventriculomegaly occurred in one of 18 patients, TH ≥ +5 mm was detected after ventriculomegaly occurred in five of 18 patients, and TH ≥ +5 mm and ventriculomegaly were detected at the same time in 12 of 18 patients. In four patients TH ≥ +5 mm was detected after placement of a VP-shunt; in two patients TH ≥ +5 mm was detected after ETV. Thirteen patients underwent VP-shunting or ETV: 10 patients were initially treated with a vault expansion followed by VP-shunt, and in three patients the order of procedures was the other way around.

Patient-specific trajectories of FOHR and tonsil position are displayed in **Figure 2**. The trajectories show the distinct differences between patients in development and progress of FOHR and tonsil position.

Table 1
Patient characteristics

Crouzon patients	63
M : F	31 : 32
Age at presentation†	0.7 (0.2 – 2.9)
FOHR ≥ 0.4*	31 (18; 13)
TH ≥+5mm*	29 (6; 23)
FOHR ≥ 0.4 and TH ≥+5mm	18
Lambdoid suture synostosis <1yr of age	12
Head circumference < -1.0 SD	22
Papilledema	33
Moderate/severe OSA	18
Surgeries	
No surgery	6
Patients that underwent a single surgery	19
Patients that underwent multiple surgeries	38
Types of surgeries	
Vault expansions‡	59 (46)
- Fronto-orbital expansion	15
-(Fronto-)biparietal remodellation	20
-Occipital expansion classic/spring distraction	24
Midface surgeries‡	26 (18)
Combination vault expansion & midface surgery‡	25 (22)
FM decompressions‡	3 (3)
VP-shunts/ETV and revisions‡	47 (13)
-VP-shunt**	8
-ETV**	2
-VP-shunt + ETV**	3
Endoscopic ventriculostomies‡	6 (4)

Values represent absolute numbers
† Median age (interquartile range) in years
‡ Number of surgeries (number of patients)
* Values represent number of patients (number of patients in whom event occurred preoperatively; number of patients in whom event occurred postoperatively)
** Values represent absolute number of patients
FOHR: fronto-occipital horn ratio, TH: cerebellar tonsillar herniation, OSA: obstructive sleep apnea, FM: foramen magnum, VP-shunt: ventriculoperitoneal shunt, ETV: endoscopic third ventriculostomy

Table 2
Genetic changes present in this cohort of Crouzon patients

FGFR	Nucleotide Change	Protein Change	n
FGFR1	c.755C>G	Pro252Arg	2
FGFR2	c.314A>G	Tyr105Cys	4
FGFR2	c.799T>C	Ser267Pro	5
FGFR2	c.812G>T	Gly271Val	1
FGFR2	c.826T>C	Phe276Val	2
FGFR2	c.833G>T	Cys278Phe	3
FGFR2	c.962A>T	Asp321Val	1
FGFR2	c.866A>C	Gln289Pro	2
FGFR2	c.868T>C	Trp290Arg	4
FGFR2	c.870G>C	Trp290Cys	1
FGFR2	c.979C>G	Leu372Val	1
FGFR2	c.1012G>C	Gly338Arg	1
FGFR2	c.1018T>C	Tyr340His	1
FGFR2	c.1019A>C	Tyr340Ser	1
FGFR2	c.1024T>A	Cys342Ser	3
FGFR2	c.1024T>C	Cys342Arg	2
FGFR2	c.1025G>A	exon 9	1
FGFR2	c.1026C>G	Cys342Trp	4
FGFR2	c.1032G>A	Ala344Ala(Splicing)	2
FGFR2	c.1040C>G	Ser347Cys	1
FGFR2	c.1061C>G	Ser354Cys	3
FGFR2	c.1069T>G	Leu357Val	1
FGFR2	c.1084+3A>G	Pro361Pro(Splicing)	1
FGFR2	c.1084G>A	Ala362Thr	1
FGFR2	c.1087+1304G>A	Cys342Tyr	8
FGFR2	c.1636G>A	Cys342Tyr	1
FGFR2	c.1694A>G	Glu565Gly	2
FGFR2	c.1851G>C	Leu617Phe	1
FGFR2	c.1922A>G	Lys641Arg	1
FGFR3	c.1172C>A	Ala391Glu	2
		Total	**63**

Nucleotide changes and protein changes that were present in the *FGFR1, FGFR2,* and *FGFR3* genes in our cohort of Crouzon patients. *FGFR*: fibroblast growth factor receptor; A: Adenine; G: Guanine; C: Cytosine; T: Thymine; Pro: Proline; Arg: Arginine; Tyr: Tyrosine; Cys: Cysteine; Ser: Serine; Gly: Glycine; Val: Valine; Phenylalanine; Asp: Aspartic Acid; Gln: Glutamine; Trp: Tryptophan; Leu: Leucine; His: Histidine; Ala: Alanine; Thr: Threonine; Glu: Glutamic Acid. Values represent absolute number of patients

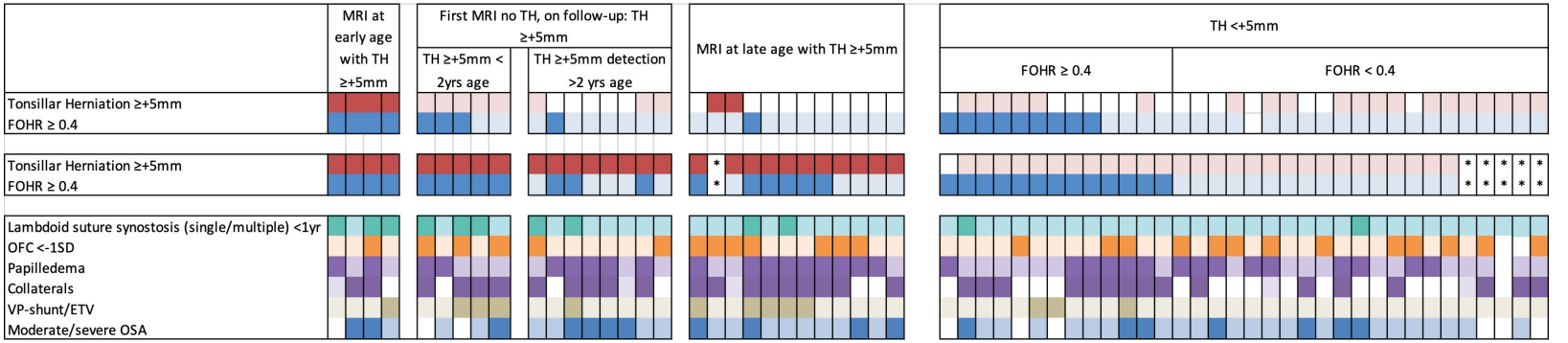

Figure 1. Heatmap depicting attributes of the 63 Crouzon patients. Patients categorized by presence of TH ≥ +5 mm and/or FOHR ≥ 0.4 before, or after first surgical intervention. Presence of abnormalities in clinical attributes are also displayed. Of each color, the darker shade represents that the abnormalities are present, the lighter shade that the abnormalities are not present, blank squares represent missing values. *Patients who have not undergone skull vault surgery: therefore, only preoperative results displayed. FOHR: fronto-occipital herniation, yr(s): year(s), OFC: occipitofrontal circumference.

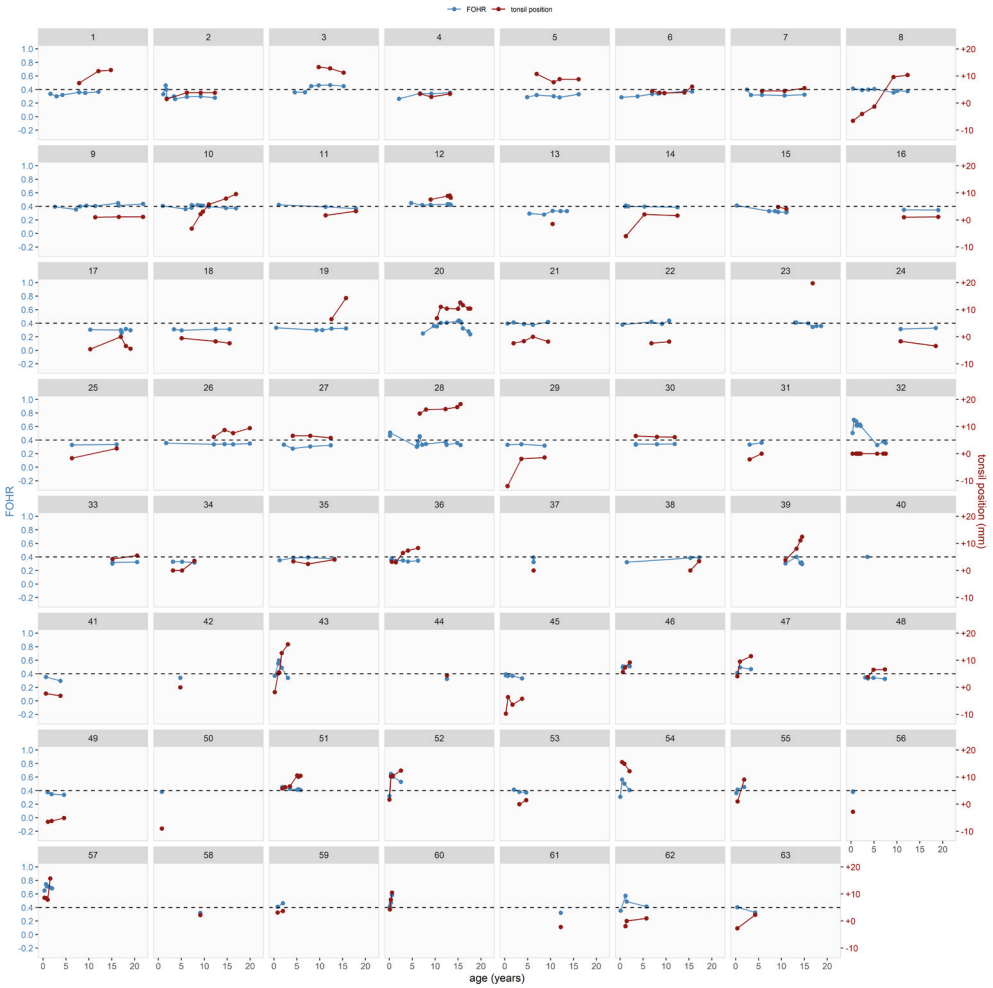

Figure 2. Patient-specific trajectories depicting progression of FOHR and tonsil position over time. Y-axes (left for FOHR, and right for tonsil position) are adjusted so that FOHR values of 0.4 are aligned with a tonsil position of +5 mm.

Relation between Ventriculomegaly and TH

The results of the mixed-model for FOHR are shown in **Table 3**. The odds ratio refers to the change in the ratio FOHR/(1-FOHR) that is associated with a 1-unit change in a covariate. **Table 3** shows that progress of tonsil position is associated with an increase in FOHR (tonsil position: odds ratio = 1.02 (95% CI[1.01–1.03]).

Table 3
Mixed-model for FOHR

			95% CI	
		OR	2.5%	97.5%
(Intercept)		0.756	0.677	0.845
Age at measurement		§		
Tonsil position		1.021	1.012	1.030
Head circumference‡		1.102	1.063	1.140
Closed lambdoid sutures< 1 year		1.103	0.971	1.266
Expected FOHR at 0 and 5 years by specific covariate values*				
Tonsil position†		Expected FOHR	95% CI	
Age 0	Q1: 0.0	0.442	0.415	0.470
	Q3: +8.6	0.486	0.449	0.524
Age 5	Q1: 0.0	0.343	0.327	0.360
	Q3: +8.6	0.384	0.363	0.405
Head-circumference‡				
Age 0	Q1: -0.66	0.434	0.403	0.467
	Q3: 1.39	0.484	0.452	0.516
Age 5	Q1: -0.66	0.336	0.317	0.355
	Q3: 1.39	0.382	0.362	0.400
Closed lambdoid sutures< 1 year				
Age 0	Open	0.462	0.431	0.493
	Closed	0.487	0.456	0.518
Age 5	Open	0.361	0.345	0.378
	Closed	0.385	0.355	0.415

CI: credible interval, OR: odds ratio, FOHR: fronto-occipital horn ratio, Q1: 1st quartile in observed data, Q3: 3rd quartile in observed data.
§ The non-linear effect of age at measurement was used in the model, but cannot be represented by a single parameter estimate and the corresponding estimates do not have direct clinical interpretation
† Values represent tonsil position in mm relative to the foramen magnum, where tonsillar herniation past the foramen magnum is represented as positive numbers, and a position above the foramen magnum as negative numbers
‡ in SD
* The other covariates were set to reference/median values (tonsillar position: +3.88 mm, head-circumference: 0.51 SD, lambdoid suture: open)

Figure 3 displays the expected FOHR and corresponding 95% CIs across age for different scenarios with respect to tonsil position, head-circumference and closed lambdoid sutures at the age of less than 1 year. It shows that FOHR starts high during the first 1.5 years of life, declines with treatment and time, and from the age of 5 years remains relatively stable. **Figure 3A** displays the expected FOHR in two scenarios where tonsil position is either 0 mm (first quartile in observed data; Q1) or +8.6 mm (third quartile in observed data; Q3). The other variables were set to the median (head-circumference: 0.51 SD) and reference category (lambdoid sutures: open). It visualizes the difference in FOHR associated with tonsil position at Q1 and Q3: at age 0 an FOHR of 0.44 (Q1 range 95% CI band: [0.42–0.47]) versus 0.49 (Q3 range 95% CI-band: [0.45–0.52]), and at age 5 years an FOHR of 0.34 (Q1 range 95% CI-band [0.33–0.36]) versus 0.38 (Q3 range 95% CI-band [0.36–0.41]).

Table 4
Mixed-model for tonsil position

			95% CI	
		Estimate	2.5%	97.5%
(Intercept)		-11.616	-17.882	-6.232
Age at measurement		§		
FOHR: Per 10% increase		+1.597	+0.410	+3.047
Head circumference‡		-0.424	-1.569	+0.303
Closed lambdoid sutures< 1 year		+6.990	+3.614	+10.276
Expected tonsil position at 0 and 5 years by specific covariate values*				
FOHR		Expected tonsil position	95% CI	
Age 0	Q1: 0.33	-6.558	-9.048	-4.020
	Q3: 0.41	-5.279	-7.233	-3.088
Age 5	Q1: 0.33	+1.518	+0.190	+3.185
	Q3: 0.41	+2.798	+1.347	+4.597
Head-circumference‡				
Age 0	Q1: -0.66	-5.431	-7.459	-3.120
	Q3: 1.39	-6.295	-9.017	-3.648
Age 5	Q1: -0.66	+2.646	+0.929	+4.801
	Q3: 1.39	+1.781	+0.269	+3.517
Closed lambdoid sutures< 1 year				
Age 0	Open	-5.920	-8.086	-3.585
	Closed	+1.079	-2.497	+4.496
Age 5	Open	+2.157	+0.878	+3.806
	Closed	+9.156	+6.105	+12.155

CI: Credible interval, FOHR: fronto-occipital horn ratio, Q1: 1st quartile in observed data, Q3: 3rd quartile in observed data
Values represent tonsil position in mm relative to the foramen magnum, where tonsillar herniation past the foramen magnum is represented as positive numbers, and a position above the foramen magnum as negative numbers.
§ The non-linear effect of age at measurement was used in the model, but cannot be represented by a single parameter estimate and the corresponding estimates do not have direct clinical interpretation
‡ in SD
* The other covariates were set to reference/median values (FOHR: 0.37, head circumference: 0.51 SD, lambdoid sutures: open)

Results of the mixed-model for tonsil position are given in **Table 4**. Ten percentage-point higher FOHR was associated with a +1. 597 mm increase in tonsil position (95% CI[0.410–3.047]). **Figure 4** visualizes the estimated development of tonsil position over time for different scenarios with regard to FOHR values, head-circumference, and closed lambdoid sutures at the age of less than 1 year. It presents a steep increase in tonsil position during the first 2.5 years of life, after which it slows down. **Figure 4A** shows the expected tonsil position in two scenarios, where FOHR is either 0.33 (Q1) or 0.41 (Q3), and shows an overlap between their 95% CIs. Again, for these scenarios, the other independent variables are set to median or reference values.

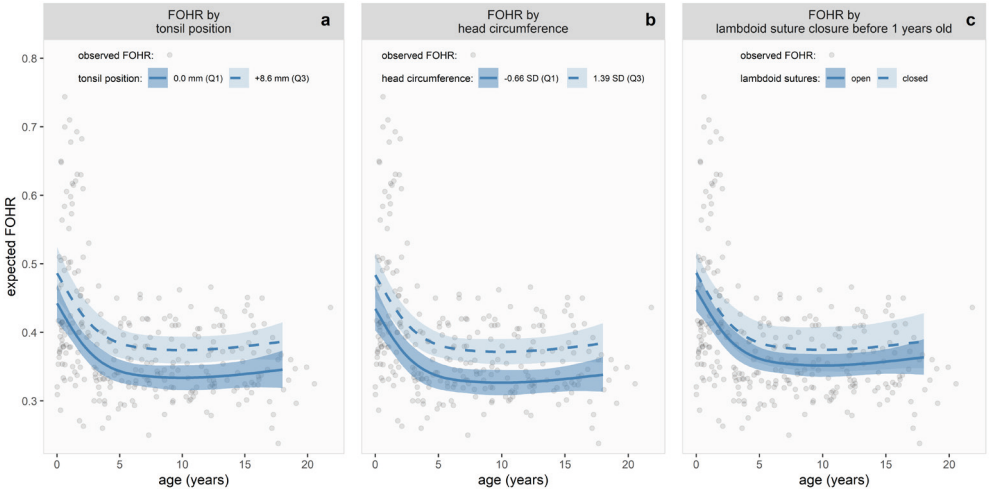

Figure 3. Expected FOHR across age by 3 different covariate values. Expected FOHR and corresponding 95% CI across age, by specific covariate values: FOHR by tonsil position (A); FOHR by head circumference (B); FOHR by lambdoid suture closure before the age of 1 year (C). Variables that are not shown in a particular panel were set to reference/median values (tonsillar position: +3.88 mm, head-circumference: 0.51 SD, lambdoid suture: open).

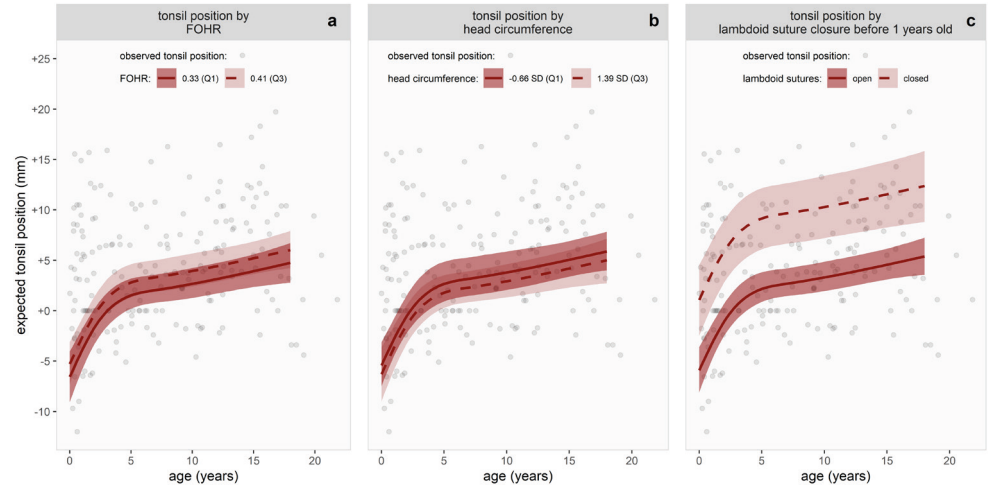

Figure 4. Expected tonsil position across age by 3 different covariate values. Expected tonsillar position and corresponding 95% CI across age, by specific covariate values: Tonsil position by FOHR (A); Tonsil position by head circumference (B); Tonsil position by lambdoid suture before the age of 1 year (C). Variables that are not shown in a particular panel were set to reference/median values (FOHR: 0.37, headcircumference: 0.51 SD, lambdoid sutures: open).

Closed Lambdoid Sutures and Head-circumference

Figure 3B, **C** display the corresponding plots of FOHR for the scenario in which head-circumference varies between its Q1 and Q3, and lambdoid suture closure at the age of less than 1 year is present, or not present. Increase in head-circumference was associated with an increase in FOHR (see **Table 3**, head-circumference: odds ratio = 1.102 (95% CI[1.063–1.140]). There was no clear evidence for differences in FOHR depending on whether patients presented with closed lambdoid sutures at the age of less than 1 year.

Figure 4B, **C** shows the corresponding effects on tonsil position for the scenarios in which head-circumference varied between Q1 and Q3, and lambdoid suture closure before 1 year of age was present or not present. **Table 4** shows that there was no evidence for an association between tonsil position and head-circumference. Closed lambdoid sutures before 1 year of age were associated with a +6.990 mm increase in tonsil position (95% CI [3.614–10.276]).

Discussion

In this study focusing on ventriculomegaly and TH in children with Crouzon syndrome, we have identified three main findings. First, we aimed to determine how ventriculomegaly and TH develop and progress over time. We found that ventriculomegaly is present in 29% at onset, the prevalence increases to 49% shortly after skull expansion, mostly in the first 1.5 years, then declines and normalizes over time and following treatment, remaining relatively stable from 5 years of age onward. TH is present in 11% at onset, with time and despite treatment (ie, vault expansion, ETV, or VP-shunting), prevalence increases to 46%, with the biggest increase happening in the first 2.5 years. Second, we aimed to determine how ventriculomegaly and TH relate to one another. We found that FOHR and tonsil position were associated, and that a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position. Third, we aimed to determine which clinical traits (if any) were associated with TH or ventriculomegaly. We found that FOHR is associated with head-circumference but not with closed lambdoid sutures before 1 year of age, and TH is associated with closed lambdoid sutures before 1 year of age, but not with head-circumference.

The prevalence of 49% of ventriculomegaly is in line with the reported prevalence of 30%–70% in children with Crouzon syndrome.[17-19] The prevalence of 46% of patients with TH ≥ +5 mm is similarly in line with reported prevalence of 38%–70% in Crouzon patients.[20,21] In the majority of our patients, ventriculomegaly preceded the development of TH. However, our cohort shows different orders of occurrence of ventriculomegaly and TH, which illustrates the unpredictable nature of developing ventriculomegaly and/or TH.

In line with studies that have shown that premature closure of the lambdoid sutures is associated with development of TH ≥ +5 mm,[22,23] we found a strong association between closed lambdoid sutures within the first year of life and a +6.990 mm increase in tonsil position (95% CI [3.614–10.276]). We found no evidence for an association between tonsil position and head-circumference. A study by Coll et al.[19] showed a statistically significant association between the presence of hydrocephalus and TH in Crouzon patients, as determined by a chi-square test. This study expands on that finding by demonstrating that a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position.

