CRANIOSYNOSTOSIS

Obstructive sleep apnea in a unifying theory for intracranial hypertension

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Craniosynostose

Obstructief slaap apneu in een alomvattende theorie voor verhoogde hersendruk

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INTRODUCTION

CHAPTER 1

Introduction

Craniosynostosis is a rare congenital disorder, characterized by the premature fusion of skull suture(s) resulting in an abnormal skull shape. A newborn's cranial vault consists of seven bones, which are separated by sutures. The main ones are the metopic, two coronal, the sagittal and two lambdoid sutures (figure 1). These sutures allow for transient skull distortion during birth, and facilitate future growth of the brain. In the first years of life, brain growth is the main incentive of skull growth. The skull sutures function as growth centers. The center of the suture contains undifferentiated cells, they proliferate and part of them undergo osteogenic differentiation to osteoblasts; they subsequently migrate to the border of the bone sheet resulting in growth of the cranial vault.[1, 2] This is an important process to allow for the brain to grow extensively in the first two years of life, during which there is a large increase in its volume. After the age of approximately six years the sutures are no longer involved in skull growth, which then takes place by resorption at the inner side of the skull and appositional growth.[3]

Children with craniosynostosis have abnormal development of the cranial vault. Normal healthy children have open sutures at birth; the posterior fontanelle closes at 2 months, followed by the metopic suture within the first year of life, the anterior fontanelle at 2 years of age, and all remaining sutures during adulthood.[4] In craniosynostosis, development is usually disrupted at 15-18 weeks of gestation[5], resulting in the agenesis or premature fusion of one or more sutures at birth. This results in a deformation of the skull due to its growth being restricted perpendicular to the affected suture, and compensatory (over)growth occurs in the other directions.[6] Premature fusion of the metopic suture results in trigonocephaly, one coronal suture in frontal plagiocephaly, both coronal sutures in brachycephaly, the sagittal suture in scaphocephaly, one lambdoid suture in pachycephaly, and involvement of all sutures is called pansynostosis (figure 1). The skull deformity that is considered the most severe, and which is usually associated with pansynostosis, is called the cloverleaf skull or kleeblattschädel.[7] A special subgroup are children with postnatal craniosynostosis, i.e., those who have open sutures at birth but in whom the sutures prematurely fuse after birth. This can still be primary, i.e., due to the genetic mutation, but it can also be secondary due to an underlying medical condition (e.g., microcephaly, hyperthyroidism, mucopolysaccharidoses, thalassemia, sickle cell anemia), medication (e.g., valproic acid), or iatrogenic (e.g., ventricular shunting).[8-10]

The incidence of craniosynostosis is 1 : 2.100-2.500[11], which means that in the Netherlands approximately 100 patients are born annually. Patients are classified as having either isolated (non-syndromic) or syndromic craniosynostosis. In 24% craniosynostosis is part of a recognized underlying syndrome[12], and there are indications that with improved genetic techniques in a number of patients with unexplained syndromic (i.e., "complex") craniosynostosis a pathogenic mutation can be found as well.[13] Syndromic craniosynostosis features not only premature skull suture fusion, but is often also associated with additional abnormalities, such as facial anomalies and malformations of the hands and feet.

The diagnosis of craniosynostosis can be difficult, partly due to unfamiliarity with the disease but also due to a wide spectrum of severity of the disease. A mild presentation might delay referral by the general practitioner or pediatrician, while this is essential for optimal treatment.[14] Additionally, craniosynostosis must be distinguished from positional (i.e., non-synostotic) skull deformities that are much more prevalent.[14] Flowcharts may help to diagnose craniosynostosis, and facilitate the referral process.[15] The diagnosis of craniosynostosis is primarily made on the basis of anamnesis and physical examination[16], and confirmed by 3D-CT scan (table 1).

An overview of the main craniosynostosis syndromes:

Apert syndrome[17] *(figure 2)*

Founder	Eugène Apert (1906)[18]: "acrocephalosyndactyly"
Mutation (genetic)	S252W mutation or P253R mutation in *FGFR2*-gene on chromosome 10 Rare: S252F mutation[19], rearrangements in exon IIIc splicing (e.g., Alu element insertion, partial gene deletion[20])
Incidence	1 : 100.000[11]
Main clinical features	Anterior fontanelle enlarged, majority bicoronal synostosis Possible turricephaly Exorbitism, hypertelorism, midface hypoplasia, malocclusion High-arched narrow palate, sometimes with a cleft Symmetric, complex syndactyly of hands and feet Mental retardation (mean IQ: 77 [SD: 13], and a higher chance of intellectual disability[21])

Crouzon & Pfeiffer syndromes

Founder	Octave Crouzon (1912)[22] & Rudolf Pfeiffer (1964)[23]
Mutation (genetic)	Several mutations in *FGFR2*-gene on chromosome 10 - Crouzon: A391E mutation in *FGFR3* on chromosome 4 - Pfeiffer: P252R mutation in *FGFR1* on chromosome 8
Incidence	1 : 62.500[11]
Main clinical features	Majority bicoronal or pan-synostosis (sometimes postnatal) Exorbitism, midface hypoplasia, malocclusion (class III) Crouzon (*FGFR 3*): acanthosis nigricans Possible limb abnormalities: broad, deviated thumbs and halluces Mean IQ: 103 (SD: 20)[21]

The diagnosis of Crouzon and Pfeiffer syndromes is a spectrum of varying severity. They are often considered as a homogeneous group, since they can be considered as phenotypic variations of the same genetic defect.[24, 25]

Muenke syndrome[26]

Founder	Gary A. Bellus (1996)[27, 28]
Mutation (genetic)	P250R mutation in *FGFR3*-gene on chromosome 4
Incidence	1 : 30.000[29]
Main clinical features	Majority coronal synostosis (mainly bilateral) Macrocephaly without craniosynostosis (rare) Hearing loss (sensorineural) Behavioral disturbances Mean IQ: 95 (SD: 16), developmental and language delay[21]

Saethre-Chotzen syndrome[30]

Founder	Haakon Saethre (1931)[31] & Fritz Chotzen (1932)[32]
Mutation (genetic)	Several mutations/deletions in the *TWIST1*-gene on chromosome 7
Incidence	1 : 37.500[33]
Main clinical features	Majority bicoronal synostosis Upper eyelid ptosis, external ear anomalies, low-set hairline Minor limb abnormalities: brachydactyly; incomplete, simple syndactyly Mean IQ: 100 (SD: 27)[21]

Complex craniosynostosis

Mutation (genetic)	Unknown (by definition) Definition: multiple suture synostoses, and no genetic cause is found yet
Incidence	1 : 25.000
Main clinical features	Coronal suture(s) synostosis is often present, although other sutures can be involved as well Additional clinical features are variable Mean IQ: 94 (SD: 22)[21]

Obstructive sleep apnea (sleep disordered breathing)

Sleep disordered breathing is a syndrome of upper airway dysfunction during sleep, characterized by snoring and/or increased respiratory effort that results from upper airway resistance and pharyngeal collapsibility.[34, 35] Sleep disordered breathing consists of a spectrum of clinical entities, including primary snoring, upper airway resistance syndrome [UARS], and obstructive sleep apnea [OSA][36, 37]:

- Primary snoring: patients who snore, but do not have apneas, hypopneas, frequent arousals from sleep or gas exchange abnormalities.

- UARS: patients who snore, have increased respiratory effort with frequent arousals, but no apneas, hypopneas, oxygen desaturations or other gas exchange abnormalities.[38, 39] UARS has been suggested to be more common in children than OSA and should particularly looked for in children with craniofacial skeletal anomalies and in families with adult sleep disordered breathing.[40] Symptoms are diverse and vary by age, which may make it difficult to clinically distinguish UARS from OSA.[40] A nasal cannula/pressure transducer will show inspiratory airflow limitation with a flattening of the tops, combined with other signs of increased respiratory effort during polysomnography, such as bursts of tachypnea without saturation drops, and increased heart rate variability [HRV].[34, 40] HRV, the continuous fluctuation of the heart rate as a reaction to stimuli (e.g., respiratory related events, such as apneas, arousals) might be increased compared to children without sleep disordered breathing.[41-43] Esophageal pressure monitoring will show increasingly negative intrathoracic pressures during inspiration, and is necessary to confirm diagnosis.[34, 44] UARS is a subtle clinical entity and by using only conventional indicators of sleep disordered breathing it appears to be underrecognized or misdiagnosed, which might subsequently lead to an underestimation of the severity of a child's condition.[45]

- OSA: patients who have partial and/or intermittent complete upper airway obstructions (apneas, hypopneas, arousals, oxygen desaturations) with disruption of normal ventilation and sleep pattern.[46]

The focus will now be on OSA, in children with syndromic or complex craniosynostosis.

Prevalence

The prevalence of OSA is 68% in children with syndromic craniosynostosis (compared to 1-4% in normal children[47]), and it is most severe in children with Apert and Crouzon/Pfeiffer syndromes.[48]

Etiology

The upper airway obstruction causing OSA is often related to maxillary(/midface) hypoplasia, which is common in patients with Apert and Crouzon/Pfeiffer syndromes.[49-51] Other anatomical abnormalities include nasal septum deviation, choanal atresia, hypertrophy of adenoid and/or tonsils, palatal deformities, mandibular hypoplasia, and tracheal cartilage anomalies (figure 3).[52-55] However, it is usually a multilevel problem in these children and therefore upper airway endoscopy to determine the exact location(s) of the obstruction is recommended before treatment.[56, 57] In addition to the abnormal upper airway anatomy, the airway can further be compromised by a dynamic pharyngeal collapse.[38] During REM sleep airway collapsibility is greatest, due to a reduced muscular tone of the pharyngeal dilators resulting in a collapse of the already narrowed airway.[58]

Symptoms

Apnea, snoring, difficulty in breathing during sleep and daytime sleepiness are amongst the commonest symptoms. The Pediatric Sleep Questionnaire is a valid questionnaire to predict OSA and its outcomes[59], and the Sleep Clinical Record has a high sensitivity in diagnosing OSA.[60] The Brouillette questionnaire does not perform as good in general[61], but has been proven to be a valid screening tool for OSA specifically in children with syndromic craniosynostosis.[62] The Brouillette score is calculated by:

- Brouillette score = 1.41*apnea *(0=no, 1=yes)* + 0.71*snoring *(0=never, 1=occasionally, 2=frequently, 3=always)* + 1.42*difficulty in breathing during sleep *(0=never, 1=occasionally, 2=frequently, 3=always)* – 3.83

The score can be used to predict the presence of OSA: >3.5 points, OSA; 3.5 to – 1, suspected for OSA; < –1, no OSA. The item 'difficulty in breathing during sleep' has a negative predictive value of 91%, i.e., asking parents whether their child has difficulty in breathing during sleep can exclude the presence of clinical significant OSA.

OSA is generally stable over time, and there is some natural improvement mainly in the first years of life.[48] However, fluctuations in the clinical presentation are possible, for example during a cold or at time of adenotonsillar hypertrophy. When significant OSA is not present early in life, without co-morbidity it is highly unlikely to develop later in life.[48]

Diagnosis

The gold standard to diagnose OSA is polysomnography.