Many theories have been postulated to explain hydrocephalus in syndromic craniosynostosis.[17,24] However, to date, no unifying theory has been able to explain all variations of manifestations of hydrocephalus and TH.[11,25] In Crouzon patients, there have been big differences in the prevalence of hydrocephalus and TH ≥ +5 mm on their own, but also in how often they occur together between studies using single time-point measurements and serial measurements.[19,22]

In this report, the great variation in sequence in which ventriculomegaly and TH ≥ +5 mm can occur is exemplified in our relatively large and homogenous group of only Crouzon patients with repeated measurements. Our study showed patients who start with TH ≥ +5 mm and develop ventriculomegaly (n = 1), but also those who start with ventriculomegaly and develop TH ≥ +5 mm (n = 5), those in whom ventriculomegaly and TH ≥ +5 mm are detected at the same time (n = 12),

those who start with ventriculomegaly and never get TH ≥ +5 mm (n = 13), and those who have TH ≥ +5 mm and never develop ventriculomegaly (n = 11). These variations exemplify why it is so difficult to predict at onset which clinical course an individual patient will follow and shows the need for individual treatment plans for Crouzon patients.

Figures 3 and 4 show that although FOHR is high at onset, it declines and remains stable from 5 years of age onward. Tonsil position, on the other hand, continues to increase even after the age of 5 years, when FOHR remains stable. This could indicate that TH ≥ +5 mm on its own does not contribute to ventriculomegaly in Crouzon patients. This is supported by our finding that only one in 18 patients who eventually developed both TH ≥ +5 mm and ventriculomegaly developed TH ≥ +5 mm before developing ventriculomegaly. Furthermore, because TH ≥ +5 mm rarely causes neurological deficits, we should question how much of the treatment protocol should be focused on treating/stabilizing TH.[11,26,27]

Recent studies show a relationship between ventriculomegaly and increased diffusivity values in white matter tracts of the corpus callosum and cingulate gyrus.[28] This is associated with internalizing and externalizing behavior, showing the importance of treating ventriculomegaly at onset in Crouzon patients.[29,30]

This study's first limitation is its retrospective aspect. Over time a shift occurred in the availability of brain imaging material. Starting in 2007, we implemented a protocol, including MRI assessment before surgery. Patients who were treated before this time underwent only CT imaging; thus, tonsil position before surgery could not be determined. Most of these patients underwent MRI assessment after first vault surgery.

The second limitation is that we did not have a control group of patients who did not undergo surgical intervention because we aimed to operate on all children before 1 year of age. We therefore cannot determine what changes in FOHR or tonsil position are due to natural progression or due to iatrogenic effects. Similarly, in our small group of patients who underwent VP-drain/ETV, some showed increase in TH; we could not determine if this was despite VP-drain/ETV, or if this was due to iatrogenic effects. These could be topics of interest for future studies.

In conclusion, we found that FOHR was large at onset and that treating ventriculomegaly gives a decrease and stabilization in FOHR over time. FOHR and tonsil position were associated, and a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position. Increased head-circumference was associated with an increased FOHR, and closed lambdoid sutures before 1 year of age were associated with a +6.92 mm increase in tonsil position. Overall, the more common sequence is first occurrence of ventriculomegaly, followed by TH, although we cannot claim a causal relationship.

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CHAPTER 6

NEUROLOGIC DEFICITS ARE PRESENT IN SYNDROMIC CRANIOSYNOSTOSIS PATIENTS WITH AND WITHOUT TONSILLAR HERNIATION

Priya N. Doerga, Bianca F.M. Rijken, Hansje Bredero-Boelhouwer, Koen F.M. Joosten, Rinze F. Neuteboom, Robert C. Tasker, Marjolein H.G. Dremmen, Maarten H. Lequin, Marie Lise C. van Veelen, Irene M.J. Mathijssen

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Abstract

BACKGROUND: Children with syndromic craniosynostosis (sCS) have a higher incidence of cerebellar tonsillar herniation (TH) than the general population. In the general population, TH ≥ 5 mm below the foramen magnum is associated with typical neurological deficits but, in sCS, we do not know whether this degree of TH is required before such deficits occur. Objective: This prospective cohort study aimed to determine the association between findings on neurological assessment and cerebellar tonsillar position.

METHODS: Magnetic resonance imaging (MRI) was used to determine TH ≥ 5 mm and the presence of syringomyelia. In regard to the outcome of neurological deficits, these were categorized according to: A, cerebellar function; B, cranial nerve abnormalities; and C, sensory or motor dysfunction.

RESULTS: Twenty of 63 patients with sCS (32% [95% confidence interval 21–45%]) had TH ≥ 5 mm and/or syringomyelia. There was no significant difference in proportion between individual forms of sCS: 16/34 Crouzon, 2/11 Muenke, 2/12 Apert, and 0/7 Saethre-Chotzen patients. Neurological deficits were prevalent (73% [95% confidence interval 60–83%]), and as frequent in patients with TH ≥ 5 mm and/or syringomyelia as those without. Surgery occurred in 3 patients overall, and only in Crouzon patients.

CONCLUSION: Determining the effect of TH ≥ 5 mm on neurologic functioning in sCS patients is used to better determine when surgical intervention is warranted. However, we have found that neurological deficits are prevalent in sCS patients, irrespective of cerebellar tonsillar position, suggesting that such findings are developmental and, in part, syndrome-specific central nervous system features.

Introduction

Craniosynostosis syndromes are characterized by premature fusion of skull sutures and skull base synchondroses[1,2] and occur in 0.9 per 10,000 live births.[3] In one-fifth of cases a pathogenic mutation is found.[4] Children with syndromic craniosynostosis (sCS) may have intracranial anomalies, such as agenesis of the corpus callosum and septum pellucidum, white matter disturbances, ventriculomegaly, Chiari malformation type I (CMI) with tonsillar herniation (TH) or syringomyelia.[5-7]

The prevalence of TH ≥ 5 mm in sCS patients is much higher than found in the general population: 14%[8] versus up to 1%.[9,10] Patients with Crouzon syndrome have the highest prevalence of TH ≥ 5 mm, while Saethre-Chotzen patients have the lowest.[8] Theories differ about the cause of CMI but, nowadays, it is considered a result of prolonged intracranial hypertension (ICH) and/or possibly related to premature closure of lambdoid sutures.[7,11] The main contributors to developing ICH are craniocerebral disproportion,[12] cerebral venous outflow obstruction,[13] hydrocephalus, and obstructive sleep apnea (OSA).[14] Typically, TH ≥ 5 mm causes symptoms and signs such as headache, neck pain, ataxia, muscle weakness, altered sensation (paresthesia and dysthesia), and dysphagia.[15,16]

A key question in regard to surgical decision-making is whether these symptoms and signs are solely related to the presence of TH ≥ 5 mm or to other intrinsic problems associated with sCS. In this study of sCS patients we aim to: 1) describe the type of neurological deficits; and 2) examine a potential association between these neurological deficits and the presence of TH ≥ 5 mm and/or syringomyelia.

Methods

The ethics committee of the Erasmus Medical Center (MC) approved this prospective cohort study (January 2012 to July 2017) at the Dutch craniofacial Center, Erasmus MC-Sophia Children's hospital, Rotterdam, the Netherlands (MEC-2005-273 and MEC-2017-1143). This national referral center sees all patients with craniosynostosis syndromes in a total pediatric population of 3.8 million.[17] This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research.

Patients aged between birth and 18 years with sCS (i.e. Apert, Crouzon, Muenke, and Saethre-Chotzen syndrome) were recruited into the study when magnetic resonance imaging (MRI) was required for clinical care, according to our local management protocol.[18] We refer to Crouzon and Pfeiffer patients as Crouzon patients, because we consider Crouzon and Pfeiffer syndrome to be a homogenous group of varying severity, that can be considered as phenotypic variations of the same genetic defect. If patients underwent neurological assessment and brain imaging multiple times during the follow-up phase of this study, we used these longitudinal assessments to determine age at which TH ≥ 5 mm and/or syringomyelia occurred, and if enlarged ventricles were part of stable ventriculomegaly or progressive ventriculomegaly. For further statistical analysis, only the most recent neurological assessment and brain imaging (i.e., closest to the end of the study) was used.

Magnetic resonance imaging

In accordance with our protocol, in all sCS cases, the timing of initial MRI was at referral (usually when aged < 1 year), and at 4 years of age to determine risk factors for ICH. In addition, in Crouzon patients, a further MRI was carried out when aged 2 years because of the high prevalence of TH ≥ 5 mm and ICH.

All MRI data were acquired using a 1.5 T MR Unit (General Electric Healthcare, Milwaukee, WI, USA), and the imaging protocol included a 3-dimensional spoiled gradient T1-weighted MR sequence. Imaging parameters included: slice thickness 2 mm, no slice gap, field of view 22.4 cm, matrix size 224 _ 224, in plane resolution 1 mm, echo time 3.1 ms and repetition time 9.9 ms.

Images were aligned in sagittal and coronal planes and the dimensions of any TH were assessed in the mid-sagittal and adjacent slices, and presence of syringomyelia was determined in all MRI scans by pediatric radiologist or neurosurgeon. We defined two groups: Normal as no TH or TH < 5 mm below the foramen magnum and no syringomyelia; and Abnormal as TH ≥ 5mm below the foramen magnum and/or presence of syringomyelia.

Neurological assessment

Neurological assessments, each performed at the time of clinic review by a pediatric neurologist, neurosurgeon or craniofacial nurse specialist, included the following. First, a review of the history: any complaints of dysphagia; and any evidence of motor delay, as described by parents' impressions of delay in fine and gross motor skills, or gait problems. Second, a focused physical examination with: assessment of eye movements; cranial nerve testing; check for any abnormality in motor function, muscle tone and strength (symmetry), sensory function, cerebellar function, deep tendon reflexes. These parts of the neurological examination were categorized as: A) cerebellar function, which contained motor delay and coordination; B) cranial nerve function, which contained nystagmus, pharyngeal asymmetry and dysphagia; and C) sensory motor function, which contained pyramidal syndrome, sensory dysfunction and motor dysfunction.

Statistical methods

Statistical analyses were carried out using IBM SPSS Statistics 25 (IBM Corp., Armonk, N.Y.). The relationship between neurological deficit categories and cerebellar position was tested statistically using a Chi-Square test or Fisher's exact test (when there were less than 5 subjects in a cell). A Bonferroni adjustment of the P value was performed for multiple comparisons with significance set at $P < .01$. Bayesian methods then determined the pretest and posttest probabilities for all neurological deficit categories and presence of TH ≥ 5 mm and/or syringomyelia. Finally, we examined how presence of TH ≥ 5 mm and/or syringomyelia was distributed amongst neurological deficits and the different syndromes. The distribution of patients who required surgery because of their neurological problems was examined in a similar fashion.

Results

Sixty-three patients underwent neurological assessment and brain imaging (**Table 1**). We had to exclude 4 Apert patients from our original series of 67 cases, because attention deficits interfered with neurological assessment. The median interval between MRI and neurological assessment was 0.3 (interquartile range [IQR] 0.2–1.2) years. During follow-up, 23 patients underwent craniofacial surgery: in 17 patients the surgeries were part of our clinical protocol; and, in another 3 patients, surgery was carried out because of the presence of ICH. In the remaining 3 patients undergoing surgery – all of whom were Crouzon patients – one had TH ≥ 5 mm and syringomyelia, one had TH ≥ 5 mm alone, and one had syringomyelia alone (with basilar invagination). One of these 3 patients needed surgical intervention at 12.8 years old, the other 2 patients both needed surgical intervention at 17.4 years old. For these three patients the reasons for surgical intervention concerned severe pyramidal syndrome and gait problems and progression of deterioration of these symptoms. In all 3 patients neurological deficits ameliorated after surgery.

During follow-up 9/63 patients had stable ventriculomegaly, and a further 7/63 patients had a ventriculoperitoneal shunt. No patient had progressive ventriculomegaly.

Table 1
Patient demographics

	Total n = 63	Apert n = 12	Crouzon n = 34	Muenke n = 11	Saethre-Chotzen n = 6
Mean age (IQR)[a]	8.0 (4.8 – 12.3)	5.7 (4.0 – 10.4)	10.9 (7.2 – 14.7)	5.5 (4.2 – 11.9)	6.6 (3.0 – 8.3)
Gender M : F	30 : 33	6 : 6	14 : 20	7 : 4	3 : 3
Cerebellar position					
Normal	44 (70%)	10 (83%)	19 (56%)	9 (82%)	6 (100%)
TH ≥ 5 mm	19 (30%)	2 (17%)	15 (44%)	2 (18%)	0 (0%)
Syringomyelia					
Not present	58 (92%)	12 (100%)	29 (85%)	11 (100%)	6 (100%)
Present	5 (8%)	0 (0%)	5 (15%)	0 (0%)	0 (0%)
TH ≥ 5 mm and/or syringomyelia					
Not present	43 (68%)	10 (83%)	18 (53%)	9 (82%)	6 (100%)
Present	20 (32%)	2 (17%)	16 (47%)	2 (18%)	0 (0%)

Numbers represent absolute values (percentage within syndrome)
[a] Mean age (interquartile range) in years
TH: cerebellar tonsillar herniation

Chiari malformation type I and syringomyelia

By the end of the study, 44 sCS patients had normal cerebellar position and 19 had TH ≥ 5 mm. The median age at detection of TH ≥ 5 mm was 10.2 (IQR 6.9–12.6) years. **Table 1** shows patient demographics and how cerebellar tonsil positions and syringomyelia were distributed amongst the different forms of sCS.

Five patients had syringomyelia at study conclusion; all Crouzon patients. Four out of 5 patients with syringomyelia also had TH ≥ 5 mm, only one patient did not. This patient had basilar

invagination. Overall, 43/63 patients had TH < 5 mm and no syringomyelia, and 20/63 patients had TH ≥ 5 mm and/or syringomyelia. Crouzon patients made up the majority of patients with TH ≥ 5 mm and/or syringomyelia, 16 out of 20 (80%), followed by Apert, 2 out of 20 (10%), and Muenke patients 2 out of 20 (10%).

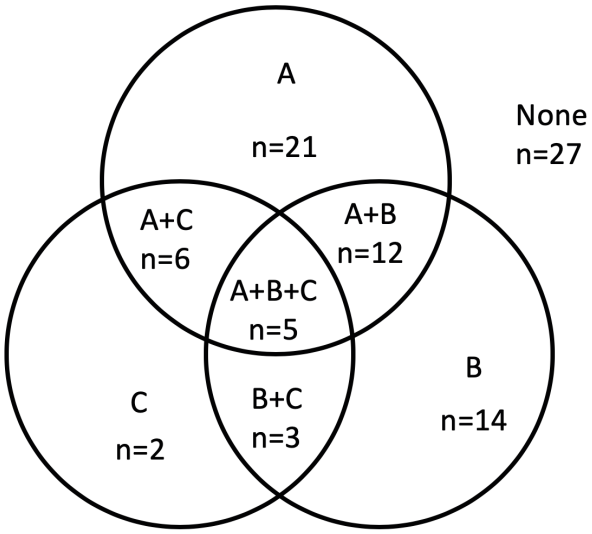

Figure 1. Venn diagram of combinations of neurological categories in sCS patients
A) cerebellar function: motor delay and coordination; B) cranial nerve function: nystagmus, pharyngeal asymmetry and dysphagia; and C) sensory motor function: pyramidal syndrome, sensory dysfunction and motor dysfunction

Neurological categories and syndromes

Neurological deficits were present in 73% of all patients. **Figure 1** shows the distribution of combinations of neurological categories in a Venn diagram. **Table 2** shows the distribution of neurological categories against presence of TH ≥ 5 mm and/or syringomyelia. Category A occurred most often (35/63 cases), followed by category B (26/63 cases), and category C (8/63 cases). There was no association between any combination of the neurological categories and the presence of TH ≥ 5 mm and/or syringomyelia. Overall, the pretest probability (or prevalence) of a sCS patient not having TH ≥ 5 mm and/or syringomyelia on follow-up was 68%. The absence of any neurological deficits (A, B or C) on follow-up does not contribute to any further certainty about whether there is no TH ≥ 5 mm and/or syringomyelia (i.e., the posttest probability is 71%).

Table 2
Distribution of neurological profiles amongst patients with TH ≥ 5 mm and/or SM, and patients with TH <5 mm and without SM

	TH ≥ 5 mm and/or SM[a]	TH < 5 mm or SM[b]	P-value	Posttest probability
A (any combination)	11 (55%)	24 (56%)	>0.99	0.18
B (any combination)	11 (55%)	15 (35%)	0.18	0.25
C (any combination)	5 (25%)	3 (7%)	0.10	0.14
None	4 (20%)	13 (30%)	0.55	0.13

TH: cerebellar tonsillar herniation, SM: syringomyelia
A) cerebellar function: motor delay and coordination; B) cranial nerve function: nystagmus, pharyngeal asymmetry and dysphagia; and C) sensory motor function: pyramidal syndrome, sensory dysfunction and motor dysfunction.
[a] Absolute number (percentage of population with TH ≥ 5 mm and/or syringomyelia n=20)
[b] Absolute number (percentage of population with TH < 5 and without syringomyelia n=43)

Figure 2 shows the distribution of neurological categories and combinations of the three categories amongst the syndromes. Neurological deficits occurred most in Apert patients (11/12), followed by Muenke patients (9/11), Saethre-Chotzen patients (4/6), and Crouzon patients (22/34).

Table 3 shows the distribution of neurological abnormalities by syndrome and presence of TH ≥ 5 mm and/or syringomyelia. There was no significant difference in the proportion between individual forms of sCS: 16/34 Crouzon, 2/11 Muenke; 2/12 Apert, and 0/7 Saethre-Chotzen patients.

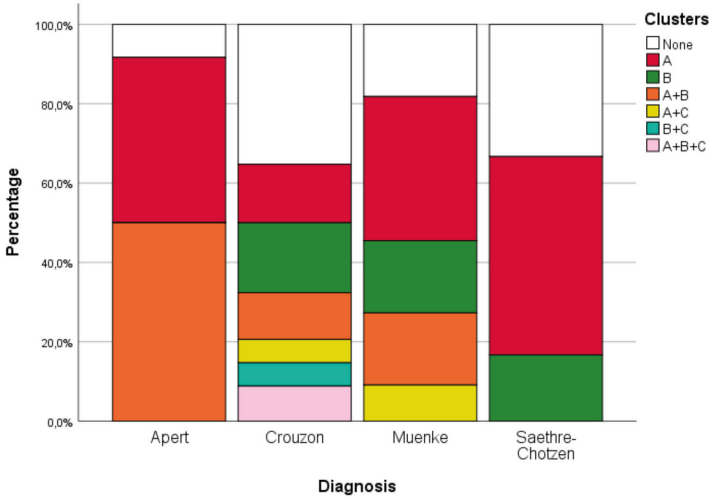

Figure 2. Distribution of combinations of neurological categories in craniosynostosis syndromes. A) cerebellar function: motor delay and coordination; B) cranial nerve function: nystagmus, pharyngeal asymmetry and dysphagia; and C) sensory motor function: pyramidal syndrome, sensory dysfunction and motor dysfunction.

Discussion

In this 66-month national referral cohort of sCS patients in the Netherlands we have focused on neurological symptoms and signs that may be related to the presence of TH ≥ 5 mm and/or syringomyelia. First, by considering any symptoms or signs in the three categories potentially related to this problem (i.e., cerebellar function, cranial nerves and dysphagia, and sensory motor dysfunction) we found, overall, that prevalence was high at 73%. Second, we found that the absence of these symptoms or signs did not provide any certainty in regard to absence of TH ≥ 5 mm and/or syringomyelia. Last, we found that only 3 patients underwent surgery for concerns about TH ≥ 5 mm and/or syringomyelia – all of whom were Crouzon patients.

Neurological symptoms and signs are highly prevalent in sCS patients. Especially category A (motor delay and coordination problems) and category B (nystagmus, pharyngeal asymmetry and dysphagia) occur very often (see **Table 2**). It occurred more often than in the general pediatric population of the Netherlands, where the prevalence of coordination problems it considered to be 2–19%.[19] A study by Cinalli et al.[7] reported neurological signs related to CMI to be present in 6/44 Crouzon patients and 0/51 Apert patients. The lower prevalence of neurological symptoms in sCS patients in their retrospective study, could be because they performed neurological examinations when CMI was present on brain imaging, not prospectively. Our results might therefore be more representative of neurological signs and symptoms in sCS patients.

Table 3
Distribution of neurological problems in different sCS patients with TH ≥ 5 mm and/or SM

	Total	Apert		Crouzon			Muenke		Saethre-Chotzen	
	n=63	n=12	TH ≥ 5 mm and/or SM (n=2)[a]	n=34	TH ≥ 5 mm and/or SM (n=16)[a]	Surgery (n=3)[b]	n=11	TH ≥ 5 mm and/or SM (n=2)	n=6	TH ≥ 5 mm and/or SM (n=0)[a]
None	17	1	0	12	4	0	2	0	2	0
A alone	17	5	0	5	2	0	4	1	3	0
B alone	9	0	0	6	2	0	2	1	1	0
C alone	0	0	0	0	0	0	0	0	0	0
A + B	12	6	2	4	3	1	2	0	0	0
A + C	3	0	0	2	2	2	1	0	0	0
B + C	2	0	0	2	2	0	0	0	0	0
A + B + C	3	0	0	3	1	0	0	0	0	0

TH: cerebellar tonsillar herniation, SM: syringomyelia
A) cerebellar function: motor delay and coordination; B) cranial nerve function: nystagmus, pharyngeal asymmetry and dysphagia; and C) sensory motor function: pyramidal syndrome, sensory dysfunction and motor dysfunction
Numbers represent absolute numbers
[a] Absolute number (percentage of population with TH ≥ 5 mm and/or syringomyelia n=20)
[b] Absolute number (percentage of population that needed surgery due to neurological problems n=3)

Remarkably, the absence of symptoms and signs that may suggest TH ≥ 5 mm and/or syringomyelia occurred, did not help in excluding TH ≥ 5 mm and/or syringomyelia. Rather, we now think that their presence most likely reflects some intrinsic brain disorder of development associated with sCS. Developmental studies have shown that the risk for intellectual disability is

higher in sCS in general, and for Apert and Muenke syndrome in particular, while Muenke patients rarely have ICH. Similarly indicating that their intellectual and behavioral disorders are more likely part of intrinsic brain development associated with sCS than the result of other causes such as ICH.[20]

Overall, in our cohort of 63 cases follow-up over a period of 66-months, we found that only 3 patients underwent surgery for concerns about TH ≥ 5 mm and/or syringomyelia – all of whom were Crouzon cases. Whilst our series cannot be used to conclude that the need for TH/syringomyelia-indicated surgery is a problem only seen in Crouzon cases (3/34 Crouzon cases vs 0/29 other sCS cases is not significantly different), it is our experience that Crouzon cases were qualitatively different in their symptomatology. For example, in this series as a whole, we did see some patients with mild problems in gait, motor function or pyramidal signs that either resolved on their own, or remained very mild. However, in the 3 Crouzon cases that underwent surgery, the decision to operate was taken when the nature of problems in gait, motor function or pyramidal signs was severe, or when there was deterioration from mild to severe signs. While Crouzon patients in this cohort also had the largest proportion of patients without any neurological symptoms or signs. This is in line with the literature, which shows the phenotypic diversity within Crouzon patients, ranges from normal or above average, to well below average in different fields of functioning: intellectual, behavioral, educational, as well as diversity in clinical course, ranging from very mild to severe, with an overall 60% incidence of ICH.[20-22]

To our knowledge this is the first study that distinguishes the different neurological deficits per craniosynostosis syndrome. It is important to show these differences and to determine if they relate to specific features of the syndrome or to intracerebral abnormalities. Apert patients for example often experience neurological problems. This finding is in line with the high prevalence of mental disability and high prevalence of structural brain malformations that are often present in patients with Apert syndrome such as abnormalities in midline development, malformations in cortical development, and a generalized reduction of white matter.[7,20,23,24]

No Saethre-Chotzen patients in this study had TH ≥ 5 mm or syringomyelia, and they showed markedly fewer neurological deficits than patients with other syndromes. The number of Saethre-Chotzen patients was only 7 and does not allow us to draw strong conclusions from this. However, these results are in line with other studies showing Saethre-Chotzen patients to have mild behavioral problems, normal IQ and close to normal white matter integrity.[6,20] This adds to the theory that TWIST1 changes might have less effect on the central nervous system compared to the FGFR2 mutations.

This study has some limitations, other than the small numbers in our 66-month convenience sample. For example, sCS patients may suffer from mental disabilities,[20] making some of the neurological tests hard to perform. In addition, assessment of psychological and physical complaints – particularly joint problems in those with Apert syndrome – may be difficult to ascertain. The lack of problems in category C (sensory motor dysfunction, which contained pyramidal syndrome, sensory dysfunction and motor dysfunction) may be due to ascertainment failure because of difficulty in separating physical complaints because of joint problems, from neurological problems due to motor dysfunction.

Taking all of the above together, two key issues arise in regard to the clinical review of symptoms/signs suggestive of TH, the utility of identifying TH ≥ 5 mm on MRI, and surgical decision-making, and treatment protocol for Crouzon patients.

First issue is the utility in following clinical monitoring of neurological signs and symptoms – this study has shown that it is important to determine clinical deterioration. Neurological symptoms and signs are present in patients with and without TH ≥ 5mm and/or syringomyelia, which questions the need to clinically monitor with brain imaging or operate on every sCS patient with TH ≥ 5 mm – as has been suggested in other studies.[5] We advise to let the decision to operate depend on the severity of neurological symptoms and signs especially in gait, motor function or pyramidal signs, and their progression over time. Our clinical protocol includes MRI assessments at presentation and at 4 years old (and an additional MRI assessment for Crouzon patients at 2 years), with the main goal to determine risk factors for ICH.[18,25] Additional MR imaging outside these assessments should be done on indication of neurological symptoms/signs, in particular changes in severity of gait, motor function or pyramidal signs. We recommend regular yearly neurological assessments at least until adulthood. We find this especially important because in this study 2 of the 3 operated patients showed change in symptoms and signs during adolescence and required surgery at 17.4 years old.

Second issue regards patients with Crouzon syndrome. While Crouzon patients in general have a mild neuropsychological profile,[20] and in this cohort had the largest proportion without neurological deficits, patients who required surgery because of their neurological symptoms were all Crouzon patients. From the results of this study, we cannot conclude that Crouzon patients might be more susceptible to deterioration of neurological symptoms and signs as a consequence of TH ≥ 5 mm and/or syringomyelia, because this only occurred in 3 cases. However, our experience with the symptomatology of neurological deficits of Crouzon patients during this study, along with their propensity to develop ICH, has led us to change our protocol. After their MRI examinations at intake and at ages 2 and 4, Crouzon patients now undergo MRI examinations at 3-year intervals.

Conclusion

Neurological symptoms and signs including cerebellar dysfunction, cranial nerve abnormality and dysphagia, and motor dysfunction are highly prevalent in children with sCS. This study shows that the absence/presence of these symptoms/signs provides no diagnostic certainty in ruling-in or ruling-out normal cerebellar tonsillar position, or TH ≥ 5 mm and/or syringomyelia. From this information we conclude that such symptoms/signs may result from sCS-related abnormality in central nervous system development.

In practice, we now recommended follow-up should last at least until adulthood; and should include yearly neurological assessments; MRI assessments only when indicated by deterioration of neurological symptoms/signs like coordination problems, motor delay and pyramidal

syndrome; regular MRI assessments for Crouzon patients; and thorough instructions of alarm signs to parents and caretakers.

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CHAPTER 7

WHAT WE KNOW ABOUT INTRACRANIAL HYPERTENSION IN CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS

Priya N. Doerga, Robbin de Goederen, Robert C. Tasker, Marie-Lise C. van Veelen, Koen F.M. Joosten, Irene M.J. Mathijssen

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Abstract

OBJECTIVE: A scoping review of literature about mechanisms leading to intracranial hypertension (ICH) in syndromic craniosynostosis (sCS) patients, followed by a narrative synopsis of whether cognitive and behavioral outcome in sCS is more related to genetic origins, rather than the result of ICH.

METHODS: The scoping review comprised of a search of keywords in EMBASE, MEDLINE, Web of science, Cochrane central register of trials, and Google scholar databases. Abstracts were read and clinical articles were selected for full-text review and data extracted using a structured template. A priori, we planned to analyze mechanistic questions about ICH in sCS by focusing on two key aspects, including: 1) the criteria for determining ICH; and 2) the role of component factors in the Monro-Kellie hypothesis/doctrine leading to ICH, i.e., cerebral blood volume (CBV), cerebrospinal fluid (CSF), and the intracranial volume (ICV).

RESULTS: Of 1893 search results, 90 full-text articles met criteria for further analysis. 1) Invasive intracranial pressure measurements are the gold standard for determining ICH. Of noninvasive alternatives to determine ICH, ophthalmologic ones like fundoscopy and retinal thickness scans are most researched. 2) The narrative review shows how the findings relate to ICH using the Monro-Kellie doctrine.

CONCLUSIONS: Development of ICH is influenced by different aspects of sCS: deflection of skull growth, OSA, venous hypertension, obstruction of CSF flow, and possibly reduced CSF absorption. Problems in cognition and behavior are more likely due to genetic origin. Cortical thinning and problems in visual function are likely the result of ICH.

Introduction

To date, much clinical research has focused on the problem of intracranial hypertension (ICH) in children with syndromic craniosynostosis (sCS). The main reason for such interest is the high prevalence of ICH, which can compromise vision and/or brain development, while its detection is challenging.[1] Here, the Monro-Kellie hypothesis/doctrine i.e., the cranial vault as a closed box containing the sum of volumes of brain tissue, intracerebral blood, and cerebrospinal fluid (CSF), has informed the discussion. That is, if there is a conflict between growth in brain volume and skull restriction because of early craniosynostosis, then there must surely be some early consequence, either singularly or in combination, on CSF, cerebral blood volume (CBV), and intracranial pressure (ICP).[2-4] And, it follows, that identification of ICH should be used to decide on timing of surgery. However, many of the studies of ICH in sCS use indirect measurement of ICP, since invasive assessments require surgery and hospital admission, and are thus not suitable as a screening tool. The reliability of alternative methods, and especially fundoscopy, has been questioned in the literature.[2]

The primary aim of this report is to provide a scoping review of literature addressing mechanisms leading to ICH in sCS. *A priori,* we planned to analyze mechanistic questions about ICH by focusing on two key aspects, including: 1) the criteria for ICH in sCS; and 2) the role of component factors in the Monro-Kellie hypothesis/doctrine leading to ICH, i.e., CBV, CSF, and intracranial volume (ICV) (**Figure 1**). Secondarily, we looked at the impact that ICH has, relating to neurocognitive development in sCS and the interaction with underlying genetic origins and ICH, in a narrative synopsis addressing the problem of cause versus consequence (i.e., determined by genetics versus resulting from ICH).

Methods

Literature search

No registered review protocol was used in this study. This report follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was carried out by a professional librarian using search terms related to ICH in sCS patients as well as search terms for conditions/problems often present in sCS patients that are considered to contribute to ICH (see supplemental file 1). All of the terms used centered on obstructive sleep apnea (OSA), hydrocephalus, Chiari malformation type I (CMI), and impaired skull growth. The final list of articles came from the following databases: EMBASE (1971 to March 2022), MEDLINE (Ovid) (1946 to March 2022), Web of science (1946 to March 2022), Cochrane central register of trials (1992 to March 2022), and Google scholar. Reference lists of relevant publications and literature reviews were searched and used to find additional sources.

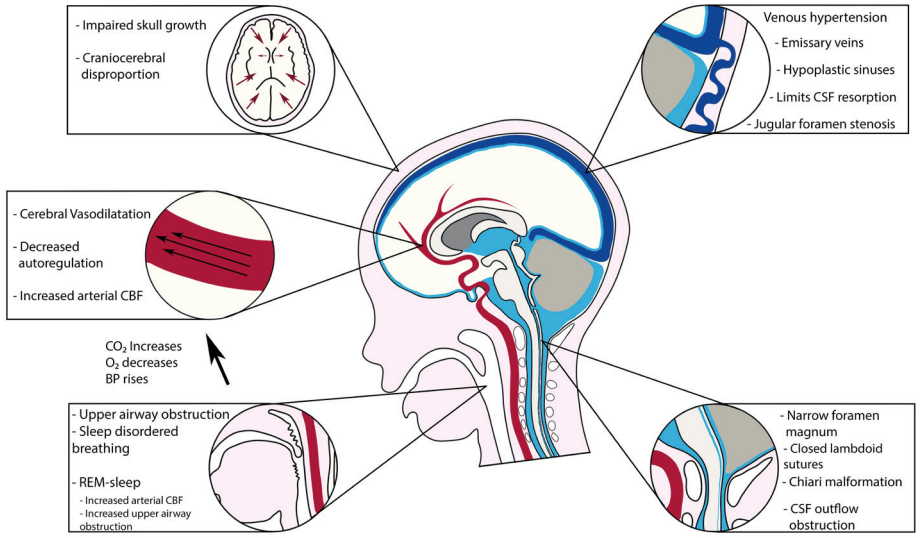

Figure 1. Pathophysiological processes concerning intracranial hypertension in children with syndromic craniosynostosis

We included any report that had at least 10 sCS patients in the study. Our exclusion criteria were: studies that involved only non-syndromic craniosynostosis, reports focusing solely on surgical results in regards to morphometrics or OSA without relation to ICH, OSA without detailed methodology, opinion pieces, and literature reviews. The final date of assessment was March 2022.

Abstract screening

The search yielded 1893 articles published between 1954 and March 2022, 7 articles were identified through references lists as additional sources. References to unique articles identified in the search were organized in EndNote X9. Two reviewers (P.D. and R.d.G.) screened the body of references on title and abstract. In cases of differences of opinion about inclusion based on title or abstract, a consensus was reached.

Literature summary

After screening full texts against eligibility criteria, we had 90 articles that were analyzed.[2-91] The PRISMA flow diagram depicted in **Figure 2**, shows the article selection in detail. *A priori,* we analyzed mechanistic questions about ICH in sCS by summarizing the data covering two key aspects, including: 1) the criteria for ICH; and 2) the role of component factors in the Monro-Kellie hypothesis/doctrine leading to ICH, i.e., CBV, CSF, and ICV. We assessed data on each genetic condition, separately. However, in the case of Crouzon and Pfeiffer syndrome we combined the data since these conditions are phenotypic variants of the same genetic defect. Hence, in studies that presented Crouzon and Pfeiffer syndrome data separately, we have combined and recalculated the results as a single group using the label Crouzon syndrome. For studies that include sCS patients and non-syndromic patients, but only report a prevalence of

ICH for the whole group, the prevalence for the subgroup of sCS patients was assumed to be the same as for the whole group.

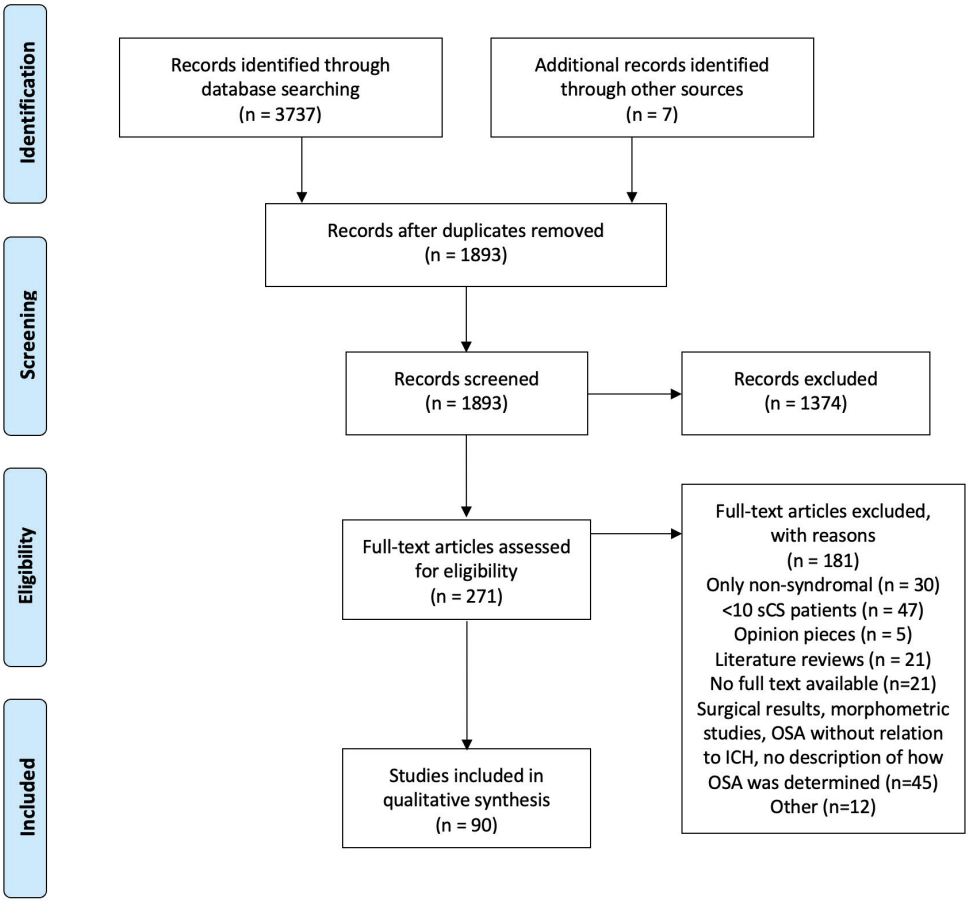

Figure 2. PRISMA flow diagram

Results – Section 1

1. Review of invasive ICP measurements in sCS

What methods are used to assess ICP?

Twenty-eight of the 90 studies used invasive ICP measurements or lumbar puncture (LP) in 1287 sCS patients (see **Table 1**),[2-23,77,84-87,89] 62 studies did not use invasive ICP or LP measurements (see **Table 2**). Terms and definitions used to for methods to determine can be seen in **Table 3**.

Of the 28 studies, 17 studies relied on invasive ICP measurements or LP alone to assess ICH.[2-6,8,17,19-21,23,77,84-87,92] A further 11 studies also used indirect methods of ICH assessment in addition to the invasive ICP or LP measurement.[7,9-16,18,22] Twenty-five studies used ICP,[2-5,8,17,20,21,23,77,84-87,89,93]

one study used LP,[17] and two used ICP and LP[15,22] to determine ICH. Of the 25 studies using ICP, 21 report both the duration and cut-off value.[2-6,8-14,20,21,23,77,84-87,89] Of the remaining 4, 1 reports duration but does not report cut-off value,[7] and 3 report neither duration nor cut-off values used to determine ICH.[16,18,19] In the 3 LP measurement studies, 1 reported duration and cut-off value,[17] 1 used the CSF opening pressure for LP measurement, reports cut-off value but not duration of ICP measurement,[15] and the last did not report duration or cut-off values for ICP and LP measurement.[22] In total, 571/1287 (44%) sCS were deemed to have ICH.

What duration of is used in ICP/LP measurement to determine ICH?

Twenty-two studies described the duration of ICP measurement used to determine the presence of ICH.[2-14,21,23,77,84-87,89,94] Ten studies used 24-hours of data,[7-14,23,87] 6 used overnight measurements,[2-6,84] and 4 used 1 minute of ICP measurements during anesthesia providing the ICP waveform was stable.[20,21,85,86] Two studies used another duration: 1 while under anesthesia for the length of surgical procedures,[77] and 1 for 48 hours.[89]

Of the three studies using LP measurements, one study reported the duration of 5-10 minutes of monitoring data during anesthesia,[17] the two other studies did not specify duration.[15,22]

What is the threshold value in ICP/LP measurement used to determine presence of ICH?

The threshold value in ICP measurement used to determine the presence of ICH was described in 22 studies. In 13 studies ICP of at least 15 mmHg was used as the sole defining criterion.[2,4-6,8,9,15,20,21,77,84-86] One study used threshold value of 20 mmHg to determine ICH.[89] In the 8 other studies a stricter definition of ICH was used: >15 mmHg as well as presence of ≥ 3 ICP B-waves in 24 hours,[23,87] or plateau waves rising ≥ 35 mmHg and lasting ≥ 20 minutes.[10-14] One study also applied age-related cut-off values, i.e., >2mmHg for neonates, >13 mmHg for children 1-7 years, and >15 mmHg for children ≥ 7 years old.[3]

In regard to the use of LP for determining ICH, 2 studies used ≥ 20 cmH_2O (i.e. ≥14.7 mmHg),[15,17] and one did not specify.[22]

Eight studies also used the term 'borderline abnormal' in instances when the ICP was 10-15 mmHg.[2,4,8,11-14,84] These reports refer to studies, reviews and book chapters[95-98] that also categorized ICP measurements in this way, but without supporting evidence. Two studies used the threshold value of 15 mmHg to determine ICH, but also report attributes associated with ICP ≥ 20 mmHg.[85,86] In the sCS studies, we identified one[20] that describes increased retinal thickness and anterior retinal projection in patients with ICP 10-15 mmHg (although borderline abnormal was not used as a category in that case series).

Indication for ICH detection

Of the 28 studies 18 screened for ICH as part of routine or prospective study,[2,3,5,6,8-15,17,20,21,85,86,89] 2 screened for ICH when there was a clinical indication for ICH,[4,84] and 8 do not report the indication for screening for ICH .[7,16,18,19,22,23,77,87] The 18 studies that screened for ICH as routine, or prospective study indicate a pre-test probability for ICH in sCS of 294/713 (41%).

To summarize, in our literature search we found:

a) Only 28/90 (31%) of the studies used the 'gold standard' invasive ICP/LP measurements in the determination of ICH.
b) Of these 28 studies, details of ICP/LP measurement in 23 studies demonstrate large variation in duration of data acquisition used for assessment (from 1 minute while under anesthesia, to 48 hours). Details in 22/28 studies also indicate a range in definitions of ICH: solely achieving a threshold pressure value (whether age-related or not) versus a more complex diagnosis combining the pressure value with some characteristic in slow-waveform features over many minutes. Last, 8/28 studies also included a diagnostic category of 'borderline abnormal'.
c) Accepting limitations that are inherent to all of the above (i.e., diagnosis and criteria), the prevalence of ICH in sCS using a 'gold standard' assessment (ICP/LP measurements) was 571/1287 (44%).
d) In 18/28 studies screening for ICH was part of routine, prospective study or when there were no signs of ICH. These studies show a pre-test probability of 41%, indicating the necessity for routine screening.

Usage of invasive ICP/LP measurements along with non-invasive ICH detection methods

We found that 11/28 studies used non-invasive methods along with invasive ICP/LP measurements to determine ICH.[7,9-16,18,22] Ten studies used fundoscopy,[7,10-16,18,22] 4 studies used OCT,[11-14] 1 study used VEP,[9] 1 study used (slowing of) skull growth curve and bulging of anterior fontanelle,[13] and 1 study used fontanometric pressure and evidence of severe ICH during operation (signs not specified).[18]

Of the 11 studies that used non-invasive ICH detection methods alongside invasive ICP/LP measurements, 6 report in how many patients ICH was detected through invasive ICP/LP measurements.[7,10,13-16] These studies found ICH in 120/480 CS and sCS patients, in 39/120 this was determined by invasive ICP/LP measurement.

Comparing invasive ICP/LP measurements to non-invasive ICH detection methods

Nine studies compared invasive ICP/LP measurements to non-invasive ICH detection methods and allowed for determination of sensitivity and specificity.[2,5,11,15,16,20,21,85,89] These studies compared invasive ICP/LP measurements to papilledema,[2,20,21,89] to various different radiological signs,[5,20,85] to slowing of the head growth curve,[11] to OCT,[20,85] to clinical signs,[20,85] to the optic nerve sheath diameter (ONSD),[15] and to pattern visually-evoked potentials (pVEP).[16,89] The results of the sensitivity and specificity of these non-invasive detection methods for ICH and in how many patients they were tested, can be seen in **Table 1**.