A sleep study can be performed in an ambulatory setting to screen for OSA. If indicated, for example because of a positive Brouillette score or after an abnormal ambulatory sleep study, a more extensive polysomnography can be performed in the hospital. Polysomnography in the hospital registers respiratory, cardiovascular, and neurologic parameters, with medical and technical support (i.e., level 1 polysomnography[63]) and is considered the reference for diagnosing OSA.[64] The main cardiorespiratory variables measured are: nasal flow (thermistor), chest and abdominal wall motion, arterial oxygen-hemoglobin saturation (*SpO2*), transcutaneous partial pressure of carbon dioxide (*pCO2*) and electrocardiography. A video recording is also made during the examination. Additionally, a capillary blood gas test is performed during the night of the polysomnography.

The use of electroencephalography [EEG] allows to score the occurrence of arousals and to construct the hypnogram.[65] An arousal is a short interruption of sleep sending one back to a lighter sleep stage; if it lasts longer, it is called an awakening. They can occur spontaneously, or due to a respiratory event or increased respiratory effort, i.e., a respiratory effort related arousal [RERA]. A person is usually not aware of arousals, but may be aware of awakenings. The hypnogram displays sleep architecture, i.e., the distribution of sleep stages: non-REM sleep (N1, N2, N3) vs. REM sleep. Non-REM sleep is characterized by little or no eye movement, decreased but preserved muscle activity, and regular breathing and heart rate.[65] N1 might see the occurrence of hypnic jerks, i.e., a myoclonus that occurs just as a person is beginning to fall asleep, and this stage is sometimes referred to as relaxed wakefulness as it mostly occurs between wakefulness and sleep. Additionally, starting in this stage is a process of decreasing muscular tone and disappearing conscious awareness of the environment. On EEG, there is alpha drop-out, increased theta activity, presence of slow eye movements and vertex sharp waves. In N2, there are sleep spindles (i.e., bursts of brain activity) and K-complexes with <20% delta activity on the EEG. N3, also called slow wave sleep or deep sleep, is the stage during which parasomnias (e.g., sleep walking, night terrors) most commonly occur, and on EEG there is >20% delta activity of >75µV. REM sleep is characterized by random eye movements, low or absent muscle tone throughout the body, irregular respirations, heart rate and body temperature, and dreams often occur in this phase[65]; the EEG shows mixed theta and alpha frequencies without K-complexes or sleep spindles, whereas sometimes saw-tooth waves can be seen on the central electrodes. On the basis of the hypnogram, the percentage of REM sleep and sleep efficiency (defined as the time that the patient is asleep as percentage of the total recording time) can be determined. The percentage of time that a person spends in REM sleep is 50-80% for neonates compared to around 20% for adults, i.e., it decreases with age.[66, 67] The exact functions of REM sleep are still unknown, although in children it is essential for brain development.[68] Furthermore, since during REM sleep the brain processes information and forms neural connections, it plays a key role in memory and recognition of faces.[69, 70] REM sleep is therefore considered the most important sleep stage in children, and it is not only the number of hours in bed that is important, but especially the ‘quality of sleep’.

The definition of OSA is ambiguous. Rules for scoring respiratory events in sleep are provided by the American Academy of Sleep Medicine [AASM][65], however several parameters (i.e., apnea-hypopnea index [AHI], obstructive apnea-hypopnea index [oAHI] and/or oxygen-desaturation index [ODI]) are used for the classification of OSA severity and there is no definite consensus on the thresholds for abnormality.[65] AHI is the most commonly used parameter for the description of sleep disordered breathing severity, although for OSA it is recommended to report the oAHI separately.[65] OSA is usually defined as one of these parameters having a value of >1[71, 72], but the cut-offs for mild, moderate and severe OSA vary.[73-75] Combining (o)AHI, SpO2, pCO2, and arousal indices should be preferred in the future.[37] Taken together, here the most conventional grading system is used[76], that defines OSA as an oAHI ≥1 per hour (figure 4). Patients are subsequently subdivided as either mild OSA (oAHI ≥1 and <5), or moderate OSA (oAHI ≥5 and <24), or severe OSA (oAHI ≥25).

Young patients may demonstrate central irregularity, which is usually caused by brain immaturity. Central sleep apnea, however, is uncommon in children with syndromic craniosynostosis, despite the presence of OSA, white matter abnormalities and cerebellar tonsillar herniation.[77]

Treatment

The type of treatment for sleep disordered breathing depends on the age of the patient, its cause, its severity, and the presence of other functional problems such as severe exorbitism and/or intracranial hypertension.[78] Interventions are applied in a stepwise fashion, and, depending on the underlying conditions and severity, different modalities can be combined. Nasal corticosteroids and/or oral leukotriene modifier therapy (e.g., Montelukast) administered for 6 to 12 weeks may decrease the severity of mild to moderate OSA.[79-82] Nasal septum correction is usually postponed until the age of 18 years, since the cartilaginous septum is the dominant growth center and it being damaged may come with the risk of interfering with facial growth.[83] Children with adenotonsillar hypertrophy may benefit from adenotonsillectomy as it can lead to improvements in behavior, quality of life and polysomnographic findings.[84-86] Respiratory support with Optiflow, or bi-level or continuous positive airway pressure may lead to improvements in neurobehavioral outcomes, school performance, and quality of life.[57, 87, 88] A nasopharyngeal tube can be used in neonates to bridge time before definite treatment is applied.[89] A more definite treatment option in patients with Apert and Crouzon/Pfeiffer syndromes where maxillary growth is limited is midface advancement (with distraction), i.e., LeFort III or monobloc surgery, which results in a decrease in oAHI and improves quality of life.[57, 87, 90] Mandibular distraction is an effective procedure to resolve upper airway obstruction in

craniofacial anomalies involving mandibular hypoplasia.[91] As a last resort, a tracheal cannula may be required in patients suffering from severe OSA.[89, 92]

Consequences

OSA can potentially impact on a child's life with the implications being quite broad and rather complex. Multiple target organs and systems can be affected, which may not be completely reversible with subsequent treatment.[37] Disease specific factors (e.g., severity and duration of OSA), co-morbidity, genetic predisposition and environmental influences all play a role in determining the susceptibility of a patient.[93] Possible consequences include failure to thrive, behavioral disturbances, learning deficits, cardiovascular and metabolic morbidity.[94-96] Hence, quality of life can be affected due to OSA[97, 98], which can be assessed with the OSA-18 questionnaire.[99]

Additionally, OSA may substantially affect cerebral blood flow [CBF] and thereby increase the risk of developing intracranial hypertension in these patients who are already at risk of intracranial hypertension.[100-102] OSA may initiate a vicious cycle that predominantly occurs during REM sleep, since in this sleep stage brain activity peaks[103] and airway collapsibility is greatest.[58] It may cause precipitating cerebral hypoperfusion stimuli (e.g., hypercapnia and hypoxia), which leads to reactive cerebral vasodilatation, thereby increasing CBF, resulting in intracranial hypertension.[104] Subsequently, cerebral perfusion pressure decreases to compensate for the high pressures, and autoregulatory responsivity leads to more vasodilatation to preserve CBF. A further rise in intracranial hypertension will follow.[105] An arousal will correct the airway obstruction and blood gases, ultimately breaking the cycle.

Intracranial hypertension

Patients with syndromic craniosynostosis are at risk of intracranial hypertension, and therefore raised intracranial pressure [ICP]. ICP represents the net effect of intracranial volume [ICV] and content, brain compliance, plus blood and cerebrospinal fluid [CSF] dynamics.[106, 107]

Prevalence

Previous studies have shown the risk of intracranial hypertension prior to vault expansion to be related to the suture(s) affected as well as the underlying syndrome[100, 108-113]: trigonocephaly, 9% (0-33%); scaphocephaly, 12% (5-24%); plagiocephaly, 10% (0-22%); brachycephaly, 37% (31-50%); Apert, 40-83% (83%: Apert patients managed by monitoring for intracranial hypertension, and only perform treatment when this has been diagnosed[114]); Crouzon/Pfeiffer, 50-70%; Muenke, 0-21%; Saethre-Chotzen, 35-45%; complex craniosynostosis, 50-80%.

Despite early vault expansion, however, intracranial hypertension might still persist or relapse in 35-43%; particularly in patients with Apert, Crouzon/Pfeiffer and Saethre-Chotzen syndromes.[111, 113, 115-117]

Etiology

The exact pathophysiology of the development of intracranial hypertension in children with syndromic craniosynostosis is still unclear. However, several risk factors have been identified, which usually do not exert their effect in isolation but in a complex interaction process:

- *OSA*: OSA may lead, via a vicious cycle during (REM) sleep, to a decrease in cerebral perfusion resulting in intracranial hypertension.[101, 102]

- *Cranio-cerebral disproportion*: The brain may grow more rapidly than the skull, since its growth could be affected by premature fusion of the calvarial sutures.[105] The occipital-frontal head circumference [OFC] reliably predicts ICV in these patients[118]; in daily clinical practice this is a feasible method to monitor skull growth, since patients remain at risk for skull growth arrest even after vault expansion and this may result in intracranial hypertension.

- *Hydrocephalus*: Progressive hydrocephalus, which is to be distinguished from non-progressive ventriculomegaly, can lead to an increase in CSF volume, resulting in intracranial hypertension.[119]

- *Venous hypertension*: Venous outflow obstruction of the brain can be caused by abnormalities of venous drainage, resulting in a raise in venous pressure, CSF pressure, and subsequently intracranial hypertension.[105, 116, 120, 121]

- *Abnormal cerebral blood flow*: Autoregulation plays an essential role in the vicious cycle of OSA, cerebral hypoperfusion, and intracranial hypertension, but additionally a more 'static' hemodynamic equilibrium of increased CBF and cerebrovascular resistance has been associated with intracranial hypertension.[122, 123]

Symptoms

Symptoms might include headaches, behavioral changes, frequent awakenings during the night, and/or deterioration of vision. The recognition of intracranial hypertension in children with syndromic craniosynostosis is difficult. Symptoms might be absent and/or a-specific.[124], intracranial hypertension develops as a gradual process, and baseline ICP is usually only slightly elevated (i.e., 15-20 mm Hg) with patients particularly suffering from pressure peaks during REM sleep overnight. Symptoms like dullness or vomiting are hardly ever present.

Diagnosis

Patients are routinely screened for intracranial hypertension. The following examinations are performed, although a normal test-result does not exclude intracranial hypertension and therefore the results are not evaluated independently but altogether:

- *Symptoms*

Headaches, behavioral changes, frequent awakenings during the night, and/or deterioration of vision.

- *Occipital frontal head circumference*

Downward deflection in the OFC trajectory.