Table 1
Summary of the 28 studies that used invasive ICP/LP measurements

Author	Syndromes (n)/Age/ Surgical status	Study design* (recruit-ment period)	ICH detection method(s)/ Indication for ICH detection	ICP/LP measurement duration and cut-off values	Comparison to non-invasive method	Sensitivity/ Specificity		sCS patients with ICH/ Total sCS patients (%)
						Sens.	Spec.	
Great Ormond Street Hospital for Children, London								
Fok et al. (1992)[3]	Apert (n=5) Crouzon (n=7) Saethre-Chotzen (n=2) Non-syndromic (n=27) • Mean age: 2.3 (0.1 – 10.2) years • Surgical status not reported	*Retro-spective review* (recruitment period not reported)	• ICP measurement • Routine screening for ICH as part of craniofacial assessment	*Duration:* At least 12 hours overnight *Cut-off:* Mean pressure calculated as average of the waveform values one third up the waveform. • Neonates: >2 mmHg • Children 1-7 years: >13 mmHg • Children ≥ 7 years: >15 mmHg	ICV	8%	Not reported	14/14 (100%)
Thompson et al. (1995)[4]	Apert (n=13) Crouzon (n=25) Saethre-Chotzen (n=14) Non-syndromal (n=84) • Mean age: not reported (range 0.1 – 14 years) • Pre-surgical	*Retro-spective chart review* (recruitment period not reported)	• ICP measurement • Clinical concern for ICH • When parents reluctant to have surgery done	*Duration:* Overnight subdural ICP measurement recorded 6-minute intervals to calculate mean. *Cut-off:* • normal: <10 mmHg • borderline 10-15 mmHg • raised >15 mmHg	-	-		27/52 (52%)
Tuite et al. (1996)[2]	Apert (n=10) Crouzon (n=23) Saethre-Chotzen (n=22) Non-syndromic (n=67) • Mean age: 2.4 (0.2 – 15) years	*Retro-spective chart review* (Recruit-ment period not reported)	• ICP measurement • Patients undergoing first craniofacial assessment	*Duration:* Overnight ICP, minimum duration of at least 3 hours, *Cut-off:* Mean ICP was calculated from 6 min intervals • Normal <10 mmHg • Borderline abnormal 10-15 mmHg	Fundoscopy	32%	98%	19/55 (35%)†

	• Pre-surgical			• Abnormal ≥15 mmHg				
Tuite et al. (1996)[5]	**Apert (n=8)** **Crouzon (n=19)** **Saethre-Chotzen (n=22)** Non-Syndromic (n=74) • Mean age: 1.9 (0.3 – 11.3) years • Pre-surgical	*Retro-spective chart review* (Recruit-ment period not reported)	• ICP measurement • Patients undergoing first craniofacial assessment	*Duration:* Overnight sleeping ICP measurement *Cut-off*: Mean ICP was calculated from 6 min intervals. • Abnormal > 15 mmHg	Copper beating Ventricular dilation Sellar erosion Suture diastasis Obliterated anterior sulci Narrowed basal cisterns	27% 40% 10% 24% 34% 29%	81% 80% 90% 92% 94% 94%	15/49 (31%)†
Gonsalez et al. (1997)[6]	Apert (n=5) Crouzon (n=7) Saethre-Chotzen (n=1) Unicoronal (n=7) • Median age: 0.8 (0.3 – 12) years • Pre-surgical	*Retro-spective analysis* (1992-1994)	• ICP measurement • Patients undergoing first craniofacial assessment	*Duration:* Sleeping ICP measurement *Cut-off*: Mean ICP levels were calculated for quiet sleep and active sleep • Abnormal: >15 mmHg	-	-		10/13 (77%)
Rich et al. (2003)[7]	Apert (n=8) Crouzon (n=8) Saethre-Chotzen (n=2) Non-syndromic (n=13) • Median age: 0.8 (0.3 – 14) years • Surgical status not reported	Retro-spective analysis (Recruit-ment period not reported)	• ICP measurement • Fundoscopy • 12 sCS patients who had ICH as determined by ICP measurement and papilledema were examined and compared to 9 sCS patients without ICH as determined by ICP measurement • Indication for ICP measurement not specified	*Duration:* 24 hours *Cut-off*: Not specified	JF diameter	-		11/18 (61%)

Hayward et al. (2005){Hayward, 2005 #135}	Apert (n=2) Crouzon (n=7) Antley-Bixler (n=1) Non-syndromic (n=1) • Mean age 2.2 (0.5 – 6.8) years • Pre-surgical and post-surgical	*Prospect-ive study* (Recruit-ment period not reported)	• ICP measurement • sCS children about to undergo vault expansion, without signs of ICH, without hydrocephalus	*Duration:* 24 hours, sleeping ICP measurements were used. *Cut-off:* • Normal <10 mmHg • Borderline 10-15 mmHg • Abnormal >15 mmHg	-		-	10/10 (100%)
Marucci et al. (2008)[9]	Apert (N=24) • Mean age at presentation: 0.1 (range 0-0.5) years • Pre-surgical	Retro-spective chart review (1992-2000)	• ICP measurement • Fundoscopy • Visual evoked potentials • Routine screening for ICH	*Duration:* 24 hours *Cut-off:* • Mean ICP > 15 mmHg is elevated	-		-	20/24 (83%)
Rufai et al. (2022)[89]	Apert(n=5) Crouzon(n=12) Muenke (n=1) Other (n=19) • Median age at first presentation: 3.8 (1.5-21.1) months	Retro-spective review (2002-2019)	• ICP measurement • Routine screening for ICH	*Duration:* 48 hours *Cut-off:* ≥ 20 mmHg	Papilledema VEP isolated VEP longitudinal ≥1 VEP longitudinal ≥2	32% 58% 47% 71%	100% 83% 100% 60%	14/18 (80%)†
Erasmus MC, University Medical Center, Rotterdam								
De Jong et al. (2010)[10]	Apert (n=36) Crouzon (n=55) Muenke (n=38) Saethre-Chotzen (n=38) • Mean age at presentation: 1.2 • Pre-surgical and post-surgical	Retro-spective chart review (1983-2008)	• ICP measurement • Fundoscopy • Routine screening for ICH using papilledema • ICP measurement: only in severe OSA, headache, or persistent papilledema after surgery (n=13)	*Duration:* 24 hours *Cut-off:* • Baseline >15 mmHg • > 3 plateau waves of ≥ 35mmHg, lasting more than 5 minutes.	-		-	55/167 (33%)
Spruijt et al. (2015)[11]	Apert (n=10)	Prospecti ve observati	• ICP measurement • Fundoscopy	Erasmus MC standard:	Slowing head growth	92%	85%	12/36 (33%)†

	Crouzon (n=11) Muenke (n=9) Saethre-Chotzen (n=6) Non-syndromic (n=26) • Mean age at presentation: 0.6 years • Pre-surgical and post-surgical	onal cohort (2007-2012)	• OCT (TRT: cut-off value not specified) • Routine screening for ICH	*Duration:* 24-hours *Cut-off:* Baseline ICP • Normal: <10 mmHg • Borderline abnormal 10-15 mmHg • Abnormal ≥15 mmHg Overnight values: Number of abnormal plateau waves judged for **1)height** • Normal: <25 mmHg • Borderline abnormal 25-35 mmHg • Abnormal ≥35 mmHg, and **2)duration** • Normal <10 min • Borderline 10-20 min • Abnormal ≥20 min	OSA	71%	42% -	
de Goedere n et al. (2019)[12]	Apert (n=20) Crouzon (n=31) Muenke (n=9) Saethre-Chotzen (n=10) Non-syndromic (n=13) • Median age at first PSG 3.1 (IQR 0.58 – 8.89) • Pre-surgical and post-surgical	Prospecti ve observati onal cohort (Recruit-ment period not reported)	• ICP measurement • Fundoscopy • OCT (TRT > 503 µm) • Routine screening for ICH	Erasmus MC standard	-	-	25/83 (30%)†
Den Otteland er et al. (2019)[13]	Muenke (N=38) • Median age at first surgery: 8.5 (2.3 –	Prospecti ve observati onal cohort	• ICP measurement • Fundoscopy • OCT (TRT < 276 µm and TRT > 503 µm) • Slowing of skull growth	Erasmus MC standard	-	-	3/28 (11%)

	18.3) months • Pre-surgical and post-surgical	(1990-2016)	• Bulging of anterior fontanelle • Routine screening for ICH					
De Goedere n et al. (2020)[14]	Apert (n=21) Crouzon (n=38) Muenke (n=11) Saethre-Chotzen (n=11) Non-syndromic (n=18) • Mean age: 3.5 years (IQR 0.63 – 5.5) • Pre-surgical and post-surgical	Prospecti ve observati onal cohort (2008-2018)	• ICP measurement • Fundoscopy • OCT (TRT, no cut-off point specified) • Routine screening for ICH	Erasmus MC standard	-		-	25/81 (31%)
University of Pittsburgh Medical Center, Pittsburgh, Sohag University Hospital, Sohag								
Haredy et al. (2018)[15]	sCS (n=31) Non-syndromic (n=25) Controls (n=49) • Mean age: 3.7 (SD 3.6) years • Surgical status not reported	Retro-spective chart review (2010-2017)	• ICP measurement • LP measurement • Fundoscopy • Routine screening for ICH using papilledema • ICP done if papilledema inconsistent or if other signs of ICH were present without in absence of papilledema	*Duration:* Not specified *Cut-off:* ICP measurement abnormal: >15mmHg LP measurement abnormal: opening pressure >20 cmH_2O	ONSD (optimal threshold 6mm)	71%	90%	13/31 (42%)†
Haredy et al. (2019)[16]	sCS (n=22) Non-syndromic (n=41) • Pre-operative age: 16.9 (2 months – 10 years) • Surgical status not reported	Retro-spective chart review (2012-2017)	• ICP measurement • Fundoscopy • Indication for ICP measurement not specified	*Duration:* Not specified *Cut-off:* Not specified	pVEP	89%	54%	3/22 (14%)†
The Children's Hospital of Philadelphia and the University of Pennsylvania, Philadelphia								

Swanson et al. (2017)[20]	CS (n=25) sCS (n=15) Positive controls (n=5) Negative controls (n=34) • Mean age: 4.1 (SD 7) years • Pre-surgical and Post-surgical	Prospective cohort (2014-2015)	• ICP measurement under anesthesia • ICH detection as part of study protocol in all CS and sCS patients undergoing surgery	*Duration*: a stable waveform for 1 minute *Cut-off*: Abnormal ≥ 15 mmHg	OCT (maximal RNFL thickness > 208µm + maximal anterior retinal projection > 159µm) Papilledema Copper beating Ventricular dilation Clinical signs	89% 11% 42% 11% 33%	62% 78-100%	7/15 (47%)†
Kalmar et al. (2021)[86]	sCS (n=19) Other (n=31) *Total (n=122);but only n=50 had ICP measured* • Median age 9.3 months (95%CI 8.3-10.9)	Prospective study (2014-2020)	• ICP measurement under anesthesia • ICH detection as part of study protocol in all CS and sCS patients undergoing surgery	*Duration*: a stable waveform for 1 minute *Cut-off*: Abnormal ≥ 15 mmHg Also report on ICP ≥ 20 mmHg	-	-	-	15/19 (79%)
Kalmar et al. (2022)[85]	Apert (n=4) Crouzon (n=10) Muenke (n=6) Saethre-Chotzen (n=6) Other (n=132) • Median age 12.6 (IQR 7.7-41.1) months • Pre-surgical and post-surgical	Prospective study (2014-2019)	• ICP measurement under anesthesia • ICH detection as part of study protocol in all CS and sCS patients undergoing surgery	*Duration*: a stable waveform for 1 minute *Cut-off*: Abnormal ≥ 15 mmHg Also report on ICP ≥ 20 mmHg	OCT (maximal RNFL thickness > 208µm + maximal anterior retinal projection > 159µm) Optimal combination of OCT parameters Papilledema Fontanelle Bulge Thumbprinting Ventricular dilation	78% 77% 16% 0% 41% 5%	60% 95% 100% 95% 100% 100%	12/22 (55%)‡

					Headache	29%	95%	
					Developmental delay	27%	85%	
Oxford University Hospitals								
Kilcoyne et al. (2019)[23]	Saethre-Chotzen (N=30) • Mean age not reported Surgical status: not reported	Retrospective chart review (1995-2017)	• ICP measurement • Indication for ICP measurement not reported	*Duration:* 24-hours *Cut-off:* • Baseline average > 15 mmHg or > 3 B-waves	-	-	-	10/30 (33%)
Kilcoyne et al. (2021)[87]	Crouzon (n=12) • Age not reported	Retrospective case review (1995-2017)	• ICP measurement • Indication for ICP measurement not reported	*Duration:* 24-hours *Cut-off:* • Baseline average > 15 mmHg or > 3 B-waves	-	-	-	8/12 (67%)
Medical centers with one publication in this category								
Park et al. (2016)[17] Ajou University School of Medicine, Suwon, Korea	sCS (n=27) Multisuture (n=22) Non-syndromic Simple CS (n=213) • Mean age: 1.7 (SD 2.0) years • Pre-surgical	Retrospective analysis (2005-2014)	• LP measurement under general anesthesia • Routine LP measurement without indications for ICH or impaired CSF flow	*Duration:* 5-10 minutes *Cut-off*: Abnormal: > 20 cmH_2O	-	-		17/27 (63%)
Collmann et al. (1988)[18] University Hospital, Würzburg	Apert (n=13) Crouzon (n=32) Saethre-Chotzen (n=30) Non-syndromic (n=146) • Mean age not reported (range 0.2 -26) years • Surgical status not reported	Retrospective chart review (Recruitment period not reported)	• Epidural pressure • Fontanometric pressure • Fundoscopy • Evidence of severe ICH during operation (signs not specified) • Indication for ICP measurement not specified	*Duration:* Not specified *Cut-off:* Not specified	Ventricular dilation	-		42/75 (56%)†

Renier et al. (2000)[19] Hôpital Necker Enfants-Malades, Paris, France	Apert (n=88) Crouzon (n=128) Saethre-Chotzen (n=54) Other syndromes (n=58) Non-syndromic (n=1809) • Mean age not reported • Surgical status not reported	Retro-spective chart review (1976-1999)	• Not specified, ICP measurement is suggested • Indication for ICP measurement not specified	*Duration:* Not specified *Cut-off:* Not specified	-	-		142/270 (53%)
Judy et al. (2018)[21] Johns Hopkins Hospital, Baltimore	Apert (n=4) Crouzon (n=2) Muenke (n=1) Saethre-Chotzen (n=4) Non-syndromal (n=34) • Mean age: 2.5 (0.3-15.4) years • Pre-surgical and post-surgical	Prospective cohort (2014-2016)	• ICP measurement under anesthesia • ICH detection as part of study protocol in all CS and sCS patients undergoing surgery • Of CS and sCS patients 82% was undergoing first surgical procedure	*Duration:* a stable waveform for 1 minute *Cut-off*: Abnormal ≥ 15mmHg	Papilledema	17%	100%	8/11 (73%)†
Pellicer et al. (2018)[22] University of Washington, School of Medicine, Seattle Children's Hospital	Apert (n=10) Crouzon (n=32) Muenke (n=14) Saethre-Chotzen (n=11) Non-syndromic (n=316) • Mean age not reported • Pre-surgical and post-surgical	Retro-spective cohort (1995-2010)	• ICP measurement • LP measurement • Fundoscopy • Indication for ICP measurement not specified	*Duration:* Not specified *Cut-off:* Not specified	Headaches	42%	55%	11/67 (16%)

Bansal et al. (2022)[77] National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India	Apert (n=5) Crouzon (n=8) Saethre-Chotzen (n=1) Other (n=16) • Mean age not reported • Age range 5 months – 9 years • 50%<1 year • Surgical status not reported	Retro-spective observational study (2009-2020)	• ICP measurement under anesthesia • Indication for ICP measurement not reported	*Duration:* Length of surgery *Cut-off:* >15 mmHg	-	-	18/28 (64%)
Frič et al. (2021)[84] Oslo University Hospital–Rikshospitalet	Apert (n=5) Crouzon (n=9) Other (n=35) • Median age 4.4 (range 0.2-18.9) years • Pre-surgical and post-surgical	Retro-spective chart review (2002-2014)	• ICP measurement • ICP measurement done on indication	*Duration:* Overnight *Cut-off:* • Borderline: 10-15 mmHg Elevated: >15 mmHg	-	-	6/14 (44%)†
						Total	571/1287 (44%)

CS: craniosynostosis, sCS: syndromic craniosynostosis, ICH: intracranial hypertension, ICP: intracranial pressure, LP: lumbar puncture, sens.: sensitivity, spec.: specificity, ICV: intracranial volume, JF: jugular foramen, OSA: obstructive sleep apnea, OCT: optical coherence tomography, TRT: total retinal thickness, CSF: cerebrospinal fluid, RNFL: retinal nerve fiber layer, VEP: visual evoked potentials
* When the study itself does not mention the study design, the study design was inferred by context and displayed in *italics* in the table.
†Number of patients or percentage of patients with ICH only reported for the whole study population, including non-syndromic patients. The percentage for the whole population was assumed to be the same for the population of sCS patients in the study and was used to calculate number of sCS patients with ICH.
‡sCS patients who underwent ICP measurements

2. Review of non-invasive detection of ICH

Because of the inherent risks associated with invasive ICP measurements, many studies use noninvasive indirect means of detecting ICH. Having discussed the 28 of 90 studies that used invasive ICP/LP measurements, we will now discuss the 62 studies that did not.

Twenty-three of 62 studies used non-invasive methods to determine ICH. The remaining 39 did not screen for ICH. The details can be seen in **Table 2**.

The 23 studies used the following methods: 10 fundoscopy,[27,29,31,32,35,36,38,42,81,82] 1 OCT,[41] 1 clinical signs,[90] 1 intention-to-treat,[40] 8 studies used multiple methods;[25,26,28,30,33,34,39,80] and 2 did not specify a method.[24,37]

The 8 studies that used multiple methods to determine ICH, used the following: 8 used fundoscopy,[25,26,28,30,33,39,40] 6 used clinical signs,[25,26,28,30,39,40] 6 used ventricular dilation,[25,33,34,39,40,80] 4 used copper beating,[26,30,34,39] 3 used anterior fontanelle bulge,[25,26,40] 1 used neurological signs,[25] 1 used progressive macrocephaly,[25] 1 used slowing skull growth,[28] 1 used developmental delay,[30] 1 used optic disc changes, deterioration of electrophysiological tests of vision, obliteration of basal cisterns, or progressive TH,[40] 1 used shunted hydrocephalus and jugular stenosis with enlarged occipitomastoid veins.[34]

In total, using noninvasive detection methods 421/1130 (37%) sCS were deemed to have ICH.

Table 2
Summary of the 62 studies that did not use invasive ICP/LP measurements

Studies using indirect method for ICH detection				
Author/Institution	**Syndromes (n)/Age/Surgical Status**	**Study design (recruitment period)**	**ICH detection method**	**sCS patients with ICH/Total sCS patients (%)**
McCarthy et al. (1995)[99] New York University medical center	Apert (n=24) Crouzon (n=30) Non-syndromal (n=126) • Mean age at surgery: 0.5 • Post-surgical	Retrospective chart review (1973-1992)	Method not specified	8/54 (15%)
Siddiqi et al. (1995)[25] University of Toronto	Apert (n=33) Crouzon (n=59) Saethre-Chotzen (n=11) Kleeblatt shädel (n=4) • Mean age: not reported • Post-surgical	Retrospective chart review (1986-1992)	Fundoscopy, neurological exam, ventricular dilation, clinical signs, anterior fontanelle bulge, progressive macrocephaly	6/107 (6%)
Connolly et al. (2004)[26] Regional medical center Seattle	Apert (n=2) Crouzon (n=18) Saethre-Chotzen (n=6) Non-syndromic (n=1) • Mean age at presentation: 3.76 (range 0.17-13) years • Pre-surgical and post-surgical	Retrospective chart review (1991-2000)	Fundoscopy, clinical signs, anterior fontanelle bulge, copper beating	26/26 (100%)*
Bannink et al. (2008)[27] ErasmusMC University Medical Center, Rotterdam	Apert (n=33) Crouzon (n=51) • Mean age: 11.4 (range 0.4-23.5) years • Pre-surgical and post-surgical	Retrospective chart review (1983-2006)	Fundoscopy	43/84 (51%)

Woods et al. (2009)[28] The Oxford Craniofacial Unit	Saethre-Chotzen N=34 • Mean age: not reported • Pre-surgical and post-surgical	Retrospective chart review (1993-2008)	Fundoscopy, clinical signs, slowing skull growth	9/34 (26%)**
Bannink et al. (2010)[29] Erasmus MC, University Medical Center, Rotterdam	Apert (n=18) Crouzon (n=26) Muenke (n=17) Saethre-Chotzen (n=20) Non-syndromic (n=29) Controls (n=353) • Mean age 7 (range 2-18) years • Pre-surgical and post-surgical	Prospective cohort (2007-2008)	Fundoscopy	17/81 (21%)
Foo et al. (2010)[30] The Children's Hospital Philadelphia	Apert n=2 Crouzon n=5 Saethre-Chotzen n=2 4Q del. N=1 Non-syndromic n=7 • Mean age at presentation: 1.1 years • Pre-surgical and post-surgical	Retrospective chart review (2000-2009)	Fundoscopy, clinical signs, developmental delay, copper beating	10/10 (100%)*
Driessen et al. (2011)[31] ErasmusMC University Medical Center, Rotterdam	Apert (n=19) Crouzon (n=32) Muenke (n=20) Saethre-Chotzen (n=25) Non-syndromic (n=32) • Mean age 6.0 (±SD 5.0) years • Pre-surgical and post-surgical	Prospective cohort (2007-2009)	Fundoscopy, ONSD	17/96 (18%)†
Driessen et al. (2013)[32] ErasmusMC University Medical Center, Rotterdam	Apert (n=13) Crouzon (n=26) Muenke (n=10) Saethre-Chotzen (n=10) Non-syndromic (n=12) • Mean age at MRI: 9 (range 0-19) years • Pre-surgical and post-surgical	Prospective cohort (2009-2011)	Fundoscopy	16/59 (27%)†
Barik et al. (2014)[33] All India Institute of Medical Sciences, New Delhi	sCS n=15 Non-syndromic n=70 • Mean age: 1.3 (±SD 0.9) years • Pre-surgical and post-surgical	Prospective study (2007-2012)	Fundoscopy, ventricular dilation	8/15 (53%)†
Dagi et al. (2014)[34] Harvard Medical School, Boston	Apert (n=4) Crouzon (n=7) Saethre-Chotzen (n=7) Non-syndromic (n=36) • Mean age: 10.6 (range 2.4-33.8) years • Surgical status not reported	Retrospective chart review (2013)	OCT, copper beating, ventricular dilation, shunted hydrocephalus, JF stenosis with enlarged occipitomastoid veins	10/18 (56%)†
Driessen et al. (2014)[35] Erasmus MC, University Medical Center, Rotterdam	Crouzon n=15 Non-syndromic n=23 • Median age: 6.2 (range 3-11) years • Pre-surgical and post-surgical	Prospective cohort (2010-2012)	Fundoscopy	2/15 (13%)†
Florisson et al. (2015)[36] Erasmus MC, University Medical Center, Rotterdam	Apert (n=11) Crouzon (n=15) Muenke (n=7) Saethre-Chotzen (n=3) Non-syndromic (n=5) Controls (n=17) • Mean age: not reported for the whole group • Pre-surgical and post-surgical	Prospective cohort (2007-2013)	Fundoscopy	13/36 (36%)

Copeland et al. (2018)[37] The Hospital for Sick Children, University of Toronto	Apert (n=11) Crouzon (n=26) Muenke (n=1) Saethre-Chotzen (n=3) • Median age 2, mean age 5 (range 0.1-17) years • Pre-surgical and post-surgical	Retrospective chart review (2000-2013)	Not reported	15/41 (37%)
Doerga et al. (2019)[38] Erasmus MC, University Medical Center, Rotterdam	Apert (n=14) Crouzon (n=23) Muenke (n=8) Saethre-Chotzen (n=3) Non-syndromic (n=10) Controls (n=86) • Mean age: 4.5 (range 0.2-19.2) years • Pre-surgical and post-surgical	Prospective cohort (2012-2016)	Fundoscopy	6/48 (13%)†
Kim et al. (2019)[39] Sungkyunkwan University School of Medicine, Seoul	Crouzon (n=16) Saethre-Chotzen (n=1) • *Mean age at surgery: 2.2 years* • Pre-surgical and post-surgical	Retrospective chart review (2004-2014)	Fundoscopy, clinical signs, copper beating, ventricular dilation	14/17 (82%)
Mondal et al. (2019)[40] Great Ormond Street Hospital for Children, London	Apert (n=17) Crouzon (n=18) • Median age: 0.4 (range 0.0-4.9) years • Pre-operative	*Prospective cohort* (2014-2016)	Intention-to-treat	21/35 (60%)
Swanson et al. (2019)[41] The Children's Hospital of Philadelphia and the University of Pennsylvania	Apert (n=4) Crouzon (n=3) Muenke (n=2) Saethre Chotzen (n=2) Other syndrome (n=2) Non-syndromic (n=68) • Median age: 1.0 (range 0.2-18.0) years • Pre-surgical and post-surgical	Prospective cohort (2014-2015)	OCT	9/13 (69%)
Wilson et al. (2020)[42] Erasmus MC, University Medical Center, Rotterdam; Yale School of Medicine, New Haven	Apert (n=38‡) Crouzon (n=86‡) Muenke (n=25‡) Saethre-Chotzen (n=22‡) • Mean age: 8.8 (range 0.1-34.0) years • Pre-surgical and post-surgical	Prospective cohort (2008-2018)	Fundoscopy	83/171† (49%)
De Planque et al. (2021)[80] Erasmus MC, University Medical Center, Rotterdam	Crouzon (N=19) • Median age 1.0 (IQR 17.8) years • Pre-surgical and post-surgical	Retrospective study (1975-2019)	• Fundoscopy • Ventricular dilation	10/19 (53%)
Den Ottelander et a. (2021)[81] Erasmus MC, University Medical Center, Rotterdam	Saethre-Chotzen (N=32) • Median age 10.1 (SD 33.4) months • Pre-surgical and post-surgical	Part retrospective, part prospective cohort (1992-2017)	Fundoscopy	9/32 (28%)
Doerga et al. (2022)[82] Erasmus MC, University Medical Center, Rotterdam	Crouzon (N=63) • Median age at presentation 0.7 (0.2-2.9) years • Pre-surgical and post-surgical	Retrospective study (1994-2019)	Fundoscopy	33/63 (52%)
Still et al. (2021)[90] University of Florida, Florida	sCS (n=19) Other (n=37) • Mean age 3.0 (range 0.223-13.5) years • Pre-surgical and post-surgical	Retrospective analysis (2009-2020)	Clinical signs	36/56 (64%)

			Total	421/1130 (37%)

Studies without ICH detection

Author/Institution	**Syndromes (n)/Age/Surgical Status**	**Study design (recruitment period)**	**Focus of study**	**Outcome**
Hanieh et al. (1989)[43] Adelaide Children's Hospital, Adelaide	Crouzon (N=42) • Mean age: Not reported • Surgical status not reported	*Retrospective chart review* (1975-1987)	Ventricular size	16/42 had ventricular dilation
Hayward et al. (1992)[44] The Hospital for Sick Children, London	Apert (n=5) Crouzon (n=15) Saethre-Chotzen (n=3) Non-syndromic (n=7) • Mean age: Not reported • Surgical status not reported	*Retrospective chart review* (recruitment period not reported)	Brain abnormalities on MRI	12/30 had ventricular dilation
Hanieh et al. (1993)[45] Adelaide Children's Hospital, Adelaide	Apert (N=33) • Mean age: not reported • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Ventricular size	13/33 had ventricular dilation
Moore et al. (1994)[46] Adelaide Children's Hospital, Adelaide	Crouzon (N=11) • Mean age: not reported • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Ventricular size	7/11 had ventricular dilation
Gosain et al. (1995)[47] New York University Medical Center	Apert (N=51) • Mean age: not reported (range 0-30 years) • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Intracranial volume	Normal intracranial volume at onset, rises at 6 months of age and remains 3 SD above normal
Proudman et al. (1995)[48] Women's and Children's Hospital. North Adelaide	Crouzon (N=38) • Mean age: not reported • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Ventricular size	25/38 had ventricular dilation
Tokumaru et al. (1996)[49] University of California, San Francisco, Kameda Medical Center, Kamogawa City, Japan	Apert (n=8) Crouzon (n=10) Saethre-Chotzen (n=1) Other syndromes (n=2) • Age: <1 year • *Pre-operative*	Retrospective chart review (recruitment period not reported)	Skull and brain abnormalities	15/21 had ventricular dilation 18/21 had skull base deformities
Gonsalez et al. (1998)[50] Great Ormond Street Hospital for Children, London	Apert (n=2) Crouzon (n=10) Non-syndromic (n=1) • Mean age 4.8 (range 0.3-11.4) years • Surgical status not reported	*Prospective study* (recruitment period not reported)	TH and sleep disordered breathing	All patients had TH: mean 9.5 (range 1.5-27) mm 2/13 had central apnea 10/13 had OSA
Robson et al. (2000)[51] Children's Hospital and Harvard Medical School, Boston	Apert (n=10) Crouzon (n=17) Non-syndromic (n=6) Controls (n=76) • Mean age not reported (range 0.1-28) years • Post-surgical	*Retrospective chart review* (recruitment period not reported)	Venous outflow (JF and jugular veins)	27/33 had enlarged basal emissary foramina, almost always in association with JF stenosis or atresia
Rollins et al. (2000)[52] Children's Medical Center, Dallas, Texas	Apert (n=2) Crouzon (n=9) Non-syndromic (n=6)	*Retrospective chart review*	Venous outflow	8/11 had venous outflow obstruction†

	• Mean age 7.3 (range 0.3-34.0) years • Post-surgical	(recruitment period not reported)		
Anderson et al. (2004)[53] Women's and Children's Hospital, Adelaide, Australia	Apert (N=22) • Mean age: not reported • Pre-surgical	*Retrospective chart review* (recruitment period not reported)	Intracranial volume	Intracranial volume was bigger in Apert patients than normative data
Yacubian-Fernandes et al. (2004)[54] University of Sao Paolo	Apert (N=18) • Mean age 8.9 (1.2-26.8) years • Pre-surgical and post-surgical	*Retrospective chart review* (2001)	Ventricular size	5/18 had ventricular dilation
Da Costa et al. (2006)[79] Murdoch Children's Research Institute, University of Melbourne, Melbourne	Apert (n=3) Crouzon (n=4) Saethre-Chotzen (n=5) Other (n=19) • Mean age 10.9 (Range 7.1-15.8) years • Post-surgical	*Prospective study* (recruitment period not reported)	Intelligence testing	The majority of children with sCS were of normal intelligence
Tay et al. (2006)[55] Sydney Children's Hospital, Sydney	Apert (n=6) Crouzon (n=32) Saethre-Chotzen (n=13) Non-syndromic (n=12) • Mean age at presentation: 6.0 (range 0.2-37.1) years • Pre-surgical and post-surgical	Retrospective chart review (1983-2004)	Ophthalmologic signs	5/51 had papilledema
Thompson et al. (2006)[56] Great Ormond Street Hospital for Children, London	Apert (n=26) Crouzon (n=38) Saethre- Chotzen (n=17) Non-syndromic (n=33) • Median age: 2.25 (range 0.17-19.75) years • Pre-surgical	*Retrospective chart review* (1994-2001)	pVEP	49/81 had evidence of visual pathway compromise
Jeevan et al. (2008)[57] John Radcliffe Hospital, Oxford	Crouzon (N=11) • Mean age: 4.9 (range 0.3-21.9) years • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Venous outflow	11/11 had abnormal venous anatomy
Fearon et al. (2009)[58] Virginia Commonwealth University Medical Center	Crouzon (N=28) • Mean age: 10.8 (range 1-39) years • Pre-surgical and post-surgical	Retrospective chart review (1990-2007)	Ventricular size	19/28 had ventricular dilation 23/28 had CMI
Booth et al. (2011)[59] Medical College of Georgia, Augusta	CS and sCS n=14 Controls n=27 • Mean age: 0.8 (0.1-1.8) years • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	Venous outflow (JF)	CS and sCS patients have a smaller JF than controls
Strahle et al. (2011)[60] University of Michigan, Ann Arbor	Crouzon (n=25) Saethre-Chotzen (n=9) Other syndromes (n=3) Non-syndromic (n=346) • Mean age: not reported • Pre-surgical and post-surgical	*Retrospective chart review* (1994-2009)	CMI	3/37 had CMI
Coll et al. (2012)[61] Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris	Crouzon (n=21) Controls (n=23) • Mean age: 2.5 (SD 2.9) • Pre-surgical and post-surgical	*Retrospective chart review* (recruitment period not reported)	FM	FM was smaller in Crouzon patients than controls

De Jong et al. (2012)[62] Erasmus MC, University Medical Center, Rotterdam	Apert (n=12) Crouzon (n=31) Muenke (n=15) Saethre-Chotzen (n=10) Non-syndromic (n=15) • Mean age: 8.1 (0.3-18.3) years • Pre-surgical and post-surgical	Prospective cohort (2004-2011)	Ventricular size, brain volume	Ventricular size was larger in Apert patients and patients with CMI Brain volume not different between sCS patients and normative data
Driessen et al. (2013)[63] Erasmus MC, University Medical Center, Rotterdam	Apert (n=20) Crouzon (n=30) Muenke (n=12) Saethre-Chotzen (n=10) Non-syndromic (n=25) • Median age: 4.4 (range 0.2-20.6) years • Pre-surgical and post-surgical	Prospective cohort (2007-2012)	Sleep disordered breathing	49/72 OSA present No correlation between cAI and oAHI when patients <1-year-old
Rijken et al. (2013)[64] Erasmus MC, University Medical Center, Rotterdam	Crouzon (n=27) Controls (n=27) • Mean age: 4.5 years • Pre-surgical and post-surgical	*Retrospective chart review* (2004-2011)	FM, CMI	FM smaller in Crouzon than controls 8/27 had CMI No relation between FM size and CMI
Di Rocco et al. (2014)[65] Hôpital Necker, APHP, Université Paris Descartes, Paris	Muenke (n=16) Saethre-Chotzen (n=10) Non-syndromal (n=14) Controls (n=18) • Mean age: not reported • *Pre-surgical*	*Retrospective chart review* (2006-2012)	FM	FM smaller in Muenke than in controls, Saethre-Chotzen not different to controls
Maliepaard et al. (2014)[66] Erasmus MC, University Medical Center, Rotterdam	Apert (n=6) Crouzon (n=23) Muenke (n=13) Saethre-Chotzen (n=14) Complex (n=20) Controls (n=876) • Median age: 8.9 (range 6-13) years • Surgical status not reported	Prospective cohort (recruitment period not reported)	Clinical functioning	IQ in sCS patients as a group not different from normative data. Per syndrome only Apert patients had a lower IQ than controls
Assadsangabi et al. (2015)[67] Children's Hospital of Philadelphia	Apert (n=26) Crouzon (n=46) Saethre-Chotzen (n=7) Non-syndromic (n=9) Controls (n=30) • Mean age: not reported • Surgical status not reported	Retrospective chart review (2001-2014)	FM	Crouzon patients had a smaller FM area and AP diameter than controls; transverse diameter was smaller than controls in Crouzon and Apert patients.
Coll et al. (2015)[68] Hôpital Necker-Enfants Malades, APHP, Paris	Apert (n=11) Crouzon (n=20) Controls (n=17) • Mean age: not reported • Pre-operative	Retrospective chart review (recruitment period not reported)	FM, JF, PF volume, cerebellar volume	Crouzon patients had a smaller area and sagittal measurements of the FM. No difference in PF and cerebellar volume between sCS patients and controls.
Rijken et al. (2015)[69] Erasmus MC, University Medical Center, Rotterdam	Apert (n=11) Crouzon (n=24) Muenke (n=7) Saethre-Chotzen (n=10) Non-syndromic (n=17) • Mean age: 5.7 (0.2-18) years • Pre-surgical and post-surgical	Retrospective chart review (2000-2014)	Intracranial volume	OFC and age were significant predictors for intracranial volume
Rijken et al. (2015)[70] Erasmus MC, University Medical Center, Rotterdam	Apert (n=10) Crouzon (n=16) Muenke (n=10) Saethre-Chotzen (n=9) Non-syndromic (n=13) Controls (n=7)	Prospective study (2006-2013)	Brain abnormalities: white matter	sCS patients had normal white matter fiber organization, but increased diffusivity parameters, suggesting abnormal microstructural tissue properties.

	• Mean age: 9.4 (range 6-18) years • Post-surgical			
Rijken et al. (2015)[71] Erasmus MC, University Medical Center, Rotterdam	Apert (n=19) Crouzon (n=31) Muenke (n=16) Saethre-Chotzen (n=18) Non-syndromic (n=29) Controls (n=34) • Mean age: not reported • Pre-surgical and post-surgical	*Retrospective chart review* (2008-2011)	Cerebellar volume, PF volume	No difference between cerebellar volume and PF volume between unoperated and operated sCS patients and control subjects Cerebellar and PF volume were not related TH
Rijken et al. (2015)[72] Erasmus MC, University Medical Center, Rotterdam	Apert (n=19) Crouzon (n=29) Muenke (n=18) Saethre-Chotzen (n=15) Non-syndromal (n=33) Controls (n=54) • Mean age: 2.9 years • Pre-surgical and post-surgical	*Retrospective chart review* (2006-2012)	FM, CMI	FM area and AP diameter were smaller than controls for all types of sCS. Posterior intra-occipital synchondroses closed earlier in Crouzon and Apert patients than in controls
Inverso et al. (2016)[73] Hospital of the University of Pennsylvania, Philadelphia; Boston Children's Hospital, Boston	Apert (n=31) Crouzon (n=31) • Mean age: 7.6 ±6.5 years • Surgical status not reported	Retrospective chart review (2000-2014)	Sleep disordered breathing	46/62 had had OSA
Driessen et al. (2017)[74] Erasmus MC, University Medical Center, Rotterdam	Crouzon (N=40) • Mean age: 8.4 years • *Post-operative*	Prospective cohort (recruitment period not reported)	Sleep disordered breathing and skull	A trend toward earlier fusion of the SOS in patients with Crouzon syndrome with OSA as compared to patients with Crouzon syndrome without OSA
Maximino et al. (2017)[75] Universidade de São Paulo	Apert (n=8) Crouzon (n=10) • Mean age: 18.8 (range 6.3-51.3) years • Surgical status not reported	Prospective cohort (2008-2011)	Clinical functioning	4/18 had intellectual disability
Breakey et al. (2018)[76] Great Ormond Street Hospital for Children, London	Apert (n=81) Crouzon (n=112) Saethre-Chotzen (n=28) Controls (n=56) • Mean age: 2.4 (0.0-17.5) years • Pre-surgical	*Retrospective chart review* (2015-2017)	Intracranial volume	Apert patients had a larger intracranial volume than controls. Strong correlation between OFC and intracranial volume, even in turricephaly
Coll et al. (2018)[78] Hôpital Necker-Enfants Malades, Paris	Crouzon (N=30) • Mean age: 2.4 years (range 1 month-12.5 years) • Pre-surgical	Retrospective case control study (recruitment period not reported)	Pattern of closure of skull base synchondroses	In Crouzon patients closure of skull base synchondroses occurs prematurely
Doerga et al. (2020)[83] Erasmus MC, University Medical Center, Rotterdam	Apert (n=12) Crouzon (n=34) Muenke (n=11) Saethre-Chotzen (n=6) • Mean age 8.0 (IQR 4.8-12.3) years • Pre-surgical and post-surgical	Prospective cohort (2012-2017)	Neurological deficits in relation to CMI	There was no difference in presence of neurological deficits in patients with or without CMI
Den Ottelander et al. (2022)[88] Erasmus MC, University Medical Center, Rotterdam	Apert (n=15) Crouzon (n=41) Muenke (n=19) Saethre-Chotzen (n=23) Other (n=28)	Prospective cohort (2018-2020)	OCT to evaluate retinal thinning and visual acuity	Macular thinning was associated with lowered visual acuity, but was not associated with duration of papilledema

	• Mean age at OCT scans 12.0 (±5.1) years • Pre-surgical and post-surgical			
Wilson et al. (2022)[91] Erasmus MC, University Medical Center, Rotterdam Yale School of Medicine, Section of Plastic Surgery, New Haven	Apert (n=37) Crouzon (n=86) Muenke (n=25) Saethre-Chotzen (n=19) Other (n=36) • Mean age at MRI scans 9.0 years (SD 5y 3mo) • Post-surgical	Prospective cohort (2008-2018)	ICV and CSA in sCS patients	In *FGFR*-mediated sCS patients, cortex development was atypical, despite adequate ICV

*At least one of the symptoms of ICH
**Post-surgically
†Number of patients or percentage of patients with ICH only reported for the whole study population, including non-syndromic patients. The percentage for the whole population was assumed to be the same for the population of sCS patients in the study and was used to calculate number of sCS patients with ICH.
‡Number of MRIs
ICP: intracranial pressure, LP: lumbar puncture, ICH: intracranial hypertension, OCT: optical coherence tomography, pVEP: pattern visually evoked potentials, MRI: magnetic resonance imaging, TH: tonsillar herniation, CMI: Chiari malformation type I, PF: posterior fossa, FM: foramen magnum, JF: jugular foramen, AP: anterior-posterior, *FGFR:* fibroblast growth factor receptor, ICV: intracranial volume, CSA: cortical surface area

3. Non-invasive methods

Fundoscopy – Papilledema

Presence of papilledema is often used in studies as a non-invasive method to determine ICH. We found 37 studies that reported papilledema. Eleven studies used papilledema alongside invasive ICP/LP measurements to determine ICH.[7,9-16,18,22] In studies that only use indirect methods of determining ICH, fundoscopy is the most used method, in 17/23 studies. Ten use papilledema as the only method to determine ICH,[27,29,31,32,35,36,38,42,81,82] 7 studies use papilledema alongside other indirect methods to determine ICH.[25,26,28,30,33,39,80] Four studies report on the prevalence of papilledema, but do not associate it with ICH,[34,55,86,88] 1 study uses OCT as determinant of ICH and compares it to papilledema.[41]

Five studies compared invasive ICH/LP measurements to papilledema in 125 sCS patients,[2,20,21,85,89] and showed that the sensitivity of papilledema to detect ICH (as determined by invasive ICP/LP measurement) is not that high, ranging between 11-32%. Showing that ICH can be present without presence of papilledema. While the sensitivity of papilledema as determinant of ICH may be low, these studies show that papilledema does have a very high specificity, 98-100%. Papilledema remains a very important clinical sign, because the severity and duration of papilledema is related to the prognosis of the patient's visual acuity.

Optical coherence tomography (OCT)

Means other than papilledema, to detect ICH that might have a better sensitivity, have been subject of many studies. A main candidate at the moment is optical coherence tomography (OCT).

Ten studies used OCT: 2 studies compared OCT to invasive ICP measurements,[20,85] and found a sensitivity of 77-89% and specificity of 60-95%, 1 study compared OCT to papilledema as determinant of ICH and found an association between ICH and an increased total retinal thickness (TRT).[35] One study used OCT alone to determine ICH,[41] 4 used OCT alongside direct ICP/LP measurements,[11-14] and none used OCT alongside indirect methods. Two studies used OCT but did not relate it to ICH,[34,88] one of which associated OCT with visual acuity.[88]

Optic nerve sheath diameter (ONSD)

Two studies examine the validity of using the optic nerve sheath diameter (ONSD) as indicator for ICH.[15,31] One study compares ONSD to invasive ICP/LP measurements and papilledema,[15] the other compares ONSD to papilledema.[31]

These two studies found a sensitivity of 11-71% and specificity of 90-97% for the ONSD to determine ICH, in 128 sCS patients.

Pattern visually evoked potentials

Pattern visually evoked potentials (pVEP) are signals in the occipital lobe in response to a visual stimulus, and have been used for early detection of visual pathway dysfunction in craniosynostosis patients. Four studies used pVEP: 2 examined the validity of pVEP by comparing it to invasive ICP measurement or papilledema,[16,89] 1 used it as a sign of ICH,[9] and the remaining 1 used it to assess the prevalence of visual dysfunction without relating it to presence of ICH.[56]

The 2 studies that examined the validity of pVEP to determine ICH found a sensitivity of 71-89% and specificity of 54-100% in 40 sCS patients.[16,89]

Change in head growth

We found one study that examined the validity of change in head growth,[11] and two studies that used a change in head growth as a sign of (impending) ICH.[13,28] Spruijt et al.[11] used serial occipitofrontal circumference measurements, and showed in a study of 36 sCS and 26 non-syndromic patients, that 12/13 patients who had ICH (defined through ICP measurement, papilledema, and OCT) had a deflection of the head growth curve, which was a significant association (P<0.001).

Ventricular dilation

We found 26 studies that used ventricular size. Four report on the validity of ventricular dilation as determinant for ICH as determined by ICP/LP measurement,[5,18,20,85] 3 to ICH as determined by indirect methods (fundoscopy, OCT, epidural or fontanometric pressure or evidence of ICH during operation [not specified further]),[27,41] 6 use ventricular dilation as a determinant for ICH,[14,25,33,34,39,80] and 14 report on the prevalence of ventriculomegaly or hydrocephalus but do not associate it to ICH.[37,42-46,48,49,52,54,58,60,62,68]

Five out of 6 studies that examined the validity of ventricular dilation as determinant for ICH found a sensitivity of 5-65% and a specificity of 78-100% in 185 sCS patients,[5,20,27,41,85] the remaining study displayed data in such a way that sensitivity and specificity could not be calculated.[18]

Presence of copper beating, thumbprinting or cranial lacunae

Convolutional markings can be present in normal children. Then they are seen mostly posteriorly and are seen as a reflection of normal exuberant brain growth at 2-3 years and 5-7 years.[100] When they are more pronounced and cover the more anterior parts of the skull, they are referred to as copper beating, or thumbprinting on radiographs, or cranial lacunae when seen on CT. Their presence suggests presence of ICH. Since copper beating and cranial lacunae are the same phenomenon using different imaging techniques, we will refer to all as copper beating.

Ten studies use presence of copper beating, 3/10 examine the validity of using copper beating to determine ICH as compared ICP/LP measurement,[5,20,85] 3/10 as compared to indirect methods (intention-to-treat, papilledema, OCT),[27,40,41] and 4/10 use copper beating as a determinant for ICH.[26,30,34,39]

The six studies that examined the validity of copper beating to determine ICH found a sensitivity between 27-88% and specificity ranging between 43-100% in 185 sCS patients.

Clinical signs

Classic clinical signs of ICH are headache, vomiting and irritability. Eleven studies use clinical signs of ICH, 3 examine the validity of clinical signs of ICH to determine ICH as determined by ICP/LP measurement,[20,22,85] 3 to ICH as determined by indirect methods (papilledema, OCT),[27,35,41] 6 use clinical signs of ICH to determine ICH.[25,26,28,30,39,90]

The 6 studies that examine the validity of clinical signs of ICH found a sensitivity of 24-50% and specificity of 51-95% in 151 sCS patients.

Venous outflow abnormalities

Eight studies focused on venous outflow abnormalities. One study looks at validity of jugular foramen (JF) diameter as determinant of ICH as determined by ICP measurement,[7] sensitivity and specificity could not be calculated. Two studies look at validity of venous outflow abnormalities as determinant of ICH as determined by indirect methods.[36,37] The study by Copeland et al.[37] found that patients who had venous anomalies were more likely to have ICH (not reported how ICH was determined), while the study by Florisson et al.[36]found no relation between JF diameter and ICH (as determined by papilledema). Sensitivity and specificity could not be calculated in either study. Five studies focus on venous outflow, without relating it to ICH.[51,52,57,59,68]

Bulging of anterior fontanelle

We found five studies that used a bulging anterior fontanelle as a sign for ICH.[13,25,26,40,85] One study examined its validity to determine ICH and could not calculate sensitivity and found a specificity of 95% in 26 sCS patients.[85]

Intracranial volume (ICV)

Seven studies focused on ICV. One study looks at the validity of ICV as determinant for ICH as compared to ICP measurement,[3] they report an 8% sensitivity, specificity is not reported in 14 sCS patients. Five examined ICV without comparison to ICH.[47,53,62,69,76]

Obstructive sleep apnea

One study relates OSA to ICH as determined by direct and indirect methods.[11] Five articles examine OSA without relating it to ICH.[32,50,63,73,74] The study that relates OSA to ICH found an association between moderate/severe OSA and ICH and a sensitivity of 71% and specificity of 42%.