- *Fundoscopy*

A pediatric ophthalmologist performs fundoscopy to screen for papilledema, which is used to indicate intracranial hypertension (figure 5).[125]

Presence of papilledema is the primary indicator of intracranial hypertension. Screening for it by means of fundoscopy is not only practical, but also useful and clinically relevant. The development of intracranial hypertension in patients with craniosynostosis is a gradual and chronic process which is likely to result in papilledema. Papilledema is a highly specific

indicator, however its sensitivity might be suboptimal especially in younger children and therefore the absence of papilledema does not rule out intracranial hypertension.[126] Therefore, if indicated, i.e., when papilledema is absent but intracranial hypertension nevertheless suspected, additional examinations are performed:

- *Optical coherence tomography:*

Optical coherence tomography [OCT] makes use of broad-band near-infrared light sources, which have a considerable penetration of up to 3 mm into tissue and can therefore provide detailed information of the retina when applied through the eye.[127-129] The thickness of the retina can be calculated by centralizing the patient's optic nerve head using a fixation light. The retinal nerve fiber layer is thicker when papilledema is present.[130, 131]

- *ICP monitoring:*

Invasive ICP monitoring during 24 hours is regarded as the gold standard to diagnose intracranial hypertension. An assessment must be made between the added value ICP measurement provides (e.g., decisive for surgery, or in case of suspected intracranial hypertension without papilledema) versus the burden for the patient and parents, narcosis, surgical intervention, risk of complications, costs, and admittance to high/intensive care; routine ICP monitoring is therefore not indicated. Additionally, there are some difficulties associated with ICP monitoring, such as a uniform protocol that lacks, no universally accepted scale of normal and abnormal ICP values in children, and different interpretations of the recordings.[117] Normal values for ICP have been reported for children[132], although it is not clear whether these values are useful in children with craniosynostosis. Regardless of this, the use of only the mean ICP to detect intracranial hypertension, as is done in earlier studies[100, 126], is unreliable. Mean ICP should be evaluated in combination with plateau waves, which are a sensitive parameter of intracranial hypertension.[117, 133] Taken together, here ICP recordings are assessed according to the following criteria[117, 134, 135]:

- *Baseline ICP value during day and overnight:* <10mmHg, normal; 10-15mmHg, borderline abnormal (number, height, and duration of plateau waves are decisive); >15mmHg, abnormal; additionally, values at the beginning and end of the night were compared to check for any overnight increase in ICP.
- *Number of abnormal plateau waves:* based on the number (>3 waves, abnormal), height (<25mmHg, normal; 25-35mmHg, borderline; >35mmHg, abnormal); and duration (<10 minutes, normal; 10-20 minutes, borderline; >20 minutes, abnormal).

Taken together, this approach of symptom review, OFC growth arrest assessment, and fundoscopy, when necessary combined with OCT and/or ICP monitoring, is the most reliable to diagnose intracranial hypertension in patients with craniosynostosis.

Treatment

Patients are routinely scheduled for cranial vault expansion within the first year of life, or shortly after referral if the child is older at presentation. The aim of surgery is to prevent or treat intracranial hypertension. The type of first craniofacial surgery depends on the diagnosis: patients with Apert or Crouzon/Pfeiffer syndrome undergo occipital expansion (with springs), children with Muenke or Saethre-Chotzen syndrome undergo fronto-orbital advancement, and in those with complex craniosynostosis type of surgery is based on the sutures involved. The only exception is when a patient suffers from severe OSA and/or severe exorbitism: a monobloc is then performed, since this has significant impact in treating OSA at the midface and in reducing intracranial hypertension.[87]

After surgery, patients have frequent routine follow-up appointments to screen for intracranial hypertension. A multidisciplinary team will assess the available data and decide on the type of treatment aimed at the causal factor in the event intracranial hypertension is (again) identified. For example, head growth arrest can be treated by second vault expansion (which is also effective treatment for most other factors contributing to intracranial hypertension). Significant OSA, the only factor not addressed by standard vault surgery, can be managed as previously described. A ventriculoperitoneal shunt for hydrocephalus is generally not preferable and contra-productive, because it reduces the intrinsic growth impulse of the brain on the skull and renders the patient dependent on its function; however, some patients may ultimately need a shunt such as those with progressive hydrocephalus after vault expansion.

Consequences

Prolonged intracranial hypertension can lead to cerebellar tonsillar herniation, e.g., Chiari type I malformation.[136] Furthermore, it can have significant impact on mental development, behavior, physical condition, and may ultimately lead to secondary optic nerve atrophy with irreversible visual loss.[113, 137]

AIMS AND OVERVIEW OF THE THESIS

The aim of this thesis is to unravel the topic of OSA in children with syndromic craniosynostosis, and especially to determine its contribution in the development of intracranial hypertension.

Chapter	Topic
II	A newborn with atypical craniofacial presentation of Apert syndrome: to illustrate the issues that can play a role in children with syndromic craniosynostosis.
III	*This chapter focuses on OSA and intracranial hypertension in children with syndromic craniosynostosis:* - Sleep architecture in the context of a theory for OSA, CBF, intracranial hypertension and (REM) sleep. - Upper airway endoscopy as a tool to optimize OSA treatment. - Transcranial Doppler to evaluate cerebral hemodynamics and blood pressure profiles in patients with intracranial hypertension.
IV	*This chapter focuses on the management of patients with syndromic craniosynostosis:* - An overview of the management of intracranial hypertension in children with syndromic craniosynostosis. - Apert and Crouzon/Pfeiffer syndromes are associated with the greatest risk of intracranial hypertension: an assessment of the preferred type of first craniofacial surgery.
V	*Summary & Discussion:* An overview of all the elements that have been covered in the papers, along with an assessment of the literature resulting in a unifying model for children with syndromic craniosynostosis.

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Table 1. Standard treatment protocol and follow-up schedule for new referred children.

Age	**Intake**	**Surgery (<1 year)**	**1 year**	**2 years**	**3, 4 years**	**5, 6 years**	**7, 8, 9, 10.5, 12, 15, 18 years**
	pre-op	*at surgery*	*post-op*				
Anamnesis/medical history	X		X	X	X	X	X
Physical examination (OFC)*	X		X	X	X	X	X
Skull X-ray	X		X	X	X	X	X
3D-CT(/CTA)-scan	X		X**				
MRI	X			X****	X****		
Polysomnography	X		X	X	X***	X***	X***
Fundoscopy*	X		X	X	X	X	X*
Clinical genetics	X						
Upper airway endoscopy		X		whenever a midface advancement procedure is scheduled			
ENT (speech/hearing)			X	X			
Orthoptist (eye motility)			X				
OCT					X**		
ICP monitoring	X**						

* OFC and fundoscopy: from the age of 1 year every 6 months until the age of 4 years. Fundoscopy after the age of 6 years is performed only if presenting symptoms are indicative for intracranial hypertension.

** Whenever intracranial hypertension is suspected, but the diagnosis is not clear (e.g., no papilledema).

*** Apert and Crouzon/Pfeiffer syndromes: polysomnography at the ages of 3 and 4 years in ambulatory setting; after this, and for the other syndromes after the age of 2 years, polysomnography is only done when clinically indicated.

**** Apert, Crouzon/Pfeiffer and Saethre-Chotzen syndromes: MR scan at the ages of 2 and 4 years.

The physician responsible for the treatment can decide on clinical grounds to perform additional tests.

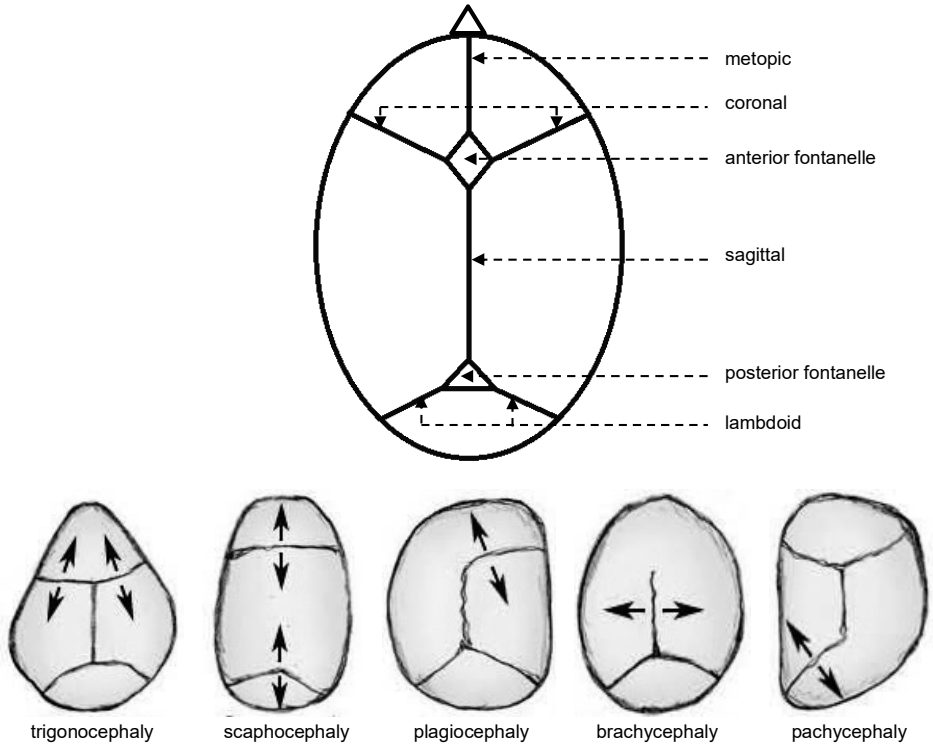

Figure 1: Normal skull of a newborn (sutures and fontanelles are shown), and the different types of craniosynostosis.[138]

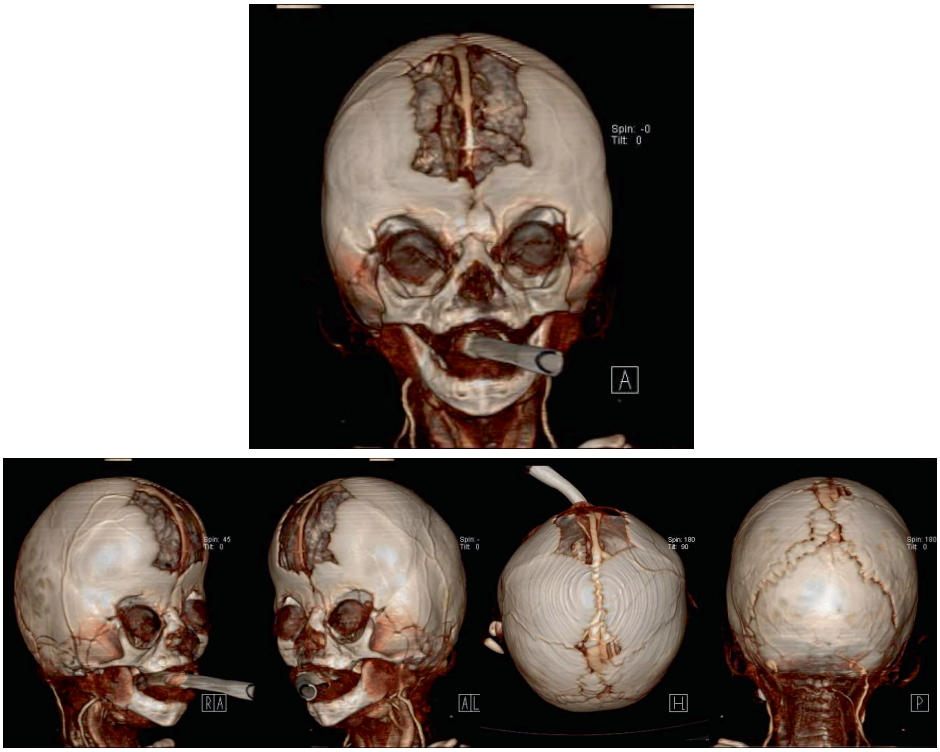

Figure 2: A patient with Apert syndrome.

The metopic suture is open with an enlarged anterior fontanelle, the coronal sutures are both fused, the sagittal suture and both lambdoid sutures are open.