Other methods

One study by Tuite et al. in a larger patient population of CS and sCS patients, compared to controls, showed that copper beaten pattern was present in both CS and control subjects, but ICP was significantly higher in patients with a diffuse copper beaten pattern in combination with sellar erosion or suture diastasis.[5] In addition to the already mentioned copper beating and ventricular dilation, this study looks at sellar erosion, suture diastasis, obliterated anterior sulci and narrowed basal cisterns. For these 4 methods the sensitivity ranges between 10-34%, and specificity ranges between 90-94%.

Four studies focused on clinical functioning. One compared it to indirect methods of ICH (papilledema), however sensitivity and specificity could not be calculated.[29] Three examined clinical functioning without relating it to ICH.[66,75,79]

Seven studies examined foramen magnum (FM).[61,64,65,67,68,72,76] None of the 7 studies related FM to ICH.

Transcranial doppler has also been put forward as a determinant for ICH. This review did not include studies using transcranial doppler, because the studies we found concerning transcranial doppler all included less than 10 sCS patients. **Table 3** gives an overview of the commonly used determinants for presence of ICH.

Table 3
Terms and definitions for methods used to determine ICH

Term	Definition
Direct methods	
1. ICP measurement	Direct invasive measurement where an ICP monitor is placed intracranially
2. LP measurement	Opening pressure when opening the spinal dura at lumbar level.
Indirect methods	
3. Fundoscopy	Papilledema, swelling of the optic disc from increased ICP
4. Copper beating, digital markings, fingerprinting	Impressions made by brain gyri on the inner table skull bone as seen on radiograph
5. Cranial lacunae/scalloping	Foci of attenuated skull bone, thinning of the inner cortex while leaving the outer cortex intact. CT equivalents of 'copper beating'
6. Ventricular dilation	Enlargement of the lateral ventricles
7. ONSD	Diameter of the optic nerve and its sheath. Its sheath distends when ICH occurs.
8. OCT	Retinal OCT can measure the thickness of different retinal layers.
9. pVEP	pVEP measures the electrical response in the visual cortex in response to a visual stimulus. pVEP is used to detect impairments in visual pathway functioning
10. Skull growth	An arrest in the skull growth curve, when observing serial measurements of head circumference. Is used as measure for ICV
11. Clinical signs	Headache, vomiting, irritability
12. Anterior fontanelle bulge	Bulging of the anterior fontanelle
13. JF stenosis	Stenosis of the foramina at the skull base through which the jugular veins transport blood from intracranial to extracranial compartment

ICH: intracranial hypertension, ICP: intracranial pressure, LP: lumbar pressure, CT: computed tomography, ONSD: optic nerve sheath diameter, OCT: optical coherence tomography, pVEP: pattern reversal visually evoked potential, ICV: intracranial volume, JF: jugular foramen

Results - Section 2

This section will put our findings of the scoping review in context. We structured it according to the principles of the Monro-Kellie hypothesis.

Cranial vault

When cranial sutures are patent, skull volume is compliant and can adjust not only to increases in brain volume, but also to the other two intracranial compartments, CBV and CSF volume. In sCS patients, skull base synchondroses close earlier than in control subjects, and sCS patients have significantly smaller FM and JF.[36,64]

Intracranial volume

Virchow (1851) determined in skull specimens that cranial deformity could be explained by lack of growth perpendicular to closed skull sutures, causing compensatory skull growth parallel to closed skull sutures. This compensatory growth was often deemed not to be adequate to accommodate brain growth, causing ICH. [30,101] Since the early 1990s however, there have been several studies examining the correlation between ICV and brain volume, that show this is often not the case in children with other types of craniosynostosis.

Our literature search identified 8 articles that report on skull volume. One study measured ICV of sCS patients and determined presence of ICH (using invasive ICP measurements) and compared it to normative data,[3] 6 studies examined ICV without detecting presence of ICH.[47,53,68,69,71,76,91] These studies found that ICV in sCS patients is normal, and for Apert syndrome larger than normal. Hence, in general, in sCS patients ICV is similar to controls. One study found that despite ICV being normal in Apert, Crouzon and Muenke syndromes, cortex development was atypical.

Two studies report a strong association between occipitofrontal circumference (OFC) and ICV, indicating that OFC is a reliable method to estimate of ICV.[69,76] Deviation in the skull OFC growth curve may be an important clinical sign that indicates either the presence of ICH or impending ICH. This was indicated in the study by Spruijt et al.[11] which used serial measurements of the OFC and found that deviation of the growth curve was present in 12 out of 13 patients with ICH (defined as papilledema, OCT or invasive ICP measurements), and only in 7 out of 47 patients without ICH (difference of 77% [95% confidence interval 48 to 87% difference], $p<0.0001$).[11] This suggests that determining whether a given patient maintains their own trajectory in skull growth is an important clinical assessment of (impending) ICH.

Two studies focus on a particular part of the ICV: the posterior fossa (PF) and how it relates to Chiari malformation type I (CMI).[68,71] These studies found that there was no significant difference in cerebellar volume and PF volume between unoperated and operated sCS patients (n=83), and control subjects (n=51).[68,71] Patients with CMI had a significantly higher cerebellar volume/PF volume ratio than control subjects,[71] and no association between hydrocephalus and cerebellar or PF volume.[68]

Skull base abnormalities

Our literature search identified 8 articles that examine the skull base. Of these 8 studies, 4 examined the FM,[61,65,67,68] 3 examined the FM and intraoccipital synchondroses,[64,72,78] 1 reports on skull base abnormalities, but does not specify what kind.[49] The 7/8 studies that examined the FM found that the FM is smaller than in controls.[61,64,65,67,68,72,78] FM surface area was not associated with CMI.[64,68,72] Two studies showed an association between a small FM size and larger ventricles.[68,72] However, these should be seen in context: in the first,[68] hydrocephalus occurred in 6 patients, which might be too small a number to draw conclusions from, in the second,[72] that the relation, while statistically significant, was not that strong with an R^2 of 0.04. The studies postulate that the smaller FM seen in sCS patients could hinder CSF passage around the skull base and may play a role in the development of ventriculomegaly and ICH.

To summarize, the studies in our literature search showed that the ICV of sCS patients is no different from control subject, and for Apert patients, bigger than control subjects. A small ICV seems less likely to be the reason for ICH. However, following skull growth is important, because arrests in skull growth can indicate (impending) ICH. The FM is smaller in sCS patients than in controls, and might play a role in the development of ventriculomegaly and ICH.

The Brain

Patients with sCS in general, do not have smaller brain volumes. In the literature search we identified 1 article that examined brain volume,[62] 2 articles that focused on cerebellar volume.[68,71]

de Jong et al.[62] carried out a cerebral magnetic resonance imaging (MRI) study in 84 sCS patients and determined that brain volumes compared to normative data at ages 1, 4, 8 and 12 years, were no different in Apert, Crouzon, Muenke, Saethre-Chotzen syndrome patients and complex craniosynostosis patients. However, Apert patients did have larger ventricular size than other sCS patients. The two studies on cerebellar volume found that cerebellar volume in 115 sCS patients was similar to that of control subjects (n=51).[68,71] In summary, brain volume in sCS patients is comparable to that of normal controls.

Intracranial blood compartment

CBV is a dynamic intracranial compartment not only under physiological control by autoregulation and arterial blood partial pressure of carbon dioxide, but also potentially limited by arterial inflow and venous outflow anatomy. In the literature we identified 11 articles that provided data on the clinical physiology of CBV in children with sCS.[7,14,33,36-38,51,52,57,59,68]

Cerebral blood flow

This study identified 2 studies that presented data on arterial cerebral blood flow (CBF). The first found that CBF under prematurely fused sutures increases after skull vault expansion.[33] The second found that untreated sCS patients <1 year old have a lower CBF than controls, CBF normalizes with age and surgery, and that the physiological peak in CBF occurs at a later age in sCS patients than in controls.[38]

Aberrant venous drainage

This study identified 9 articles that presented data on aberrant venous drainage/outflow relating to JF and/or dural sinuses.

There is indirect evidence that the structure of venous outflow vessels from the intracranial vault may be abnormal, we found 9 studies that report on this, 6/9 report on the JF,[7,36,51,52,59,68] 2/9 discusses JF and dural sinuses,[37,57] and 1/9 discusses dural venous sinuses alone.[14]

Four of the 9 studies report on the JF. They report a prevalence of JF stenosis or occlusion in 62/92 sCS patients (67%), in majority Crouzon and Apert patients.[37,51,52,57] Four studies compared measurements of the JF in sCS patients to controls and found that the JF measurements were significantly smaller in sCS patients, [36,59,61,68] and one compares the measurements of sCS patients with ICH to those of simple CS patients and sCS patients without ICH.[7]

Two studies relate JF measurements to presence of ICH (determined by invasive ICP [cut-off values not reported],[7] and papilledema[36]). Their findings diverge. The first[7] found a significantly smaller mean jugular diameter in sCS patients and non-syndromic multisuture patients with ICH (n=12), than in the controls without ICH (n=19). Whereas the second study[36] found no significant difference in area of the JF between sCS patients with (n=15) and without papilledema (n=26).

Of the 3 studies that assessed dural sinus abnormalities, one reported a prevalence of dural vein stenosis of 68% (28/41),[37] another reported a prevalence of transverse sinus atresia in 64% (7/11).[57] The third study[14] reported on the volume of dural sinuses in 81 sCS children, and found no difference in total cerebral venous blood volume between sCS children with ICH and without ICH.

There is evidence that there may be venous vascular adaptation to impaired intracranial venous outflow in sCS. We found 6 studies that reported on emissary veins (i.e. veins that connect the intracranial venous sinuses with the extracranial venous system). Prominent occipital emissary veins occurred often in patients with Apert, Crouzon and Saethre-Chotzen, and rarely in patients with Muenke syndrome. Emissary veins were present in 159/248 patients (64%).[14,36,37,51,52,57]

Two studies relate emissary veins to presence of ICH.[14,36] The studies do not concur about an association between presence of emissary veins and ICH.

In summary, the JF are smaller in sCS patients than in normal controls. Emissary veins occur more often in sCS patients than in normal controls. Mechanistically, the failure in developmental regression of emissary veins may be related to the presence of JF stenosis or occlusion which was found in 67% of sCS patients.[37,51,52,57] The JF stenosis and occlusions are most likely due to cartilaginous synchondroses of the skull base ossifying sooner in sCS patients than in controls.[64,72] There is no clear consensus between studies on whether emissary veins occur more in patients with ICH than those without. Some of the studies theorize that in some sCS patients venous emissary veins play a major role in moving blood from the intracranial to extracranial compartment. When this delicate balance is interrupted, (e.g. due to slowing head growth, or increased arterial blood flow due to OSA) this might lead to ICH.

Abnormal dynamic or physiological control of CBF and CBV - Evidence of abnormal cerebral autoregulation

We found one study that focuses on cerebral autoregulation in sCS patients. The study by Hayward et al.[8] performed overnight sleeping invasive ICP measurements, with simultaneous polysomnography (PSG) and arterial blood pressure (ABP) monitoring to determine cerebral perfusion pressure (CPP, calculated as: mean ABP – mean ICP), which is used as indicator for CBF. This study found that increases in ICP during active sleep led to some increase in ABP, but not enough to prevent marked drops in CPP. The study cannot confirm whether the drops in CPP went along with a drop in CBF, or whether the brain's autoregulatory mechanisms adjusted for it. They hypothesize that if adjustments for CBF do occur, this would be by vasodilation of cerebral arteries which would go along with an increase in CBV. This would cause the ICP to rise further, leading to peaks in ICP during active sleep, like the peaks of 50-60 mmHg they found lasting for several minutes.

Obstructive sleep apnea and ICH - evidence of raised $PaCO_2$

We found 9 studies that reported on obstructive sleep apnea (OSA).[8,10-13,32,42,73,102] Two of the 9 studies examined the relation between OSA and ICH.[8,11] The 9 studies found that OSA was present in 232/580 sCS patients, 40%, moderate-severe OSA was present in 100/409 sCS patients, 25% (only counting studies that used category moderate or severe OSA).[10,12,73,102]

The 2/9 studies found a relation between OSA and ICH. First, Hayward et al.[8] found that during active sleep, the pharyngeal muscles relax and apneas occur, and found a rise in ICP using invasive ICP measurements simultaneous with sleep monitoring. The theory is that because of the rise in $PaCO_2$ during apneas, vasodilation of cerebral arteries occurs, the drop in CPP causes a rise in ABP, which then causes a rise in ICP because of the increase in intracranial blood volume. Second, Spruijt et al.[11] showed that moderate/severe OSA (defined as an obstructive apnea-hypopnea index [oAHI] ≥ 5) is associated with increased risk of ICH (as determined by invasive ICP measurement, papilledema, or OCT).

Four out of 9 studies provided information about the prevalence of moderate-severe OSA.[10,12,73,102] In Apert and Crouzon syndromes, upper airway obstruction often occurs with midface, with or without mandibular hypoplasia. This goes along with a high prevalence of OSA, which is mostly moderate/severe.[10,73] In syndromes such as Muenke and Saethre-Chotzen, that have a more normal midface and mandibular growth, OSA occurs less often and is often mild.[10,13]

In summary, OSA leads to raised $PaCO_2$ during active sleep, which ultimately leads to increased ICP plateaus which can be as high as 50-60 mmHg. Moderate-severe OSA are associated with an increased risk for ICH. Moderate-severe OSA occur most in Apert and Crouzon syndrome, due to midface hypoplasia with or without mandibular hypoplasia.

Cerebrospinal fluid

There are various mechanisms by which alteration in CSF volume, distribution and circulation may lead to raised ICP or ICH. Very little direct research has been done on CSF, because of the inherent risks associated with invasive CSF measurement. There are theories about how

production of CSF, CSF flow and absorption of CSF might be affected by the different traits associated with sCS. Below you will find the main theories.

Production of cerebrospinal fluid
There have been theories about potential overproduction of CSF caused by *FGFR* mutations in the choroid plexus. This literature search could not identify any studies that measured CSF production.

Flow or resistance to flow of cerebrospinal fluid
This literature search could not identify studies that measured CSF flow rate or resistance to flow.

Obstruction of outflow of cerebral spinal fluid
CSF flows from the fourth ventricle through Magendie and Luschka to the extracerebral arachnoid space, both up to the arachnoid villi and down through the FM around the spinal cord. A number of studies in sCS have described a smaller area of the FM, as described above. This smaller FM could impede the free flow of CSF from the intracranial compartment to extracranially. This problem can be worsened by the presence of CMI.[61,68] This could result into increased resistance for free flow of CSF out of the ventricles and out of the intracranial compartment and for CSF absorption, which can then lead to an accumulation of CSF intraventricularly as hydrocephalus, and/or intracranially as idiopathic intracranial hypertension.[103-107]

We found one study that confirmed the finding that premature closure of lambdoid sutures has a strong association with CMI.[60] We found 3 studies that examined the association between CMI and ventricle size.[58,60,62] One showed that patients with CMI had larger ventricles than those without.[62] The second showed that hydrocephalus was present in 15/29 patients with CMI.[60] Almost all patients who required a VP-shunt due to hydrocephalus, developed CMI (18/19 patients).[58,60]

Absorption of cerebrospinal fluid
For CSF absorption into the venous system to occur, the CSF pressure is normally slightly greater than venous pressure of the superior sagittal sinus, to maintain a pressure gradient that drives absorption of CSF. When venous pressure is higher, this is thought to complicate CSF absorption, while CSF production continues, leading to excess CSF.[103,108] In sCS patients their venous anomalies might cause higher venous pressure. This could cause CSF pressure to rise until a positive pressure gradient occurs for CSF to be absorbed into the venous system. Increased venous pressure could also cause decreased CSF absorption, which leads to idiopathic intracranial hypertension.

In summary, most evidence of alterations of CSF volume in sCS patients focuses on obstruction of outflow of CSF. This obstruction is caused by a smaller FM, because of early closure of the intraoccipital synchondroses, and CMI. Increased production of CSF due to *FGFR2* changes in the choroid plexus, or decreased absorption because of venous hypertension due to venous anomalies, have not yet been proven.

Craniosynostosis syndromes and ICH

Not all patients with syndromic craniosynostosis develop ICH. Large differences exist between syndromes and their incidence of ICH. Likely because the prevalences of specific risk factors for ICH vary vastly between different syndromes, as shown in **Table 4**. Understanding how the regulatory mechanisms for ICP are influenced by the risk factors in craniosynostosis syndromes, gives us more insight into the question why ICH occurs more in certain syndromic craniosynostosis syndromes than others.

Factors that influence the regulation of ICP in craniosynostosis syndromes are displayed in **Table 4**. In Apert and Crouzon patients, the factors concern mainly moderate/severe OSA, deviation of skull growth curve, venous hypertension, and obstructions in CSF flow. In Saethre-Chotzen aspects concern mainly deviation of skull growth curve and venous hypertension. OSA does not occur very often, when it does it is mild, CMI and hydrocephalus are rare. Muenke patients rarely have deviation of skull growth curve, rarely have OSA, and when they do, it is mild, and rarely have hydrocephalus. The low prevalence of ICH in Muenke syndrome is in accordance with the low prevalence of these risk factors for ICH.

Table 4
Overview of aspects of most common craniosynostosis syndromes.

	Apert	Crouzon	Muenke	Saethre-Chotzen
Skull Vault				
Sutures	Bicoronal, often leading to the characteristic turribrachycephaly	Mostly pansynostosis, however, varies from pansynostosis to all sutures patent	Unilateral or bilateral coronal, macrocephaly with all sutures patent	Unicoronal or bicoronal
Intracranial volume [47,53,76]	Increased	Normal	Normal	Normal
Brain				
Brain volume[62,68,71]	Normal	Normal	Normal	Normal
ICH[9,11,13,23]	80%	60%	8%	15%
Deviating skull growth curve [11,13]	32%	32%	5%	41-75%
Other[48,49,109-111]	Agenesis/thin of corpus callosum, defective septum pellucidum, mesial temporal abnormalities, ventriculomegaly (non-progressive), PF arachnoid cyst, limbic malformations, mega cisterna magna	Agenesis of corpus callosum, ventriculomegaly (non-progressive), schizencephaly, septum pellucidum abnormalities	Rare, case reports of hippocampal and bilateral medial temporal dysgenesis, ventricular dilation, a small cerebellum, porencephalic cyst of the occipital horn, and absence of the corpus callosum. Epilepsy and seizures have also been reported.	Rare
Blood				
OSA[63]	70%	65%	7%	15%
Hypoplastic or absent transverse and/or sigmoid sinus[36,37]	14-55%	71-81%	0%	33-50%
Emissary veins[36,37]	36-57%	75-81%	0%	33-50%
Jugular foramen stenosis [36,37]	55%	38-50%	0%	33%
CSF				
CMI[62,71]	8-11%	23-32%	7%	6%
Hydrocephalus[13,43,45,46,48]	4-39%	9-64%	0%	0%

ICH: intracranial hypertension, CMI: Chiari Malformation Type I, OSA: obstructive sleep apnea, CSF: cerebrospinal fluid, PF: posterior fossa

What is evidence of impaired brain development?

To determine the importance of presence and prevention of ICH in sCS children, many studies have tried to determine the effects of ICH. To determine these effects, studies have examined areas of cognitive functioning, and of brain imaging in sCS children, with or without ICH. Studies that examine deficits in sCS children without ICH are important to determine what brain impairment might be present in absence of ICH, and thus the result of syndrome specific development pattern and help discern what brain impairment is a consequence of ICH.

Neurocognition is difficult to determine, and requires different types of testing for different age categories in children. Some studies use intelligence quotient (IQ) to determine intelligence, but had very little detail about how IQ data was collected, in others confounders such as socioeconomic level were major potential confounders, or had small patient populations.[75,95] Three studies used validated questionnaires in large study populations of sCS patients focusing on intellectual, behavioral and emotional functioning and health related quality of life. They show that Apert and Muenke patients experience the most problems, relative to normative data and relative to children of other syndromes.[29,66,79] When considering language or speech development, impaired hearing is an important factor in Muenke and Saethre-Chotzen syndromes, and cleft palate an important factor in Apert syndrome.[13,23]

Neurological problems can be a sign of impaired brain development. We found one study that prospectively determines neurological problems (by testing motor skills, sensory function, cranial nerve function) in sCS patients, and related them to CMI and syringomyelia.[83] They found that neurological deficits had a high prevalence, irrespective of the presence of CMI or syringomyelia. They did find value in longitudinal neurological assessments to determine a deterioration in neurological deficits.

Obvious signs of impaired brain development are structural brain abnormalities (**Table 4**). They occur most in Apert and Crouzon patients, and rarely in Muenke and Saethre-Chotzen patients. Some studies use new imaging techniques to explore potential brain impairment by determining differences in brain function. One used diffusion tensor imaging and found increased diffusivity parameters in sCS patients when compared to controls, indicating abnormal microstructural tissue properties, which in turn indicates myelin pathology. The white matter fiber organization was comparable between sCS patients and controls.[70] Reduced CBF is thought to be a potential indicator for impaired brain development. One study explored this, and showed a lower CBF in sCS patients <1-year-old prior to skull vault expansion, when compared to controls.[38] This normalized with age and skull vault expansion to that of normal controls. However, this study could not determine if this normalization was caused by the skull vault expansion itself, or by the natural consequence of aging. One study examined ICV and related it to cortical surface area (CSA) as a determinant for gyration and cortical development.[91] This study found that in Apert patients specifically, there was reduced scaling of CSA to ICV in the parietal and occipital lobes, and observed corresponding deficits in scholastic achievement.

To what extent is outcome dependent on genetic origin versus result of ICH versus result of problem in other processes?

This question has led craniofacial departments to different thoughts on whether to preventatively perform skull vault expansion in all sCS patients, or whether to wait for signs of ICH to perform skull vault expansion.[112]

Key in answering the question is determining objective signs of the effect of ICH on sCS patients, other than the obviously detrimental effects of lasting papilledema on visual acuity.[113] This has proven to be difficult, since it is difficult to separate what abnormalities are due to the syndrome itself, or purely consequence of ICH.

Some studies have shed some light on this problem by examining IQ.[29,66,79] They showed that the majority of sCS patient were of normal intelligence. Patients with Crouzon syndrome, have a normal full-scale IQ, and less behavioral problems, despite having ICH relatively frequently. Apert and Muenke patients differed most significantly from normative values. Patients with Muenke syndrome experience ICH much less often than Crouzon patients. One more study,[91] looked at educational data and found that the majority of Apert patients who required modified education, suffered from motor or intellectual disability. In Muenke patients psychological or behavioral issues were more common. These findings support the theory that in Apert and Muenke patients, behavioral problems and lowered mental capabilities are inherent to their syndrome, and not a consequence of ICH, although ICH could further impair their cognition.