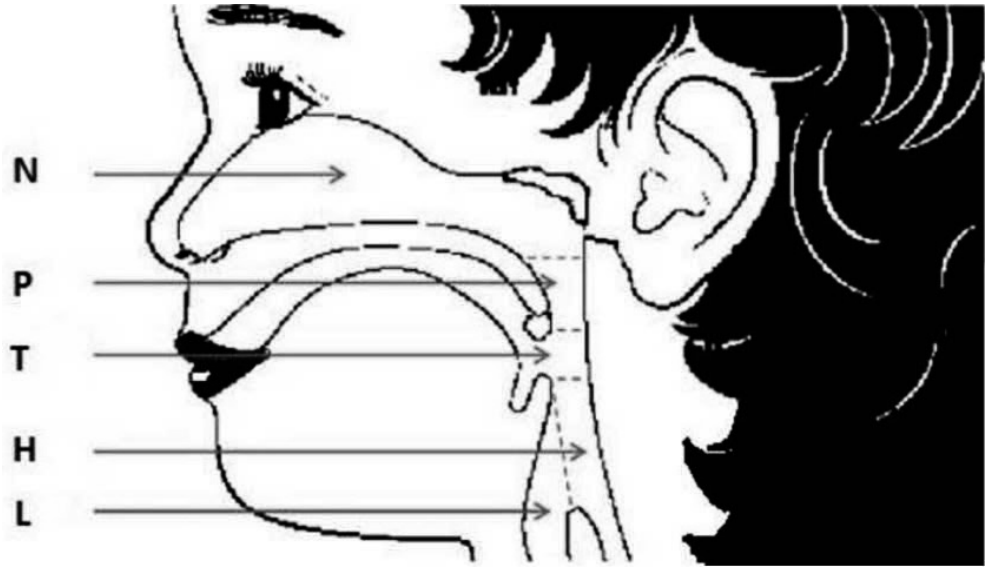

Figure 3: Levels of the upper respiratory tract.

N: nose and nasopharynx; P: uvulopalatine plane; T: tongue base; H: hypopharynx; L: larynx

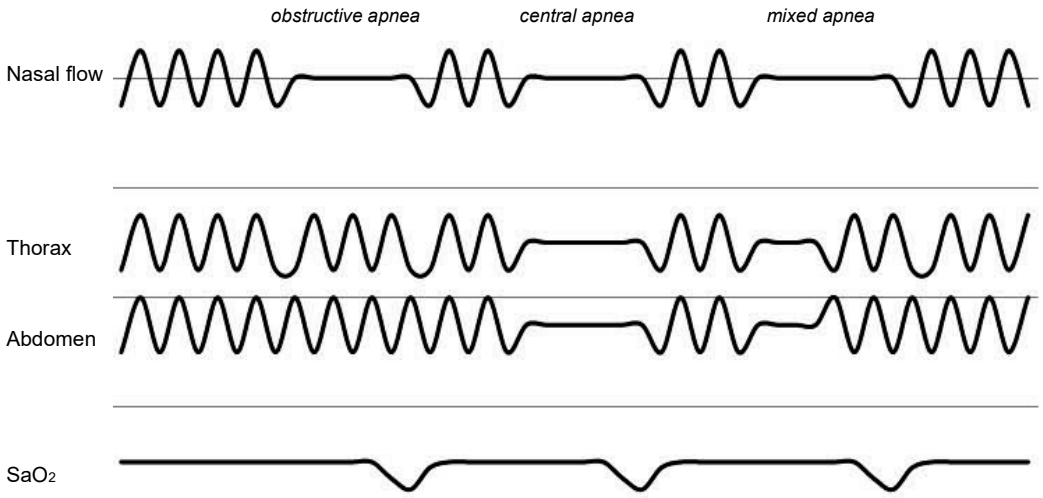

Figure 4: Polysomnography recording: an obstructive apnea (note the paradoxical breathing), central apnea, and mixed apnea are shown.

oAHI (index) is defined as number of obstructive apneas, mixed apneas and obstructive hypopneas with subsequent SpO_2 desaturation ≥3% and/or arousal, indexed by the total sleep time.

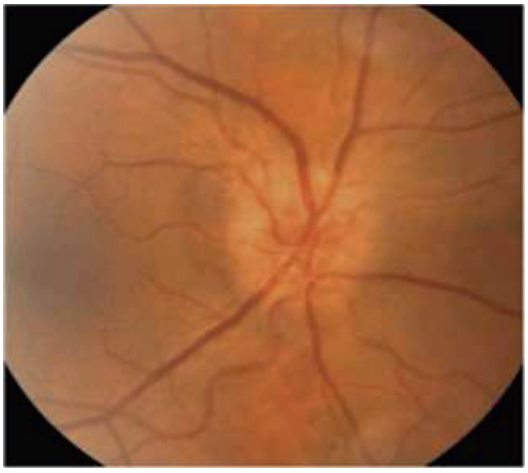

Figure 5: Papilledema as observed during fundoscopy.

PART II
-
A NEWBORN WITH APERT SYNDROME
(PREFACE TO SYNDROMIC CRANIOSYNOSTOSIS)

CHAPTER 2

Atypical presentation of a newborn with Apert syndrome

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Childs Nerv Syst. 2015 Mar;31(3):481-6.

Abstract

Introduction: Apert syndrome is a rare syndrome characterized by a consistent phenotype including bilateral coronal suture synostosis with an enlarged anterior fontanel, midface hypoplasia and complex symmetric syndactyly of hands and feet.

Case report: We present a boy with Apert syndrome caused by the pathogenic c.755C>G p.Ser252Trp mutation in the *FGFR2* gene with atypical characteristics, including premature fusion of the metopic suture with a small anterior fontanel, hypotelorism and a massive posterior fontanel. Directly after birth he showed papilledema, epilepsy and central apneas.

Conclusion: We present a newborn with Apert syndrome with atypical craniofacial presentation.

Introduction

Apert syndrome is a rare congenital disorder characterized by bilateral coronal suture synostosis, enlarged anterior fontanel, midface hypoplasia and complex symmetric syndactyly of hands and feet, almost always caused by pathogenic mutations of p.Ser252Trp or p.Pro253Arg in the *FGFR2*-gene.[1, 2] Although Apert syndrome is an autosomal dominant disorder, the majority of cases are sporadic. Other features include exorbitism, lagophthalmus, hypertelorism, high-arched narrow palate, and class III malocclusion. These children often develop obstructive sleep apnea (OSA), due to an anatomical disbalance of midface, oropharynx and hypopharynx.[3]

In addition, Apert patients have a high risk of 83% or more for developing increased intracranial pressure (ICP).[4] Risk factors include cranio-cerebral disproportion, OSA, hydrocephalus and venous outflow obstruction.[3, 5, 6]

Case report

The patient's mother (G3P1A1) was 37 and the father was 45 years old, and both were healthy. The pregnancy was the result of a spontaneous conception.

Although the ultrasound at week 20 of gestation showed no abnormalities, an extra ultrasound at week 29 was required because of positive discongruence. This showed a large for gestational age child (+1.28 SD) with midface hypoplasia and abnormal hands and feet (fig. 1a). An MR scan showed a well-developed but strongly bended corpus callosum, enlarged lateral and third ventricles, absent septum pellucidum and enlarged choroid plexus suspected to be hypertrophic. Consequently, molecular analysis revealed the c.755C>G p.Ser252Trp mutation in the *FGFR2* gene in the fetal DNA. DNA isolated from peripheral blood cells of the parents was negative for this pathogenic mutation.

Birth and phenotype

The patient's birth was induced at 38 2/7 weeks at our children's hospital, because of the risk of respiratory problems. Apgar scores were 7, 8 and 10, birth weight 3755g (+0.6 SD) and head circumference 34.4 cm (-0.6 SD). The boy had clear craniofacial anomalies, including bicoronal and metopic suture synostosis, resulting in a small anterior fontanel, and a massive posterior fontanel, midface hypoplasia and a high arched narrow palate without cleft (fig. 1b).

Another atypical aspect of this patient was the asymmetrical syndactyly of the hands, i.e. the patient had a type 1 Apert hand on his left side (shallow first webspace, side-to-side fusion of the middle three fingers and a simple incomplete syndactyly of the fourth webspace) and a type 2 on the right hand (simple syndactyly of the first web, clinodactyly of the second finger, fusion of all fingertips forming a concave palm and a simple complete syndactyly of the fourth webspace), however, with an incomplete syndactyly of the 4th web on this side referring to a type 1.[7]

Respiration

Directly after birth the patient was in respiratory distress for which continuous positive airway pressure (CPAP) was started and an oral airway device (Guedel) was inserted, which relieved the symptoms. However, several hours later severe desaturations were observed, mainly due to central apneas. Therefore, Caffeine, intravenous Doxapram and airway support (Optiflow®) were not effective. In addition, flexible endoscopy performed by the otolaryngologist revealed a nasal cavity that was extremely narrow on the right side and totally constricted on the left side. Vocal cords were normal with normal abduction. Rigid endoscopy revealed a Cotton-Myer grade II subglottic stenosis, based on a trapped first tracheal ring (fig. 2). Because of persistent respiratory distress a nasopharyngeal tube size 3.0 was placed in the left nostril over which

CPAP was continued for 3 days, followed by oxygen via nasal prongs. However, incidents with deep desaturations remained. A polysomnography showed periods of immature breathing with frequent central apneas, a decreased respiration rate and desaturations to 50% without oxygen supply, while no obstructive apneas were recorded. Gradually respiration improved and the patient was discharged at day 20 without respiratory support.

Intracranial pressure

An ultrasound showed marginally enlarged lateral ventricles, partial agenesis of the septum pellucidum and a normal aspect of the peripheral CSF spaces and sagittal sinus. Hypertrophy of the choroid plexus was confirmed as well.

The CT scan showed closed coronal sutures, midface hypoplasia and wide sagittal and lambdoid sutures, resulting in a massive posterior skull defect. The caudal part of the metopic suture was closed causing mild hypotelorism (fig. 3a-c). Both jugular foramens were patent and small collaterals were present behind both mastoids. The myelination pattern as seen on MR scan was according to the patient's age. Size of the lateral ventricles was stable compared to the ultrasound, while there was a normal aspect of the cerebellum (no tonsillar herniation). However, at the front of the skull there were indications of increased pressure including herniation of the frontal lobe onto the anterior skull base with noticeable bulging and scalloping of the clivus. In addition, a trace of papilledema was found by fundoscopy already at the age of 3 weeks. Head circumference at the age of two months (38 cm) was -1.14 SD below average.

At the age of 3.5 months, a new CT and MR scan showed an increased amount of impressiones digitatae around the anterior fontanel. The occipito-mastoid sutures and metopic suture were completely fused, whereas the squamosal, spheno-frontal, fronto-zygomatic and parieto-mastoid sutures were narrowed at both sides. The lambdoid sutures were only partially closed at their caudal part and in combination with the wide sagittal suture still resulting in a massive posterior skull defect, impairing an occipital expansion that is preferably done (fig. 3d-f). In addition, there still was a good CSF flow through the aqueduct and foramen magnum, the sinus rectus was prominent and the central CSF spaces were enlarged but showed no progression (fig. 4). The amount of CSF around the optic nerve had increased and optic nerves and chiasma had a hypoplastic appearance. At four months of age just before surgery (fig. 1c), growth of the head circumference had further decreased (40.0 cm, -1.86 SD).

At this age, a single event caused desaturations down to 31% overnight. An EEG and polysomnography showed epileptic activity, followed by bradypnea, central apneas (>20 sec) and desaturations down to 79%. The epilepsy was located in the frontocentrotemporal part of the brain and more evident on the left side, at the similar location as the impressiones on the CT scan (fig. 5). There were no indications for structural brain anomalies and it was postulated that the epileptic activity was triggered by local pressure on the brain. Consequently, Levetiracetam

(20mg/kg) was started, after which no further insults and desaturations occurred. Neurodevelopment was according to the patient's age.

Surgery

Soon thereafter, a monobloc procedure with distraction was performed to treat the papilledema, exorbitism, progressive lagophthalmus, and possibly remove the trigger for epileptic activity (fig. 1d). Distraction was performed with 0.5mm a day to a total advancement of 20 mm. Within 1 week head circumference reached 42.0cm (-0.56 SD), followed by 43.5cm (+0.31 SD) at day 14.

Follow-up

Following surgery, the patient had a more natural appearance. The papilledema resided during the postoperative period. Four months later, he developed bulging at the osteotomy sites near the former coronal sutures and a tense dura, indicating elevated ICP. Therefore, an occipital vault expansion with springs was undertaken as the occipital defect now allowed it. Just before surgery, presence of papilledema was detected again. The bulging of the brain disappeared soon after occipital expansion, as did the papilledema. The patient subsequently had a normal mental development (conform Apert syndrome; fig. 1e), and despite suffering from a meningitis at 1 year of age, he rehabilitated and is now healthy and in decent clinical condition.

Discussion

We present a boy with Apert syndrome with premature fusion of the metopic and coronal sutures, papilledema, epilepsy and central apneas.

To our knowledge, only one other Apert patient with metopic suture synostosis has been described[8], but no information on ICP, presence of OSA or epilepsy was given. Prematurely closed coronal sutures in combination with that of the metopic suture resulted in our patient in a small anterior fontanel and anterior skull base with signs of localized elevated ICP, despite a very large posterior fontanel. We hypothesized that the papilledema, impressiones digitatae and defects in the frontal bone, and frontocentrotemporal epileptic activity were signs of this localized elevated ICP. We therefore felt that a surgical release of the frontal lobes was more indicated than an occipital expansion which is done routinely in Apert syndrome.

Given the fact that the papilledema was mild and non-progressive, and ventricular size remained stable a VP-shunt was not considered. After ruling out the central apneas as a cause for the papilledema, a monobloc procedure with distraction was performed as initial procedure, also to treat the progressive exorbitism. After the monobloc, the papilledema resided, no central apneas occurred and no epileptic activity was recorded, even after terminating the use of Levetiracetam. This clinical course suggests that our hypothesis was correct. However, this procedure obviously did not gain enough intracranial volume which the secondary occipital expansion did.

Finally, we note that Apert syndrome has been associated with an older paternal age, and since the father was 45 years old this paternal age effect might have played a role in our patient as well.[9] Additionally, independent of paternal age, there is a variable clinical presentation of the disease. Although the phenotype attributable to the two mutations (p.Ser252Trp and p.Pro253Arg in *FGFR2*) is similar, there are subtle differences and a genotype-phenotype correlation has been described.[10] Several authors have reported that the p.Ser252Trp mutation is associated with a more severe craniofacial phenotype, but less severe syndactyly and better mental outcome (table 1).[11-13] Our patient's presentation was consistent with these reports, as he especially had atypical severe craniofacial characteristics with a normal mental development in the spectrum of Apert syndrome.[14]

Acknowledgments

We would like to thank Prof. A.O.M. Wilkie from the Weatherall Institute of Molecular Medicine, Oxford Craniofacial Unit/ John Radcliffe Hospital and Department of Clinical Genetics, Oxford, United Kingdom for our fruitful discussions regarding possible genetic causes. In addition, we would like to thank the following members of the Sophia Children's Hospital – Erasmus University Medical Center who were all involved in the care of the patient and contributed to the manuscript: Dr. A. Machotta (anaesthesiology), Dr. L.M.E. Staals (anaesthesiology), Dr. K. Geleijns (neurology), G.C.B. Bindels – de Heus (pediatrics), Dr. R. Boogaard (pediatric endocrinology), J.A.C. Goos (plastic surgery), Dr. A.M.W. van den Ouweland (clinical genetics), Prof. C.C.W. Klaver (ophthalmology), Dr. C.A. van Nieuwenhoven (plastic surgery) and R.C. Dullemond (gynaecology).

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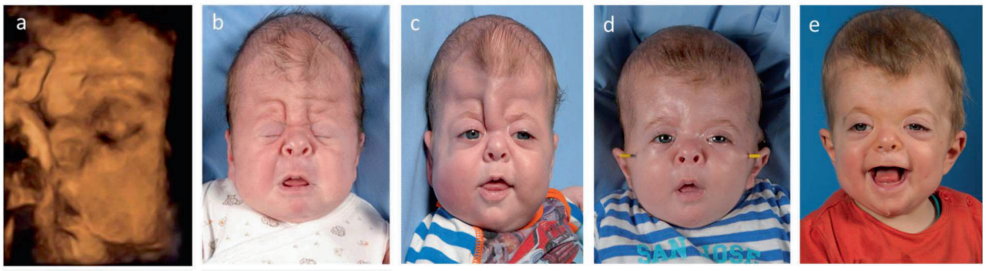

Figure 1: a. Prenatal ultrasound at 36 weeks of gestation showing midface hypoplasia. b. Patient at 3 weeks of age with clear bicoronal and metopic suture synostosis resulting in hypotelorism. c. Patient at 4 months of age showing increasing prominence of the synostosis. d. Patient at 5 months of age after monobloc procedure with facial pin resulting in amongst others a flattening of the forehead. e. Patient at 1 year of age after monobloc procedure and occipital distraction.

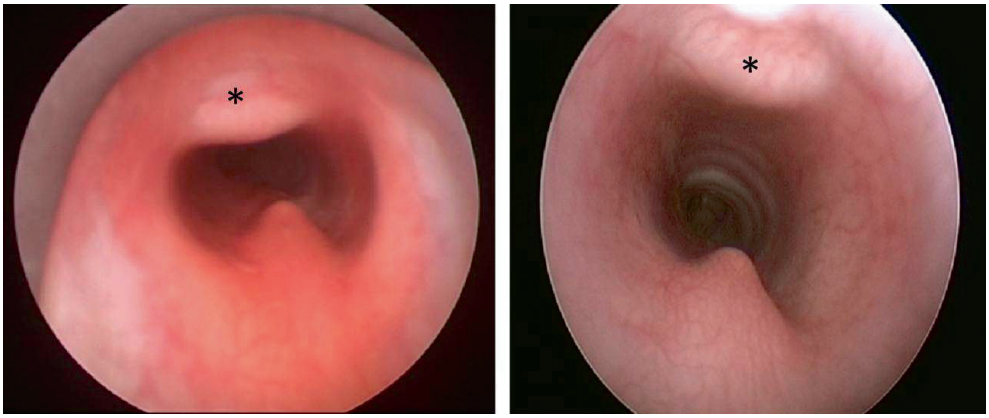

Figure 2: Endoscopic view of the larynx with the subglottic stenosis (Cotton-Myer grade II), based on a trapped first tracheal ring (indicated by *), 2 days post-partum (left) and at four and a half months just before first surgery (right). It should be noticed that the stenosis of the lumen is significantly less at the time of surgery than just after birth, which made intubation more feasible.

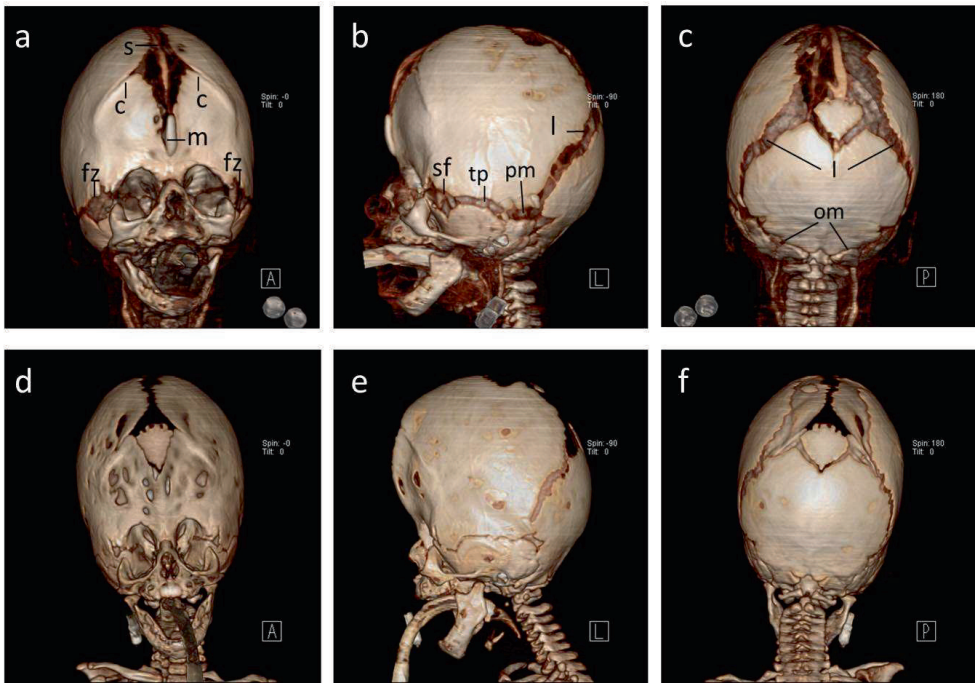

Figure 3: a-c. Patient's skull at the age of 2.5 weeks; totally closed coronal (c) sutures, partially closed metopic (m) suture, wide sagittal (s) and lambdoid (l) sutures and open fronto-zygomatic (fz), temporo-parietal (or squamosal) (tp), spheno-frontal (sf), parieto-mastoid (pm) and occipito-mastoid (om) sutures. Note the massive posterior skull defect. d-f. At the age of 3.5 months; the posterior skull defect remains, however there is total closure of the metopic and occipito-mastoid sutures and strong narrowing of nearly all other sutures (fz, sf, tp, pm, l).