A study by Wilson et al. showed thinning of the cerebral cortex in patients that have had papilledema and in patients with hydrocephalus.[42] The authors postulate that by the time papilledema is detectable through fundoscopy, cortical neurons may have already suffered enough stress to result in cortical thinning. This is a novel and tangible finding that supports the method of preventative skull vault expansion, to avoid the effects of ICH on the cerebral cortex.

Limitations and recommendations for future studies

While reviewing these studies in sCS patients, we found one thing to be consistent: no consistency. Even in a seemingly objective assessment such as invasive ICP measurements. Most studies agree to a cut-off at 15 mmHg, but the huge variety in how the measurements themselves were analyzed complicates comparisons of the results between studies (e.g. usage of mean ICP, baseline ICP, or number of peaks during REM sleep). We should attempt at more coherence in how we report our data, so we can more easily compare our results. An important part of this, is consensus between different craniofacial centers about study parameters. Steps to attempt at this consensus have been made already for parameters of care for craniosynostosis patients.[114,115] A similar consensus on how we conduct and report our research could lead to leaps forward in our understanding of problems in sCS patients.

A good starting point would be to decide on what outcome is most relevant to patients and parents, and what outcome best reflects the treatment pathways. Based on this, we should agree on when and how to measure, and how to report this. This will allow us to compare results of the various craniofacial centers and better understand the effects and differences between their various treatment methods (e.g. preventative vs. expectant).

Another issue in studies concerning sCS patients is an obvious one, small patient populations. Small patient populations complicate statistical testing. Differences found in studies with small patient populations, have a higher risk of being based on chance. This risk is made bigger by the lack of correcting for multiple testing, as seen in many studies. Increased collaboration between different craniofacial centers might lead to studies with bigger patient populations, which will allow us to determine results with more certainty.

In doing this review we encountered another issue due to small patient populations. Because a small number of craniofacial centers have contributed a great many studies in sCS patients, we deduced that data of the same sCS patients is utilized in different studies. This has most likely led to an overestimation of the number of sCS patients in this review. To account for this and to give the most reliable representation of the results, we presented results mostly in ratios and percentages.

Many studies examine the compound group of sCS patients, or compare this compound group to normal controls. While this could be desirable to obtain enough patients for statistical analysis, we know the differences between the craniofacial syndromes are very diverse. Compounding them diminishes the distinct and valuable differences that are present between the different syndromes. We recommend more studies focusing on separate syndromes, so the distinct aspects of these individual syndromes can be better explored.

An interesting area for future research may be CSF outflow. An experimental study in mice by Ahn et al., has shown the importance of meningeal lymphatic vessels at the skull base for absorption of CSF. [105] This study showed that CSF drainage is highly dependent on meningeal lymphatic vessels at the skull base. This may be of particular importance in patients with CMI, since crowding of the PF might then impede CSF absorption into the meningeal lymphatic vessels of the skull base. This could suggest that CMI does not only cause an obstruction of free CSF flow, but also of CSF absorption. Recent advances in MR imaging allow non-invasive visualization of CSF flow and absorption, and could tell us more about how this functions in sCS children.[116,117]

In this review we have theorized about the function and importance of emissary veins. Methods such as ultrasound could be used to evaluate the flow in emissary veins, as has been done to evaluate flow in dural sinuses,[118] and might be very helpful in determining the function of emissary veins and the part they play in maintaining ICP.

There are two main limitations of this scoping literary review. First, we used the Monro-Kellie hypothesis as a framework to help understand the mechanisms at work in ICH in sCS children. The Monro-Kellie hypothesis is not fact however, and there are people that disagree with it.[119,120] The reason we still do not understand the mechanisms at work in ICH in sCS children, could be because it does not follow the hypothesis based on the findings of Monro and Kellie, but some other mechanism. Second, we excluded articles if the abstract did not mention anything about ICH (or indicators/parameters for ICH) in sCS patients. It is possible we have excluded some studies that had valuable information in the article that were not mentioned in the abstract. However, we tried to minimize the possibility of missing these types of articles by also going through reference lists of relevant articles and literature reviews.

Conclusion

Development of ICH is influenced by different aspects of sCS: craniocerebral disproportion when there is a deflection of skull growth, OSA, venous hypertension, obstruction of CSF flow, and possibly reduced CSF absorption. To what degree these issues are present, differs greatly per syndrome. This makes studies that report results per syndrome very valuable. Evidence of ICH in sCS patients is determined invasively by ICP measurements.

Non-invasive methods that have shown to be good alternatives are fundoscopy and a combination of RNFL thickness and maximal anterior retinal projection on OCT. Another method that seems promising, but requires more investigation, is the ONSD as measured on MR-imaging.

Evidence of brain impairment has mainly been shown through evaluation of cognition and behavior. Prevalence of abnormalities in cognition and behavior differs amongst the different craniosynostosis syndromes. Whether outcome is dependent on genetic origin or ICH is difficult to determine. Problems in cognition and behavior seem to be mostly due to genetic origin, but a further decline can occur if ICH is left untreated. Two outcome measures that are strongly indicated to be the consequence of ICH, are cortical thinning and problems in visual function.

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Supplemental File 1:
10-03-2022 search strategy
Intracranial pressure craniosynosthosis

Embase.com (1971-)	1615	1603
Medline ALL Ovid (1946-)	1197	186
Web of science Core Collection (1975-)	722	28
Cochrane CENTRAL register of trials (1992)	3	1
Google scholar	200	74
Total	**3737**	**1892**

Embase.com

('intracranial pressure'/de OR 'intracranial pressure monitoring'/de OR 'intracranial pressure monitoring device'/de OR 'hydrocephalus'/exp OR 'Arnold Chiari malformation'/de OR 'intracranial hypertension'/exp OR 'brain edema'/de OR 'brain perfusion'/de OR 'brain blood flow'/de OR Papilledema/de OR 'sleep disordered breathing'/de OR (((intracranial* OR intra-cranial* OR intracerebr* OR intra-cerebr* OR brain) NEAR/3 (pressure* OR tension OR hypertension* OR oedema OR edema OR compress* OR restrict*)) OR icp OR hydrocephal* OR (ventric* NEAR/6 dilatat*) OR (aqueduct* NEAR/6 stenosis) OR Chiari OR ventriculomegal* OR (crani* NEAR/6 cerebr* NEAR/6 disproportion*) OR ((brain OR cerebral*) NEAR/3 (perfusion* OR 'blood flow')) OR (sleep NEAR/3 disorder* NEAR/3 breath*) OR osas OR (obstructi* NEAR/3 sleep) OR OSA OR Papilledem* OR Papilloedem*):ab,ti) AND ('craniofacial synostosis'/de OR 'acrocephalosyndactyly'/de OR 'Crouzon syndrome'/de OR (synostosis/de AND ('cranial suture'/de OR 'skull suture'/de OR suture/de)) OR (((crani* OR prematur* OR suture* OR syndrom* OR corona* OR lambdoid*) NEAR/3 synosto*) OR craniosynosto* OR craniostenos* OR (prematur* NEAR/6 (cranial* OR corona* OR lambdoid*) NEAR/6 suture*) OR acrocephalosyndact* OR ((acrocephalo OR acro) NEXT/1 (syndact* OR cephalosyndact*)) OR apert OR Crouzon OR muenke OR (Saethre NEAR/3 Chotzen) OR (Pfeiffer NEAR/3 syndrome) OR pansynostosis OR cloverleaf):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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("Intracranial Pressure"/ OR exp "hydrocephalus"/ OR "Arnold-Chiari Malformation"/ OR "Intracranial Hypertension"/ OR "brain edema"/ OR "brain perfusion"/ OR exp brain/bl OR exp brain/bs OR Papilledema/ OR exp "Sleep Apnea Syndromes"/ OR (((intracranial* OR intra-cranial* OR intracerebr* OR intra-cerebr* OR brain) ADJ3 (pressure* OR tension OR hypertension* OR oedema OR edema OR compress* OR restrict*)) OR icp OR hydrocephal* OR (ventric* ADJ6 dilatat*) OR (aqueduct* ADJ6 stenosis) OR Chiari OR ventriculomegal* OR (crani* ADJ6 cerebr* ADJ6 disproportion*) OR ((brain OR cerebral*) ADJ3 (perfusion* OR "blood flow")) OR (sleep ADJ3 disorder* ADJ3 breath*) OR osas OR (obstructi* ADJ3 sleep) OR OSA OR Papilledem* OR Papilloedem*).ab,ti.) AND (exp "Craniosynostoses"/ OR "Craniofacial Dysostosis"/ OR (synostosis/ AND ("Cranial Sutures"/ OR sutures/)) OR (((crani* OR prematur* OR suture* OR syndrom* OR corona* OR lambdoid*) ADJ3 synosto*) OR craniosynosto* OR craniostenos* OR (prematur* ADJ6 (cranial* OR corona* OR lambdoid*) ADJ6 suture*) OR acrocephalosyndact* OR ((acrocephalo OR acro) ADJ (syndact* OR cephalosyndact*)) OR apert OR Crouzon OR muenke OR (Saethre ADJ3 Chotzen) OR (Pfeiffer ADJ3 syndrome) OR pansynostosis OR cloverleaf).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

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Web of science

AB=(((((intracranial* OR intra-cranial* OR intracerebr* OR intra-cerebr* OR brain) NEAR/2 (pressure* OR tension OR hypertension* OR oedema OR edema OR compress* OR restrict*)) OR icp OR hydrocephal* OR (ventric* NEAR/5 dilatat*) OR (aqueduct* NEAR/5 stenosis) OR Chiari OR ventriculomegal* OR (crani* NEAR/5 cerebr* NEAR/5 disproportion*) OR ((brain OR cerebral*) NEAR/2 (perfusion* OR "blood flow")) OR (sleep NEAR/2 disorder* NEAR/2 breath*) OR osas OR (obstructi* NEAR/2 sleep) OR OSA OR Papilledem* OR Papilloedem*)) AND ((((crani* OR prematur* OR suture* OR syndrom* OR corona* OR lambdoid*) NEAR/2 synosto*) OR craniosynosto* OR craniostenos* OR (prematur* NEAR/5 (cranial* OR corona* OR lambdoid*) NEAR/5 suture*) OR acrocephalosyndact* OR ((acrocephalo OR acro) NEAR/1 (syndact* OR cephalosyndact*)) OR apert OR Crouzon OR muenke OR (Saethre NEAR/2 Chotzen) OR (Pfeiffer NEAR/2 syndrome) OR pansynostosis OR cloverleaf)) NOT ((animal* OR mice OR mouse OR rat OR rats OR murine OR rabbit*) NOT (human* OR patient* OR child*))) AND DT=(article) AND LA=(english)

Google scholar

"intracranial|intracerebral pressure|tension|hypertension"|hydrocephalus "cranial|cranio synostosis"|craniosynostosis|craniostenosis|acrocephalosyndactyly|apert|Crouzon|muenke|"Saethre Chotzen"

CHAPTER 8

GENERAL DISCUSSION

General Discussion

In trying to understand the mechanisms at work for maintaining ICP the most commonly held theory is that of Monro-Kellie.[1-3] It sees the cranial vault as a closed box, filled with brain, CSF and blood. Since the cranial vault is not compliant, an increase in one of the three compartments has an effect on the other two and on the intracranial pressure. Syndromic craniosynostosis (sCS) has different ways of impacting this dynamic. First, the cranial vault itself. Craniocerebral disproportion caused by a too small cranial vault as a result of premature closure of vault sutures, was for a long time seen as the main reason ICH occurred in sCS patients. It has been shown however, that intracranial volume in sCS patients is mostly normal and that brain volume is normal,[4,5] except in cases of pansynostosis.[6] A falling off of the skull growth curve however, has been shown to be a very important factor associated to ICH, and has shown to occur mostly around the ages of 3-5 years.[7]

sCS is thought to influence the CSF compartment in multiple ways. First, the small posterior fossa and foramen magnum can obstruct the free flow of CSF between intracranial and extracranial compartments of the central nervous system, especially when there is crowding of the posterior fossa, tonsillar herniation or Chiari malformation type I (CMI), causing an intracranial accumulation and ultimately hydrocephalus. Second, is through venous hypertension. The abnormal venous anatomy can restrict outflow and cause venous hypertension.[8-10] CSF pressure normally needs to be slightly higher than venous pressure to maintain a pressure gradient that drives reabsorption of CSF into the venous system. Increased venous pressure could complicate CSF absorption. Recently it has been shown that a large part of CSF is absorbed into meningeal lymphatic vessels at the skull base, which drains fluid from the glymphatic system to deep cervical lymph nodes.[11,12] This site of absorption could also be affected in sCS patients with an overcrowded posterior fossa, or CMI. Third, is the theory of CSF overproduction. FGFR2 has been shown to be present in the choroid plexus,[13] and mutations in FGFR2 could hypothetically give rise to CSF overproduction, leading to increases in CSF.

The blood compartment is impacted by associated conditions such as obstructive sleep apnea (OSA). During REM sleep muscles of the pharyngeal wall relax. This is why children with OSA are more likely to have obstructive apneas during REM sleep, than during any other sleep phase. Since sCS children already have a narrower upper airway due to midface hypoplasia and/or mandibular hypoplasia, pharyngeal collapse and obstruction can occur more easily. This is thought to lead to hypercapnia, which causes vasodilation of cerebral arteries. To maintain cerebral perfusion pressure, arterial blood pressure will rise, and more blood will travel to the brain, increasing the volume of blood in the cranial vault.[7] The physiological increase in CBF due to increased brain activity during REM sleep, makes REM sleep a sleep phase that often shows increased ICP in sCS patients, even without OSA.[14] It is thought that the abnormal venous anatomy, in particular jugular foramen stenosis, stymies the outflow of blood, increasing the risk of ICH. Prominent occipital emissary veins seem to be a way to try to increase output capacity.[9] When blood inflow increases go beyond the capacity for outflow, this could lead to increases in ICP.

Intracranial venous hypertension occurs more often in sCS and sagittal suture synostosis patients. Presence of intracranial venous hypertension is difficult to prove, because it cannot be measured directly, without invasive measurement. Therefore, in **Chapter 2** we assessed the cerebral blood flow velocity and blood wave form in sagittal suture synostosis and sCS patients

and compared it with control subjects using Doppler ultrasound of the superior sagittal sinus (SSS) and the internal cerebral vein (ICV). We found that before surgery, craniosynostosis patients had a lower SSS flow velocity, and this increased after vault expansion. In internal cerebral vein velocity there was no difference to controls, before or after surgery.

A lower SSS flow velocity has been seen in children with achondroplasia and hydrocephalus, and was thought to be the result of venous outflow obstruction.[15] We think that in sCS patients the premature closure of cranial sutures may in itself be related to reduced SSS flow velocity, and thereby to reduced cerebral venous drainage from the superficial system, but is not related to ICV flow velocity. This indicates that closed cranial sutures affect superficial venous drainage, rather than deep venous drainage.

There are very few studies to which we can compare our data. The only other study we have found was by Mursch et al.[16] who examined venous intracranial hemodynamics in craniosynostosis patients, and found a higher SSS flow velocity in craniosynostosis patients. The location of measurement was very different in their study however. They measured the SSS flow velocity at the site of constriction, which might explain the difference in findings. Recently, a study from our center, focused on dural sinus volume showed increased volume of the straight sinus in sCS children with ICH, but no significant difference of the superficial sinuses, when compared to sCS children without ICH.[17] This suggests a redistribution of venous blood in cases of ICH. One of the theories the authors offer is that superficial sinuses are restricted by the bones of the skull (indicated by thinning of the bone superficial to the dural sinuses), whereas the straight sinus is not, allowing for the straight sinus to increase in volume. These results might indicate restriction of dural sinuses by the skull bones and supports our results indicating that prematurely closed cranial sutures affect superficial venous drainage.

We then wanted to examine arterial cerebral blood flow (CBF) in sCS patients and compare it to that of controls subjects in **Chapter 3**, using a relatively new magnetic resonance imaging (MRI) sequence called arterial spin labeling (ASL). ASL estimates CBF by using the body's own blood as tracer, eliminating the need for administering intravenous contrast substances. This makes this MRI sequence particularly suitable for children. In this study, we determined that there were three major differences in the CBF of children with sCS and normal controls. First, untreated sCS children <1 year old had a lower than expected CBF. Second, with surgical vault expansion and with age their CBF eventually reached a level within the range of CBF of controls. Third, the early childhood peak in CBF occurred at the age of 5-6 years in sCS patients, while this occurs at around 3-4 years of age in controls.

Our first finding that CBF is lower in untreated sCS children before surgical vault expansion is interesting because this can be assumed to be the effect of the craniosynostosis syndrome itself, without any intervention. Our second finding, that CBF normalizes to the values close to that of control subjects could be due to the surgical intervention of cranial vault expansion, but could also be the natural consequence of age and development. This study could not determine which of these two was the cause of the normalization of CBF after 3 years of age. Similar studies determining CBF in a different population of untreated sCS patients could give us more clarity on this subject.

Our third finding, that the physiological childhood peak in CBF occurred at a later age in sCS children (5-6 years of age) than in control subjects (3-4 years of age) is a new observation and may be a piece of the puzzle of ICH in sCS children. The age of 5-6 years is the time at which sCS children often develop ICH. It could be that venous outflow cannot keep up with the peak in CBF

inflow due to the abnormal venous anatomy that is often present in sCS children. This age period of a peak in CBF maturational profile might well be a vulnerable period for these children, due to a limit in drainage capacity.

Unlike the differences in CBF between sCS and controls, a recent study from our center showed no such differences between trigonocephaly patients and controls.[18] This aligns with the low risk for ICH, and normal intracranial volume trigonocephaly patients are known to have.[19,20]

In clinical practice these studies have added to the realization of the importance of venous hypertension in ICH. Presence of many, or many prominent emissary veins, or emissary veins with palpable thrills, are closely followed. We believe these emissary veins may function as a way of increasing intracranial venous outflow capacity, and that they help maintain a careful balance in ICP. We follow patients for signs that might disturb this balance, like deviation of their skull growth curve or development of OSA, and when surgery is indicated, we try to maintain the emissary veins.

Clinical studies

Since OSA is a major player in causing ICH in children with Apert and Crouzon syndrome, treatment of moderate and severe OSA is a crucial part of preventing and treating ICH. In **Chapter 4** we used upper airway endoscopy in children with Apert and Crouzon syndrome and found that OSA is often caused by obstructions on multiple levels. We also found that upper airway assessments following the system of Bachar et al.[21] are significantly associated with severity of OSA and determines which patients could benefit from mandibular advancement in addition to their midface advancement. Treating Apert and Crouzon children with a midface advancement, and mandibular advancement if indicated, reduces the upper airway obstruction, and OSA severity.

This study shows the importance of performing upper airway endoscopy before intervention for OSA. Since children with Apert and Crouzon syndrome often have midface hypoplasia, midface advancement is often the treatment of choice in these children when severe OSA is present. However, it may not successfully relieve the symptoms if levels of obstructions are not first assessed using upper airway endoscopy. We compared two scoring systems of upper airway obstructions and determined if they were associated with degree of OSA. Severity score determined using the scoring system by Bachar et al. correlated significantly with the degree of OSA. The VOTE scoring system is commonly used in adults, and does not evaluate obstructions of the nose/nasopharynx.[22] The VOTE scoring system was not significantly associated with OSA severity. Bachar's severity index decreased after midface advancement and/or mandibular distraction, due to decrease in the number of levels of obstruction, but also due to decrease in severity of obstruction.

In patients with severe OSA all patients showed substantial decrease in severity, however, mild/moderate OSA remained. As became clear in during the 2019 International Society of Craniofacial Surgery pre-conference course, solely performing midface advancement resulted in persistent reliance on tracheostomy in 30-40% of patients. Other craniofacial centers have reported persistent severe or moderate/severe OSA, or persistent reliance on tracheostomy after midface advancements.[23,24] This might be due to significant obstructions at the tongue base, these obstructions might be decreased by mandibular advancements. Over the course of this study the importance of obstructions at the level of the tongue base became clear to us, partly due to two

children with a complete obstruction at tongue base. This has led to a change in our policy, where based on endoscopy findings, these two patients underwent a midface advancement as well as a mandibular advancement. This has led to substantial reduction of their OSA, which would have been unlikely if midface advancement alone had been done. Clinically this study has led to a change in our policy. We now perform upper airway assessments to determine levels of obstruction and perform midface and, if necessary, mandibular distraction in the same session.

When Chiari I Malformation occurs in sCS patients, physicians often perform neurologic examinations to determine if there are any neurological problems as a consequence of CMI. Neurological problems can then easily be attributed to CMI. It is not known however, how often and what types of neurological problems occur in different craniosynostosis syndromes and if the found neurologic problems are the consequence of CMI or consequence of the syndrome itself. In **Chapter 5**, we prospectively performed neurological assessments and brain imaging, as part of protocol. This resulted in a more complete overview of the types of neurological deficits sCS patients have, since in most studies neurological assessments are done only on clinical indication, i.e. when there are complaints, or when CMI and/or syringomyelia (SM) is found on brain imaging. We found that neurologic problems occur very often in sCS patients, and that there is no difference in how often they occur in sCS patients with and without CMI and/or SM. Neurological deficits appear to be part of their syndrome and represent intrinsic brain disorders, which can then be further influenced by CMI. It appears to be more valuable to repeat neurological assessments, to determine changes and deterioration in neurological deficits.

Along with big differences between syndromes in prevalence of CMI and of SM, we found equally big differences between syndromes in the types of neurological problems that occur most. The neurologic profile per syndrome showed that neurological deficits occurred often in Apert syndrome, while CMI and/or SM did not. Their neurological problems therefore seem to be part of their syndrome, rather than a consequence of CMI and/or SM. Crouzon syndrome had the widest variety of neurological deficits, and they were the only patients who had SM. The results appear to suggest that in Crouzon patients, CMI and/or SM adds to their neurological deficits. This is underlined by Crouzon patients being the only patients who needed surgery because of their neurological problems. Saethre-Chotzen syndrome on the other hand, showed to have a very mild neurological profile. Saethre-Chotzen patients had the lowest prevalence of neurological deficits, small variety of combinations and no occurrence of CMI and/or SM. This suggests that TWIST1 changes might have less effect on the nervous system than FGFR2 mutations. Diffusion tensor imaging studies on sCS patients have shown that Saethre-Chotzen patients' white matter integrity was closest to that of control subjects, which supports this theory.[25] Furthermore, genetic studies have shown that FGFRs (and thus FGFR2 mutations) come into play earlier in the signaling pathway of cranial development than TWIST1 (and thus TWIST1 mutations).[26] This could explain why the consequences of FGFR2 mutations are more extensive than TWIST1 mutations.

A study by Cinalli et al.[27] has found similar results on cerebellar position in Crouzon patients, where 72% had chronic tonsillar herniation and 16% had SM. Neurological signs were present in 19% of Crouzon patients with chronic tonsillar herniation. This is a lower percentage than we found in our population of Crouzon patients. However, the study by Cinalli et al. does not discuss what these neurological signs were specifically, nor what neurological problems Crouzon patients without chronic tonsillar herniation had. MRIs in their study were performed when patients had complaints, not prospectively. Our study therefore provides a more complete image of prevalence

of CMI and presence of neurological deficits in sCS patients and how they relate to the presence of CMI and SM.