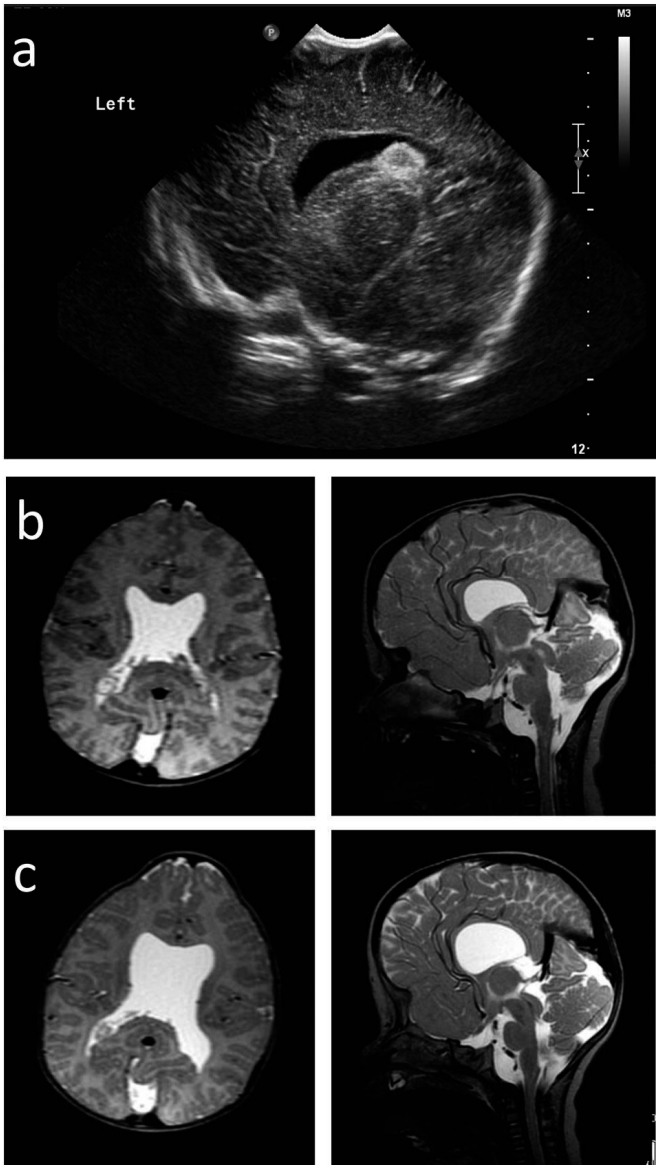

Figure 4: a. Postnatal ultrasound at 2 weeks of age with sagittal plane showing marginally enlarged lateral ventricles and choroid plexus hypertrophy. b. MR scan at 3 weeks of age showing a stable size of the lateral ventricles compared to the ultrasound. c. MR scan at 3.5 months of age showing enlarged central CSF spaces but no progression compared to the previous MR scan (ventriculomegaly).

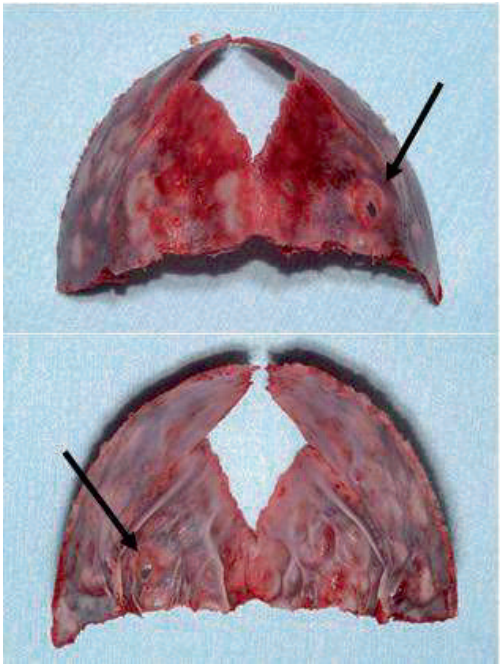

Figure 5: Frontal bone; notice the amount of impressiones digitatae and perforated bone at the left frontal part (arrows), which is the same area as where epileptic insults were initiated.

Table 1: Overview of the characteristics of our patient and of Apert syndrome in general

Apert syndrome
Our patient (c.755C>G p.Ser252Trp in *FGFR2*)
- *Metopic and bicoronal suture synostosis* - *Small anterior fontanel* - *Hypotelorism* - *Midface hypoplasia* - *Massive posterior fontanel* - *High arched narrow palate without cleft* - *Asymmetrical syndactyly of the hands* - *Normal mental development within the spectrum of Apert*
General characteristics of Apert syndrome
- *Craniosynostosis (bilateral coronal)* - *Anterior fontanel enlarged* - *Midface hypoplasia* - *Complex symmetric syndactyly of hands and feet* - *Intellectual disability*

Genotype-phenotype correlation

Genotype	*c.755C>G p.Ser252Trp in FGFR2*	*c.758C>G p.Pro253Arg in FGFR2*
Phenotype (differences)	*More severe craniofacial features* *(e.g. more often cleft palate)*	*More severe syndactyly of hands and feet* *Worse mental outcome*

PART III
-
OBSTRUCTIVE SLEEP APNEA & INTRACRANIAL HYPERTENSION IN CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS

CHAPTER 3

Sleep architecture linked to airway obstruction and intracranial hypertension in children with syndromic craniosynostosis

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Abstract

Background: Children with syndromic craniosynostosis often have obstructive sleep apnea (OSA) and intracranial hypertension. We aimed to evaluate 1) sleep architecture, and determine whether this is influenced by the presence of OSA and/or intracranial hypertension; 2) the effect of treatment on sleep architecture.

Methods: Patients with syndromic craniosynostosis treated at a national referral center, undergoing screening for OSA and intracranial hypertension. OSA was identified by polysomnography, and categorized into no, mild, moderate or severe. Intracranial hypertension was identified by presence of papilledema on fundoscopy, supplemented by optical coherence tomography and/or intracranial pressure monitoring. Sleep architecture: sleep was divided into rapid eye movement (REM) or non-REM sleep; respiratory effort related arousals (RERA) and sleep efficiency were scored.

Results: We included 39 patients (median age 5.9 years): 19 with neither OSA nor intracranial hypertension; 11 with OSA (4 moderate/severe); 6 with intracranial hypertension; 3 with OSA and intracranial hypertension. Patients with syndromic craniosynostosis, independent of presence of mild OSA and/or intracranial hypertension, have normal sleep architecture compared to age-matched controls. Patients with moderate/severe OSA have a higher RERA-index ($P<0.01$), lower sleep efficiency ($P=0.01$), and less REM sleep ($P=0.04$). An improvement in sleep architecture was observed following monobloc surgery (n=5; REM sleep: +5.3%, $P=0.04$).

Conclusions: Children with syndromic craniosynostosis have in principle normal sleep architecture. However, moderate/severe OSA does lead to disturbed sleep architecture, which fits within a framework of a unifying theory for OSA, intracranial hypertension and sleep.

Introduction

Children with syndromic craniosynostosis are at risk of both obstructive sleep apnea (OSA) and intracranial hypertension. OSA is common in these patients (68%) early in life[1], and the upper airway obstruction occurs at several levels.[2] Overtime, OSA may be stable or improves, although in some cases, OSA can impact on a child's life with potential neurobehavioral, cardiovascular and metabolic consequences[3], and even intracranial hypertension.[4, 5] Recently, we reported that a falling-off in occipital-frontal head circumference growth trajectory—a strong predictor of intracranial volume in these patients[6]—and moderate/severe OSA are important risk factors for the re-occurrence of intracranial hypertension after initial vault expansion.[7]

OSA and intracranial hypertension are, predominantly, rapid eye movement (REM) sleep-related phenomena.[4, 5, 8] The reverse relationship, i.e., the influence of OSA and intracranial hypertension on sleep architecture, is relatively unknown. Hayward proposed a model in craniosynostosis patients. OSA initiates a vicious cycle during REM sleep by hypoxia and hypercapnia, leading to cerebral vasodilatation, an increase in cerebral blood flow (/volume), and intracranial hypertension. Next, building on the so-called Rosner hypothesis[9, 10], a decrease in cerebral perfusion pressure follows, autoregulation ensures compensatory more vasodilatation to preserve cerebral blood flow, resulting in a further rise in intracranial hypertension; an arousal will ultimately break the cycle.[11]

We hypothesized that children with syndromic craniosynostosis, due to the presence of OSA and/or intracranial hypertension, are at risk of developing disturbed sleep architecture. This study has two main objectives: 1) to evaluate sleep architecture, and determine the influence of OSA and/or intracranial hypertension; 2) to assess the effect of treatment on sleep architecture.

Methods

Patients

A prospective observational cohort study (enrollment January 2012 – December 2014), was performed at the Dutch Craniofacial Center (Sophia Children's Hospital – Erasmus University Medical Center [MC], Rotterdam, the Netherlands). The Ethics Committee of the Erasmus MC (MEC-2005-273) approved the study. We included children with syndromic (i.e., Apert, Crouzon, Muenke, Saethre-Chotzen syndromes, based on genetic analysis) or complex craniosynostosis (defined as multiple suture synostoses in which no genetic cause is found yet), who underwent polysomnography (polygraphy combined with electroencephalography [EEG]) and screening for intracranial hypertension. Patients had a healthy weight based on BMI (see table 1), and none had a tracheostomy or cardiopulmonary disease. Parents of all subjects provided written informed consent.

Control group

Children with syndromic craniosynostosis were compared with aged-matched control subjects who were referred for polysomnography for reasons other than OSA (e.g., apparently life threatening event, unexplained daytime sleepiness). The control subjects did not have any co-morbidities (e.g., normal BMI (85th percentile), absence of tracheostomy, adenotonsillar hypertrophy, macroglossia, cardiopulmonary disease) or intracranial hypertension. Patients and controls were age-matched with a ratio of 1:1. Patients aged <1 year were matched to a control subject with a maximum difference in age at the time of polysomnography of 1 month; patients aged between 1 – 2 years were matched to a control subject with a maximum difference in age of 2 months; etc.

Standard protocol[7]

Our standardized treatment protocol includes vault expansion within the first year of life, or shortly after referral if the child was older at first presentation. For Apert and Crouzon syndromes the standard treatment is occipital expansion using springs, for Muenke and Saethre-Chotzen syndromes fronto-orbital advancement is preferred, and for complex craniosynostosis the type of surgery depends on the sutures involved. In case a patient suffers from significant obstructive sleep apnea and/or severe exorbitism a monobloc advancement with distraction is performed as initial procedure. In the absence of these strict functional indications, midface advancement is postponed until the age of 7-9 years for patients with Apert or Crouzon syndrome.

Polysomnography

All patients underwent polysomnography in the hospital, during which a variety of cardiorespiratory and neurophysiologic variables were assessed, accompanied by video.[12] Cardiorespiratory variables included: nasal airflow (thermistor), chest and abdominal wall motion, arterial oxygen-hemoglobin saturation using pulse oximetry (*SpO2*), snoring, and electrocardiogram. Additionally, a capillary blood gas test was performed, from which a capillary partial pressure of carbon dioxide (*ca pCO2*) was obtained.

A polysomnography study was considered suited for analysis if it provided a total sleep time (TST) of at least 360 minutes, free of artifact. Summary statistics and events were scored according to the updated rules for scoring respiratory events by the American Academy of Sleep Medicine (AASM).[13] An obstructive event was defined as reduction in nasal airflow of ≥90% (apnea) or 30-90% (hypopnea) for the duration of at least two breaths, in the presence of thoracic and abdominal breathing movement. A hypopnea was only included if it was associated with subsequent *SpO2*-desaturation of at least 3% from baseline or with an arousal. A mixed apnea is a combination of an obstructive apnea and a central apnea (central: no thoracic and abdominal breathing movement), followed by a *SpO2*-desaturation of ≥3% from baseline or an arousal.

The obstructive apnea-hypopnea index (oAHI) was calculated by adding the number of obstructive apneas, mixed apneas and obstructive hypopneas with *SpO2*-desaturation or arousal, divided by the TST; OSA was defined as an oAHI ≥ 1 per hour[14], and patients were subsequently subdivided into categories: mild OSA (oAHI ≥1 and <5), moderate OSA (oAHI ≥5 and <25) or severe OSA (oAHI ≥25).[15, 16]

Intracranial hypertension

Patients were screened for the presence of intracranial hypertension according to a standardized protocol:[7]

- Symptoms: history of headaches during the night or early morning, behavioral changes, frequent awakenings during the night, deterioration of vision
- Occipital-frontal head circumference growth trajectory: a downward deflection (defined as ≥0.5 standard deviation fall from baseline within 2 years).[7]
- Fundoscopy: pediatric ophthalmologist examination to diagnose papilledema[17]

When intracranial hypertension was suspected, but papilledema was absent also during repeat fundoscopy after 6 weeks, additional tests such as optical coherence tomography and/or invasive intracranial pressure (ICP) monitoring were performed:

- Optical coherence tomography: this examination makes use of broad-band near-infrared light sources, which can provide detailed information of the retina when applied through the eye.[18] The retinal nerve fiber layer is thicker when papilledema is present.[19, 20]
- Invasive ICP monitoring: this 24 hours examination was evaluated according to the following criteria[21-23]:
    - Baseline ICP value during the day and overnight: <10mmHg, normal; 10-15mmHg, borderline abnormal depending on the height and duration of abnormal plateaus (see below); >15mmHg, abnormal. Additionally, the trend of ICP values was evaluated, to check for any increase overnight.
    - Number of abnormal plateau waves: based on height (<25mmHg, normal; 25-35mmHg, borderline; >35mmHg, abnormal) and duration (<10 minutes, normal; 10-20 minutes, borderline; >20 minutes, abnormal).

Patients with papilledema, increased retina thickness, and increased ICP were all considered to have intracranial hypertension.

Sleep architecture

EEG was performed simultaneously with the polygraphy. Three electrodes (10-20 International System referenced to contralateral mastoid: frontal, central, and occipital) were placed. Electro-oculogram was recorded by two electrodes, placed 1 cm above the outer canthus of the right eye and 1 cm below the inner canthus of the left eye both referenced to the contralateral mastoid. Surface electromyogram was recorded using an electrocardiography electrode placed under the chin.

Scoring of EEG

The EEG was scored according to the AASM criteria, using sequential epochs of 30 seconds.[13] The occurrence of arousals and awakenings was scored with their possible relationship with respiratory events being assessed, and the hypnogram was constructed. Sleep stages were defined as REM sleep or non-REM sleep; non-REM was subdivided into stages N1, N2 and N3. Sleep efficiency was defined as TST indexed by total recording time.

Awake EEG was characterized by presence of occipital rhythm, eye blinks and muscle artifacts. Non-REM sleep stages N1, N2 and N3 were characterized by regular breathing, heart rate and decreased but preserved activity on chin EMG. N1 was defined by alpha drop-out, increased theta activity, presence of slow eye movements and vertex sharp waves. N2 was defined by sleep spindles and K-complexes with <20% delta activity. N3 was defined by >20% delta activity of >75μV. REM sleep was characterized by rapid saccadic eye movements,

irregular respirations, low or absent chin EMG activity and EEG showing mixed theta and alpha frequencies without K-complexes and sleep spindles. Arousals were scored if there was an abrupt shift of EEG frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3 seconds, with at least 10 seconds of stable sleep preceding the change; an arousal during REM sleep requires a concurrent increase in submental EMG lasting at least 1 second. A respiratory effort related arousal (RERA) was defined as a sequence of breaths lasting at least 10 seconds which does not meet criteria for an apnea or hypopnea and is characterized by increasing respiratory effort leading to an arousal from sleep. Major body movements were scored when movements and muscle artifacts obscured the EEG for more than half the epoch (>15 sec). Arousals, RERAs and major body movements were divided by TST to calculate an index per hour.

Statistical analysis

We performed the following analysis:

1. Children with syndromic craniosynostosis with neither OSA nor intracranial hypertension vs. age matched control subjects (normative values for sleep architecture are age-dependent).[24] *Multivariate analysis of variance (MANOVA) was used.*
2. Children with syndromic craniosynostosis with neither OSA nor intracranial hypertension (used as reference) vs. children with syndromic craniosynostosis with OSA and/or intracranial hypertension.
    A. We first compared patients with neither OSA nor intracranial hypertension to:
        a) patients with mild OSA, but without intracranial hypertension
        b) patients with moderate/severe OSA, but without intracranial hypertension.
    B. Next, we compared patients with neither OSA nor intracranial hypertension to patients with intracranial hypertension. Since patients with mild OSA (previous step) showed no difference in sleep architecture, we also included the patients who had both mild OSA and intracranial hypertension at the same time into the intracranial hypertension group.

Due to the relatively small numbers in each group, splitting patients into different age-subgroups (as in step 1) was not possible. However, compared to patients with neither OSA nor intracranial hypertension, the OSA groups had a similar *median* age making comparisons between these groups as a whole valid. The intracranial hypertension group had a lower median age, therefore this group was compared to a sample out of the group with neither OSA nor intracranial hypertension with similar median age; this is of importance because there exists a relationship between age and intracranial hypertension in craniosynostosis.[21, 25] *MANOVA was used.*

3. The effect of monobloc surgery (pre- to post-operative) on sleep architecture in children with syndromic craniosynostosis. Patients were evaluated before monobloc advancement surgery, and 6 weeks afterwards. In the event that these children have disturbed sleep architecture caused by OSA and/or intracranial hypertension, treatment would be expected to restore their sleep pattern. The effect of treatment might give an indication of the possible causal relationship of these factors with sleep architecture. *A repeated MANOVA model was used.*

Statistical significance was defined as P-value <0.05.

Results

Thirty-nine patients (20 boys, 51.3%) with syndromic craniosynostosis underwent polysomnography and screening for intracranial hypertension, and included cases of Apert (n=10), Crouzon (n=14), Muenke (n=3), Saethre-Chotzen (n=4) syndromes, and complex craniosynostosis (n=8). Median age at time of polysomnography was 5.9 years (range 0.2 – 17.2). See table 1.

There were 19 patients with neither OSA nor intracranial hypertension; 11 with only OSA (7 mild [median oAHI: 1.5, range 1.0-3.4], 4 moderate/severe [median oAHI: 13.9, range: 10.0-40.0]); 6 with only intracranial hypertension; and 3 had both mild OSA and intracranial hypertension.

Sleep architecture

Craniosynostosis vs. control patients

Sleep architecture of children with syndromic craniosynostosis with neither OSA nor intracranial hypertension is similar to that of age-matched control patients (table2).

Craniosynostosis: OSA and intracranial hypertension

Craniosynostosis patients with only mild OSA have similar sleep architecture compared to patients with neither OSA nor intracranial hypertension (table 2). Patients with intracranial hypertension (n=9, including 3 patients who also had mild OSA) have similar sleep architecture compared to those with neither OSA nor intracranial hypertension as well, with the exception of a higher RERA-index (1.3 vs. 0.7 per hour, P=0.01).

Patients with moderate/severe OSA have more N1 sleep (P<0.01), a higher arousal-index and RERA-index (both P<0.01), a lower sleep efficiency (P=0.01), and a decrease in REM sleep (P=0.04).

Distribution of respiratory events across sleep stages

Patients with OSA have respiratory events that occur more often during REM sleep than non-REM sleep. For the oAHI-index the distribution REM vs. non-REM is 53.9% vs. 46.1% (non-REM N1: 11.7; N2: 22.2; N3: 12.2), for the RERA-index this is 55.1% vs. 44.9% (non-REM N1: 18.9; N2: 16.9; N3: 9.1). However, in 3 of the 4 patients with moderate/severe OSA, the obstructive events and RERAs were so frequent that they occurred independent of sleep stage.

Capillary pCO2

Patients with moderate/severe OSA have higher *ca pCO2* than those with neither OSA nor intracranial hypertension (5.8 kPa vs. 5.1 kPa, P=0.04). The patients with mild OSA and those with intracranial hypertension do not have elevated *ca pCO2*.

Monobloc surgery: effect on sleep architecture

Five patients underwent monobloc advancement, and were evaluated for OSA and intracranial hypertension before and after surgery (see table 3). All patients had a decrease in RERA-index (mean -3.0/hour) and increase in REM sleep (mean +5.3%). However, only the pre- to post-operative increase of REM sleep is significant (F: 9.78, df: 1, P=0.04; see table 4).

Case illustration of the unifying theory for craniosynostosis

A 4-year-old boy with Crouzon syndrome is presented as illustration of our unifying theory for OSA, intracranial hypertension and sleep in syndromic craniosynostosis. The patient was referred relatively late and had papilledema already before first vault expansion at 1.1 years of age. Papilledema persisted, however, and he was subsequently treated by adenotonsillectomy (severe OSA) and ventriculoperitoneal shunt (hydrocephalus) which had unsatisfactory effect. A second vault expansion followed, after which papilledema initially disappeared, although it relapsed after 8 months. He demonstrated a clearly disturbed polysomnography with frequent apnea/hypopnea with desaturations provoking plateaus of raised ICP (see figure, Supplemental Digital Content). Overall, he had moderate OSA and raised baseline ICP with seven abnormal ICP-plateaus >35 mmHg, all of them occurring during REM sleep. Continuous positive airway pressure (CPAP) was started to treat OSA, after which papilledema disappeared and there was an improvement in sleep architecture.

Discussion

This study of sleep architecture in children with syndromic craniosynostosis has two key findings. First, children with syndromic craniosynostosis, independent of presence of mild OSA and/or intracranial hypertension, have normal sleep architecture. Patients with moderate/severe OSA do have disturbed sleep architecture with more RERAs, resulting in reduced sleep efficiency and a decrease in REM sleep. Second, monobloc advancement reduces OSA and intracranial hypertension, thereby improving sleep architecture.

Children with syndromic craniosynostosis have normal sleep architecture, i.e., similar to the healthy control subjects and comparable to descriptions in the literature.[24] Central sleep apnea in infants with syndromic craniosynostosis is highly related to young age and reduces with advancing age.[26] In patients with moderate/severe OSA—in keeping with our previous report, where this degree of OSA was associated with intracranial hypertension[7]—sleep architecture is disturbed. So far, in otherwise healthy children with OSA, there have been conflicting reports about sleep architecture. One report found that such patients have relatively normal sleep architecture[8], whereas two publications report disturbed sleep patterns (with decrease in REM sleep) in a small group of patients with severe OSA.[27, 28] In adults, disturbances are more consistent, with decrease in N3 sleep and REM sleep often reported.[29-31]

The relationship between OSA and intracranial hypertension has previously been described.[3, 4, 7] Monobloc advancement has the potential to treat both OSA and achieve resolution of intracranial hypertension.[2, 32] In our patients we cannot distinguish which element of the monobloc procedure contributed most to the improved sleep pattern. We nevertheless postulate that the improved sleep architecture after monobloc is mainly due to the reduction of OSA, since (moderate/severe) OSA leads to disturbed sleep architecture whereas the effect of intracranial hypertension on sleep architecture was limited to an increased number of RERAs in our patients.

Despite the above findings, there are limitations that need to be considered. First, patients with syndromic craniosynostosis present with variable severities, and, although the prevalence of OSA is high, relatively few patients have moderate/severe OSA. Second, we wonder whether all types of airway improvements have similar effects on intracranial hypertension and sleep architecture. For example, patients such as the one described in our case illustration who are treated with CPAP which is aimed specifically at OSA only would provide interesting insights. Unfortunately, insufficient data was available about other types of treatment for moderate/severe forms of OSA. Third, we use the presence of papilledema as the primary approach to indicate intracranial hypertension. Fundoscopy is a practical, useful and clinically relevant assessment in craniosynostosis because the development of intracranial hypertension is a gradual process and the main risk is optic nerve atrophy with visual loss. We are aware that the sensitivity of papilledema might be suboptimal particularly in younger children[33], therefore additional optical coherence tomography and/or ICP monitoring are performed when necessary, making this, in our

view, the most feasible approach to identify intracranial hypertension in patients with craniosynostosis.