We now know that neurological problems are highly prevalent in most syndromes, irrespective of tonsillar position. In practice we now regularly perform neurological assessments, to determine if there are changes in severity of their neurological deficits. We do keep a closer eye on Crouzon patients, whose neurological problems might be more often influenced by their CMI and/or syringomyelia. These patients warrant a closer follow up with regular MRI and neurological assessments.

Through these studies in sCS children, it has become clear that Crouzon patients make up a diverse group of patients with a very wide range in phenotypic severity. Some patients hardly have any problems, and for example only present at the outpatient clinic at 4 or 5 years old, while others present within several days after birth with severe abnormalities of the skull vault and brain, and require multiple surgeries because of hydrocephalus or ICH. To elucidate how ventricle size and tonsillar herniation relate to each other, in **Chapter 6** we examined our own cohort of Crouzon patients and determined which attributes were associated with ventricle size and hydrocephalus.

What is striking is that Crouzon patients seem to have severe intracranial abnormalities shown on brain imaging, such as CMI, SM, and hydrocephalus or ventriculomegaly, but clinically the cognitive development of Crouzon patients is rarely affected. In Apert patients structural cerebral anomalies and cognitive impairment occur more often. FGFR2 mutations in Apert syndrome occur on domains IgII and IgIII, and they increase affinity and broaden specificity of FGF-ligand binding.[28] The majority (94%) of FGFR2 mutations in Crouzon syndrome occur on IgIII, the remainder on seven other exons of the gene. On IgIII the mutations cause constitutive activation of receptor monomers by covalent cross-linking.[29] This shows that while both Apert and Crouzon patients have mutations in FGFR2, the effect of their respective mutations on cerebral development differs substantially.[30] These differences in outcome between syndromes, show the importance of separating the compound group of sCS patients by their syndrome. As long as ICH is absent or treated when occurring, differences in presentation of the various syndromes are more likely related to their genetic background than to ICH.

Through this thesis we have aimed to answer the question of how sCS relates to ICH. By examining different aspects of pathologic processes in sCS we have attributed to understanding how ICH develops in sCS (see **Figure 1**). In **Chapter 7** we evaluate the literature in a scoping review to determine how ICH is determined in sCS patients and we categorize the literature by the Monro-Kellie hypothesis to expand our understanding of how the pathologic processes in sCS contribute to ICH. We found that there was much diversity in how different craniofacial centers determine ICH. Even when using the gold standard of direct ICP measurement different craniofacial centers use different cut-off values, durations of measurement, and some measure while patient is under anesthesia. This lack of uniformity is regrettable, since sCS is so rare, being able to combine or compare data from different craniofacial centers would be very valuable.

Of the non-invasive methods of determining ICH, one of the most utilized is presence of papilledema, as determined through fundoscopy. Studies that examine cognition and behavior were useful in showing evidence of brain impairment. Determining whether brain impairment is more likely due to genetic origin or to ICH remains difficult. The studies we found indicate that brain impairment is mostly due to genetic origin, however, a further decline can occur if ICH is left untreated. We found that many studies combine all sCS data, most likely to achieve large enough

patient populations to do statistical testing. This is regrettable because by doing this the distinct differences between the individual syndromes are lost. More standardization in how results are reported in research about sCS might lead research groups to be able to combine and compare data more easily, resulting in bigger patient populations, while still maintaining the distinctions amongst the individual syndromes.

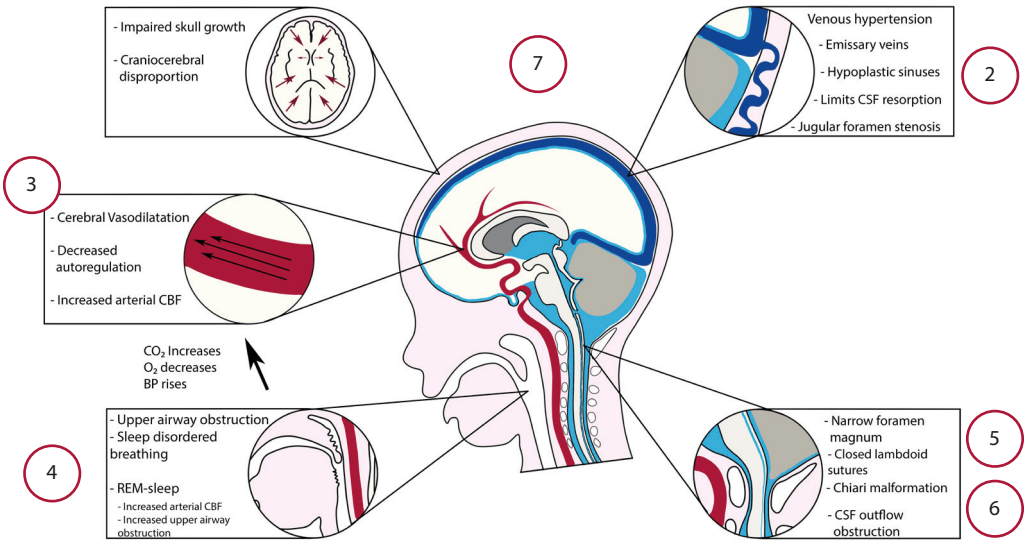

Figure 1. Pathophysiological processes concerning intracranial hypertension in children with syndromic craniosynostosis. *The numbers in red circles represent the chapters in this thesis and are placed near the areas to which they have contributed.*

Future perspectives

Questions that remain in clinical practice regard recognizing which patients are at risk for ICH. The issue of ICH in syndromic craniosynostosis is complex. It is clear that not all syndromes are affected to the same degree with presence of ICH. Our experience and the many studies on syndromic craniosynostosis, show big differences in the risk factors for ICH between different craniosynostosis syndromes. Studies that focus on specific syndromes, and syndrome specific risk profiles can be useful resources in treating the individual patient. This might be especially useful in Crouzon syndrome, where there is a large range in severity of phenotype; the key might be in their genetic code. Because craniosynostosis syndromes are so rare, multicenter studies are needed to create genetic profiles for syndromes such as Crouzon syndrome.

As more possibilities in imaging become available with advances in technology, this allows for more research in areas that thus far have been difficult to research. As such, we have used the relatively novel technique of arterial spin labelling (ASL) to estimate cerebral blood flow (CBF). Newer ASL sequences can more accurately estimate the CBF, minimizing the issue of CSF contamination. Measurements in our study were done by hand. Better programming will allow for automated placing of ROI's. Until now this has been problematic in sCS children, because they

often have cerebral abnormalities. Recent advances facilitate automated measuring CBF and would permit its use in a clinical setting. Our patient population undergoes vault expansion within their first year of life. To determine what problems in sCS children might be due to the syndrome itself, studies examining CBF in a population of older sCS patients who did not undergo this standard vault expansion would be very valuable. We could then see if the observed normalization of CBF after 3 years of age, is due to surgical intervention, or natural consequence of age and development.

Different craniofacial centers have held different schools of thought on whether preventative skull vault expansion to try to prevent ICH is wise.[31] This has led to much research to try to determine if ICH results in cognitive or neurological or physical impairment. A recent study that has provided support for this preventative treatment strategy, and is also a good example of the potential of automated measurements, is the study by Wilson et al.[32] Wilson et al. used automated measurements of cortical thickness of sCS children. They showed that children who had had papilledema, or hydrocephalus had thinner cortical thickness than sCS children who had not. The authors postulate that since papilledema occurs as a consequence of prolonged exposure to ICH, that by the time ICH is detectable through presence of papilledema, cortical neurons may have already sustained sufficient stress to result in abnormal remodeling, leading to cortical thinning. This supports the treatment strategy to preventatively perform skull vault expansion, rather than to wait for signs of ICH by presence of papilledema.

For future studies it would be interesting to see how cortical thickness relates to formal IQ testing, or neurological assessments.

A lot is assumed, but very little is known about CSF production, flow and absorption in sCS patients. Recently, in animal studies, it has been shown that a large part of CSF absorption occurs in dural lymphatic vessels in the skull base.[11] Studies examining CSF absorption in the skull base of sCS patients would be very valuable, especially in patients who have a crowded posterior fossa, TH or CMI, to determine whether absorption is reduced in these situations, as we believe. Promising new techniques like Time Spatial Inversion Pulse (Time-SLIP) and time static tagging and mono contrast preservation (Time-STAMP) use the body's own CSF as tracer and can visualize CSF dynamics,[33,34] and might be able to give us answers to these questions.

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CHAPTER 9

SUMMARY

Summary

The aim of this thesis is to better understand aspects of syndromic craniosynostosis (sCS), their treatment methods and how they relate to intracranial hypertension (ICH).

In this thesis we utilize the Monro-Kellie hypothesis of the skull as a box with three compartments: brain, blood and cerebrospinal fluid. **Chapters 2** and **3** focus on the blood compartment. **Chapter 2** examines venous cerebral blood flow (CBF) through ultrasound. In this study we found that venous flow in the superior sagittal sinus was decreased, while the venous flow of the deeper located internal cerebral vein was not decreased in patients with prematurely closed skull sutures. This indicates that superficial venous drainage is impacted by prematurely closed cranial sutures, while the deeper venous drainage is not. **Chapter 3** examines the CBF in sCS patients and controls using an MRI sequence called arterial spin labeling. This study found that the CBF is lower in sCS patients than in controls before the age of 1 year. With age and treatment CBF normalizes to that of controls. It is not clear if this normalization is due to normal aging process in sCS patients or due to skull vault expansion.

Chapter 4 and **5** discuss treatment methods in sCS patients. **Chapter 4** examined the follow up of children with sCS by determining the presence of neurological deficits, and how they relate to Chiari Malformation type I (CMI). We found that neurological deficits are present in sCS children irrespective of CMI. What appears to be more valuable than the mere presence of neurological deficits, is following up on neurological deficits, so that a deterioration can be detected to guide treatment. **Chapter 5** examined surgical treatment for obstructive sleep apnea (OSA) in Apert and Crouzon patients. In these children OSA is often caused by obstructions on multiple levels of the upper airways. Some institutions aim to treat this by routine midface advancement, targeting one level only. By using upper airway endoscopy, we found that the location and degree of upper airway obstructions were related to the severity of their OSA. We also found that after surgery there was improvement of their degree of upper airway obstruction and OSA. In cases where there were severe obstructions on multiple levels, they were treated in the same setting. Addressing multilevel obstructions improved the degree of obstruction and their OSA.

Chapter 6 focuses on Crouzon syndrome. The phenotype of Crouzon patients is very diverse. It ranges from very mild to all risk factors for ICH. In this study we examined how ventricle size and tonsillar position change over time. We found that ventricular size was large at onset in about a third of Crouzon patients, this prevalence increases to nearly half shortly after cranial vault expansion. It then normalizes over time and following treatment. Ventricular size was associated with head circumference and tonsillar herniation. Tonsillar herniation was present in 11% of patients at onset, its prevalence increased to 46% over time. Tonsillar herniation was associated with closed lambdoid sutures and ventricle size. The most common sequence of events was that ventriculomegaly occurred first, followed by tonsillar herniation, however, we cannot claim there is a causal relationship.

Chapter 7 reviews the literature on ICH in sCS patients. We found that there is a wide variation in how studies about ICH in sCS patients are conducted, which parameters they use for indirect determination of ICH, but also wide variation in the gold standard of direct intracranial pressure (ICP) measurement. ICH as determined by direct ICP measurement was present in 44% of sCS patients. When determined by indirect methods, ICH was present in 37% of sCS patients. Many studies examine different aspects that might cause ICH in sCS patients. Such as brain volume, OSA, hydrocephalus, and CMI.

We tried to find the answer to what extent outcome in sCS patients is due to genetic origin, ICH or a problem in other processes. While it remains a difficult question to answer, we found studies that shed light on this by examining IQ, neurological aspects, and brain imaging.

One thing that became clear in this review, is that differences in how research groups research matters and how they present the results concerning ICH in sCS, make it difficult to compare the results. This is regrettable, because being able to compare results between different research groups might provide us with deeper insight into aspects of ICH in sCS, and insights on optimal surgery timing: when there are signs of ICH, or preventatively before ICH occurs. A consensus in the craniofacial research community about how research concerning ICH in sCS should be reported would go a long way to achieving new and valuable insights.

CHAPTER 10

SAMENVATTING

Samenvatting

Het doel van dit proefschrift is het beter begrijpen van de verschillende aspecten van syndromale craniosynostose (sCS), en hoe die aspecten in relatie staan met intracraniële druk en met de behandelmethoden.

In dit proefschrift gebruiken wij de Monro-Kellie hypothese die de schedel als een doos ziet met drie compartimenten: hersenen, bloed en liquor. **Hoofdstukken 2** en **3** richten zich op het bloed compartiment. In **hoofdstuk 2** onderzochten wij cerebrale veneuze bloedstroom door middel van echo. In deze studie vonden wij dat in patiënten met craniosynostose de veneuze bloedstroom in de sinus sagittalis superior verminderd was, terwijl de veneuze bloedstroom van de dieper gelegen vena cerebralis interna niet verminderd. Dit indiceert dat oppervlakkige veneuze drainage aangedaan is bij te vroeg gesloten schedelnaden, terwijl de dieper gelegen veneuze drainage dat niet is.

Hoofdstuk 3 kijkt naar de cerebrale bloedstroom in sCS patiënten en controle patiënten door middel van een MRI-sequentie genaamd arterial spin labeling. Deze studie vond dat de cerebrale bloedstroom lager was in sCS patiënten dan in controle patiënten bij een leeftijd jonger dan 1 jaar. Met het ouder worden en met behandeling normaliseerde de cerebrale bloedstroom zich naar dat van controles. Het is niet duidelijke of deze normalisatie het gevolg is van het normale verouderingsproces in sCS patiënten, of het gevolg is van chirurgische behandeling zoals verruiming van de schedel.

Hoofdstukken 4 en **5** gaan over de behandelmethodes in sCS patiënten. In **hoofdstuk 4** onderzochten we de follow-up van kinderen met sCS door te kijken naar de aanwezigheid van neurologische afwijkingen, en hoe die relateert aan Chiari malformatie type I (CMI). We vonden dat neurologische afwijkingen aanwezig waren bij kinderen met sCS, ongeacht de aanwezigheid van CMI. Om te bepalen wanneer chirurgisch ingrijpen nodig is, lijkt het belangrijker te zijn om de neurologische afwijkingen in de tijd te volgen, zodat een knik in het neurologisch functioneren gedetecteerd kan worden. **Hoofdstuk 5** betrof de chirurgische behandeling voor obstructief slaap apneu (OSA) in Apert en Crouzon patiënten. In deze kinderen wordt de OSA vaak veroorzaakt door obstructies op multipele niveaus van de bovenste luchtwegen. Sommige craniofaciale centra beogen dit te behandelen door routinematig een midface advancement uit te voeren, waarmee enkel één niveau behandeld wordt. Door endoscopie uit te voeren van de bovenste luchtwegen, vonden we dat de locatie en mate van obstructie van de bovenste luchtwegen, gerelateerd was aan de mate van ernst van hun OSA. We vonden ook dat er een verbetering van de mate van obstructie van de bovenste luchtwegen en van hun OSA na chirurgische behandeling. Wanneer patiënten ernstige obstructies hadden op multipele niveaus, werden de die multipele niveaus in dezelfde operatie behandeld. Om op deze manier de multipele obstructies behandelen, verbeterde aanzienlijk hun mate van obstructie en hun OSA.

Hoofdstuk 6 gaat over Crouzon syndroom. Het fenotype van Crouzon patiënten loopt erg uiteen. Het fenotype reikt van zeer milde afwijkingen, naar alle risicofactoren voor ICH. In deze studie hebben we gekeken naar hoe de grootte van de laterale ventrikels en de positie van de cerebellaire tonsillen veranderen over de tijd. We vonden dat bij een jonge leeftijd de ventrikels vergroot waren in ongeveer een derde van de Crouzon patiënten. Deze prevalentie neemt toe tot bijna de helft van de patiënten vlak na schedel expansie. Hierna normaliseert het over de tijd en met behandeling. Ventrikel grootte was geassocieerd met hoofd omtrek en met tonsillaire herniatie. Tonsillaire herniatie was aanwezig in 11% van de patiënten bij jonge leeftijd, mettertijd

nam de prevalentie toe tot 46%. Tonsillaire herniatie was geassocieerd met gesloten lambdoid naden en met ventrikel grootte. De meest voorkomende volgorde was dat ventriculomegalie eerst aanwezig was, gevolgd door tonsillaire herniatie. Wij konden geen causaal verband aantonen.

In hoofdstuk 7 hebben wij een review van de literatuur gedaan over studies die gaan over de aspecten van ICH bij sCS patiënten. We vonden dat er een grote variatie was in hoe studies over ICH in sCS patiënten uitgevoerd worden, welke parameters zij gebruikten voor direct (door middel van invasieve intracraniële drukmeting) en indirect vaststellen van ICH. ICH werd vastgesteld door middel van directe intracraniële drukmeting in 44% van de sCS patiënten. ICH werd vastgesteld door middel van indirecte methoden in 37% van de sCS patiënten. Veel studies bestuderen verschillende aspecten die misschien ICH veroorzaken in sCS patiënten, zoals hersenvolume, OSA, hydrocephalus en CMI.

We probeerden een antwoord te vinden op de vraag in hoeverre de uitkomst in sCS patiënten komt door een genetische oorzaak, ICH of een probleem in andere processen. Hoewel dit nog steeds een moeilijke vraag blijft om te beantwoorden, hebben we studies gevonden die hier meer licht op schijnen door te kijken naar IQ, neurologische aspecten en beeldvorming van de hersenen.

Iets wat duidelijk werd in dit review, is dat de variabiliteit in hoe verschillende onderzoeksgroepen onderzoek doen en hoe zij hun resultaten presenteren, het moeilijk maakt om de resultaten te vergelijken. Dit is spijtig, omdat het kunnen vergelijken van resultaten van verschillende onderzoeksgroepen ons dieper inzicht kan geven in aspecten van ICH in sCS. Bijvoorbeeld meer inzicht in de optimale timing voor opereren: wanneer er tekenen zijn van ICH, of juist preventief, nog vóór er sprake is van ICH. Een consensus binnen de craniofaciale onderzoeks-gemeenschap over hoe verslag gedaan wordt van onderzoek over ICH in sCS, zou kunnen zorgen voor het bereiken van nieuwe en kostbare inzichten.

APPENDICES

LIST OF PUBLICATIONS

A reliable protocol for the manual segmentation of the human amygdala and its subregions using ultra-high resolution MRI.
Entis JJ, **Doerga P**, Barrett LF, Dickerson BC.
Neuroimage. 2012;60(2):1226-1235.

The burned ear; possibilities and challenges in framework reconstruction and coverage.
Bos EJ, **Doerga P**, Breugem CC, van Zuijlen PP.
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Doerga PN, Spruijt B, Mathijssen IM, Wolvius EB, Joosten KF, van der Schroeff MP.
J Craniomaxillofac Surg. 2016;44(2):191-196.

The effect of early fusion of the spheno-occipital synchondrosis on midface hypoplasia and obstructive sleep apnea in patients with Crouzon syndrome.
Driessen C, Rijken BF, **Doerga PN**, Dremmen MH, Joosten KF, Mathijssen IM.
J Craniomaxillofac Surg. 2016;44(2):191-196.

Pilot study of intracranial venous physiology in craniosynostosis.
Cornelissen MJ, de Goederen R, **Doerga P**, et al.
J Neurosurg Pediatr. 2018;21(6):626-631.

Cerebral blood flow in children with syndromic craniosynostosis: cohort arterial spin labeling studies.
Doerga PN, Lequin MH, Dremmen MHG, et al.
J Neurosurg Pediatr. 2019:1-11.

Neurological deficits are present in syndromic craniosynostosis patients with and without tonsillar herniation.
Doerga PN, Rijken BFM, Bredero-Boelhouwer H, et al.
Eur J Paediatr Neurol. 2020.

The Course and Interaction of Ventriculomegaly and Cerebellar Tonsillar Herniation in Crouzon Syndrome over Time
Doerga PN, de Planque CA, Erler, NS, van Veelen MLC, Mathijssen IMJ
Plast and Reconstr Surg Glob Open. 2022; 10(1):e3979.

CURRICULUM VITAE

Priya Doerga was born in the Hague and raised in Zaandam. She completed medical school at the VU University in Amsterdam, completed a scientific internship at Harvard Medical School in Boston, and completed an elective rotation in Plastic Surgery at Mount Sinai in New York.

After a short while teaching first year medical students at the VU University in Amsterdam, she started with her PhD at Erasmus MC in her first city by the Maas, Rotterdam. During this time, she became passionate about the subject of syndromic craniosynostosis.

After her time at Erasmus MC, she started as a resident not in training for ophthalmologist at the Amphia hospital in Breda, where she developed a passion for Ophthalmology. Not long thereafter, she started as a resident in Ophthalmology in her second city by the Maas, beautiful Maastricht.

PORTFOLIO

PhD Portfolio
Summary of PhD training and teaching

Name PhD student: Priya N. Doerga
Erasmus MC Department: Plastic and Reconstructive Surgery, and Hand Surgery

PhD period: 2014 - 2023
Promotor: Prof. dr. I.M.J. Mathijssen
Co-Promotors: Dr. M.H. Lequin, dr. M.L.C. van Veelen

1. PhD training

	Year	Workload (ECTS)
General courses		
- Biomedical English Writing and Communication		
- Research Integrity	2016	0.3
- Laboratory animal science		
- Introduction to Data-analysis (ESP03)	2015	1.0
- Methodology	2015	0.6
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	2015	1.0
- The basic introduction course on SPSS	2015	1.0
Specific courses (e.g. Research school, Medical Training)		
- EMRI Basic MRI physics	2014	2.0
- OpenClinica training	2014	0.3
- Basic SPSS course	2015	0.6
Seminars and workshops		
- Skillslab – Pees-hecht-workshop	2014	0.2
- Skillslab – Zenuw-hecht-workshop	2015	0.2
- Skillslab – lappen cursus	2015	0.2
- Patient Oriented Research: design, conduct, analysis and clinical implications	2015	0.3
Presentations		
- Occipitofrontal circumference predicts intracranial volume in craniosynostosis syndromes. ISCSF meeting, Tokyo, Japan	2015	1.0
- Cerebral blood flow in children with syndromic craniosynostosis: cohort arterial spin labeling studies, ESCFS meeting, Birmingham, United Kingdom; ISCSF meeting, Cancún, Mexico	2016 2017	0.3 1.0

(Inter)national conferences

- Esser course – on your nerves	2014	1.0
- Esser course – ins and outs of nose surgery	2014	1.0
- NVSCA	2014	1.0
- International conference of the congenital hand	2015	0.6
- International Society of Craniofacial Surgery (ISCFS), Tokyo, Japan	2015	1.0
- European Society of Craniofacial Surgery (ESCFS), Birmingham, United Kingdom	2016	0.3
- International Society of Craniofacial Surgery (ISCFS), Cancún, Mexico	2017	1.0

2. Teaching

	Year	Workload (ECTS)
Syndroomdiagnostiek	2015-2017	3.0
Anatomie – handen	2015-2016	2.0

Supervision

Supervising research projects third year medical students (MM), Erasmus MC	2016	5.0

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