Taken together, this sequence can be looked at within the framework of a unifying theory for craniosynostosis described by Hayward.[11] A vicious cycle exists between OSA, precipitating cerebral hypoperfusion stimuli (e.g., hypercapnia), reduced cerebral perfusion and autoregulatory responsivity, resulting in raised ICP (figure 1).[2, 7, 11, 26, 34, 35] OSA in craniosynostosis is additionally confirmed to be predominantly a REM sleep phenomenon, although this association is not as clear as described in normal children.[4, 5, 36-38] Patients with the most severe forms of OSA will ultimately have (obstructive) respiratory events occurring independent of sleep stage.

Conclusion

Children with syndromic craniosynostosis are not a priori at risk of developing disturbed sleep architecture. Patients with moderate/severe OSA, however, sometimes with concomitant intracranial hypertension, have more RERAs and consequently a decrease in REM sleep. Craniofacial surgery, such as monobloc surgery, appears to improve sleep architecture primarily by treating OSA and not direct reduction of intracranial hypertension.

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Table 1: Demographics

Patient characteristics	
Age (years)†	5.9 (range: 0.2 – 17.2)
Male	20 (51.3%)
Diagnosis	
- Apert	10
- Crouzon	14
- Muenke	3
- Saethre-Chotzen	4
- complex craniosynostosis	8
	N=39

BMI††		
Underweight	(p<5)	2
Healthy weight	(p5-85)	36
Overweight	(p85-95)	1
Obese	(p>95)	0

OSA and intracranial hypertension status	
Patients:	
- without OSA or intracranial hypertension	19
- OSA	11 *(7 mild, 4 moderate/severe)*
- intracranial hypertension	6
- OSA + intracranial hypertension	3

Numbers represent absolute numbers.

†Median

††Patients' BMI was calculated and subsequently compared to the percentile for children of the same gender and age, while for children under the age of 2 years old the WHO standards were consulted.

[Centers for Disease Control and Prevention; http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html; Retrieved 29-01-2016]

Table 2: Sleep architecture for healthy control subjects and patients with syndromic craniosynostosis, with OSA and intracranial hypertension subgroups

	N	Age (years)	TST	N1 (% of TST)	N2 (% of TST)	N3 (% of TST)	REM (% of TST)	REM-periods (no.)	Sleep efficiency (%)	Arousal index (no./hour)	RERA index (no./hour)	MBM index (no./hour)
HEALTHY CONTROLS												
<1 year	2	0.38	488	16.1	31.3	24.9	27.8	12	73.6	8.3	1.7	2.3
1-6 years	5	3.0 ± 1.4	537 ± 46	21.2 ± 17.2	32.3 ± 8.6	28.2 ± 15.9	18.3 ± 4.6	6.8 ± 2.5	78.0 ± 12.4	5.9 ± 1.0	0.2 ± 0.1	1.3 ± 0.6
>6 years	12	10.3 ± 3.7	475 ± 83	12.2 ± 10.1	45.2 ± 9.9	24.4 ± 13.3	18.2 ± 6.9	4.5 ± 1.4	80.6 ± 12.2	4.6 ± 1.8	0.1 ± 0.2	1.5 ± 0.9
P-value			*0.79*	*0.79*	*0.88*	*0.85*	*0.88*	*0.43*	*0.78*	*0.22*	*0.05*	*0.97*
CRANIOSYNOSTOSIS												
Patients without OSA or intracranial hypertension												
	19	**7.3 ± 5.0 6.8†**	**486 ± 78**	**14.0 ± 9.7**	**40.9 ± 10.3**	**26.2 ± 11.9**	**18.9 ± 7.4**	**5.2 ± 2.6**	**80.3 ± 13.3**	**6.4 ± 2.8**	**0.7 ± 0.5**	**1.5 ± 0.9**
Split into age groups												
<1 year	2	0.33	544	12.1	39.9	23.3	24.9	8	82.5	11.1	1.7	3.2
1-6 years	5	3.0 ± 1.2	503 ± 71	16.9 ± 6.7	34.0 ± 8.5	29.3 ± 16.5	19.8 ± 7.9	5.2 ± 2.2	78.4 ± 10.2	3.9 ± 1.6	0.5 ± 0.3	1.3 ± 0.7
>6 years	12	10.2 ± 3.7	469 ± 83	13.2 ± 11.5	43.9 ± 10.6	25.4 ± 10.9	17.5 ± 5.9	4.7 ± 2.5	80.8 ± 15.4	6.6 ± 2.2	0.6 ± 0.4	1.4 ± 0.8
Patients with mild OSA												
	7	5.9 ± 3.0 5.9†	546 ± 51	22.3 ± 13.3	35.9 ± 10.4	19.4 ± 5.9	22.3 ± 4.0	6.4 ± 1.4	83.5 ± 5.8	4.7 ± 2.2	0.7 ± 0.4	1.4 ± 0.8
P-value			*0.07*	*0.09*	*0.29*	*0.17*	*0.26*	*0.24*	*0.55*	*0.18*	*0.92*	*0.70*
Patients with moderate/severe OSA†												
	4	4.8	404	34.0	27.3	19.2	12.9	2.0	54.1	13.5	3.9	1.1
		0.8-12.4	332-531	22.0-64.2	16.2-46.0	13.2-27.4	3.1-14.9	0.3-5.3	48.7-74.8	7.3-22.3	3.3-6.9	0.9-1.8
P-value			*0.18*	*<0.01**	*0.09*	*0.33*	*0.04**	*0.08*	*0.01**	*<0.01**	*<0.01**	*0.55*
Patients with intracranial hypertension‡												
	9	4.1 ± 5.0 1.6†	528 ± 56	16.9 ± 13.9	36.5 ± 9.4	23.9 ± 8.5	22.7 ± 7.0	6.9 ± 2.2	81.6 ± 12.9	8.3 ± 3.7	1.3 ± 0.6	1.9 ± 0.7
P-value			*0.16*	*0.53*	*0.29*	*0.61*	*0.21*	*0.10*	*0.82*	*0.14*	*0.01**	*0.29*

Mean ± SD

†Median (IQR)

Patients with neither OSA nor intracranial hypertension were used as reference for comparisons.

A separate group for children aged <1 year was used, since they have a substantial higher percentage of REM sleep; however, given the low number of 2 patients in this group no SD is given.

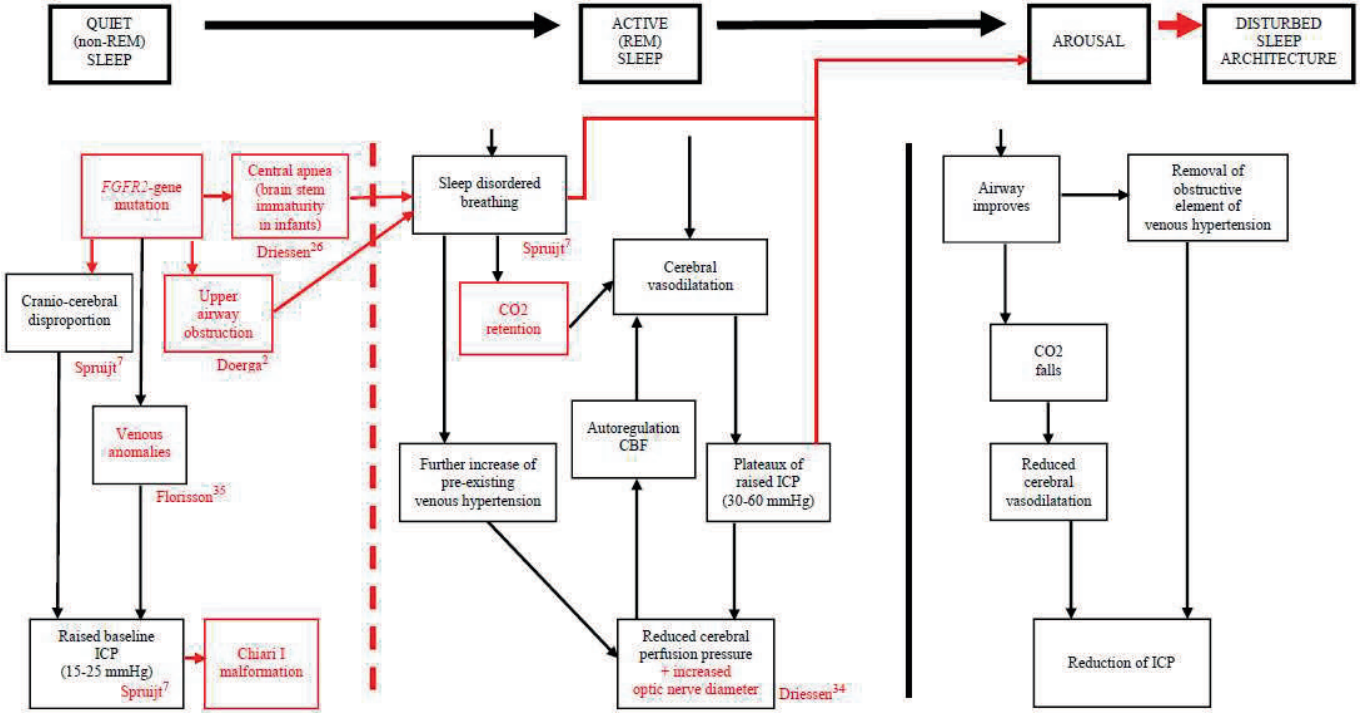
Table 3: Patient characteristics of the subjects evaluated before and after monobloc advancement

Patient	**Age at treatment** (years)	**Diagnosis**	**Primary indication for monobloc**	**Amount of midface advancement** (mm)	**OSA** (oAHI) *[pre-op vs. post-op]*	**Intracranial hypertension** *[pre-op. vs. post-op]*
1	0.4	Apert	OSA + intracranial hypertension	20.0	10.0 – 1.0	Yes – No
2	4.1	Apert	OSA + intracranial hypertension	20.0	40.0 – 7.4	Yes – No
3	7.9	Crouzon	OSA	17.5	10.4 – 0.1	No – No
4	9.7	Crouzon	OSA + exorbitism	17.0	1.2 – 0.7	No – No
5	5.5	Apert	OSA + intracranial hypertension	16.5	3.4 – 1.2	Yes – No

Table 4: Repeated measures MANOVA results, before and after surgery

	Mean ± SEM (preoperative)	**Mean ± SEM** (postoperative)	**F**	**df**	**p-value**
N1	26.5 ± 4.4	17.4 ± 4.5	3.13	1	0.15
N2	19.7 ± 6.3	29.8 ± 3.6	1.74	1	0.26
N3	38.8 ± 5.8	32.4 ± 4.8	1.29	1	0.32
REM	15.0 ± 0.7	20.3 ± 1.4	9.78	1	0.04*
REM periods	6.2 ± 1.1	5.2 ± 0.6	2.50	1	0.19
Sleep efficiency	74.7 ± 10.0	83.8 ± 5.2	1.84	1	0.25
Arousal index	12.9 ± 3.4	5.2 ± 1.4	3.14	1	0.15
RERA index	3.9 ± 1.0	0.8 ± 0.4	6.08	1	0.07
MBM index	1.5 ± 0.2	1.6 ± 0.7	0.04	1	0.85

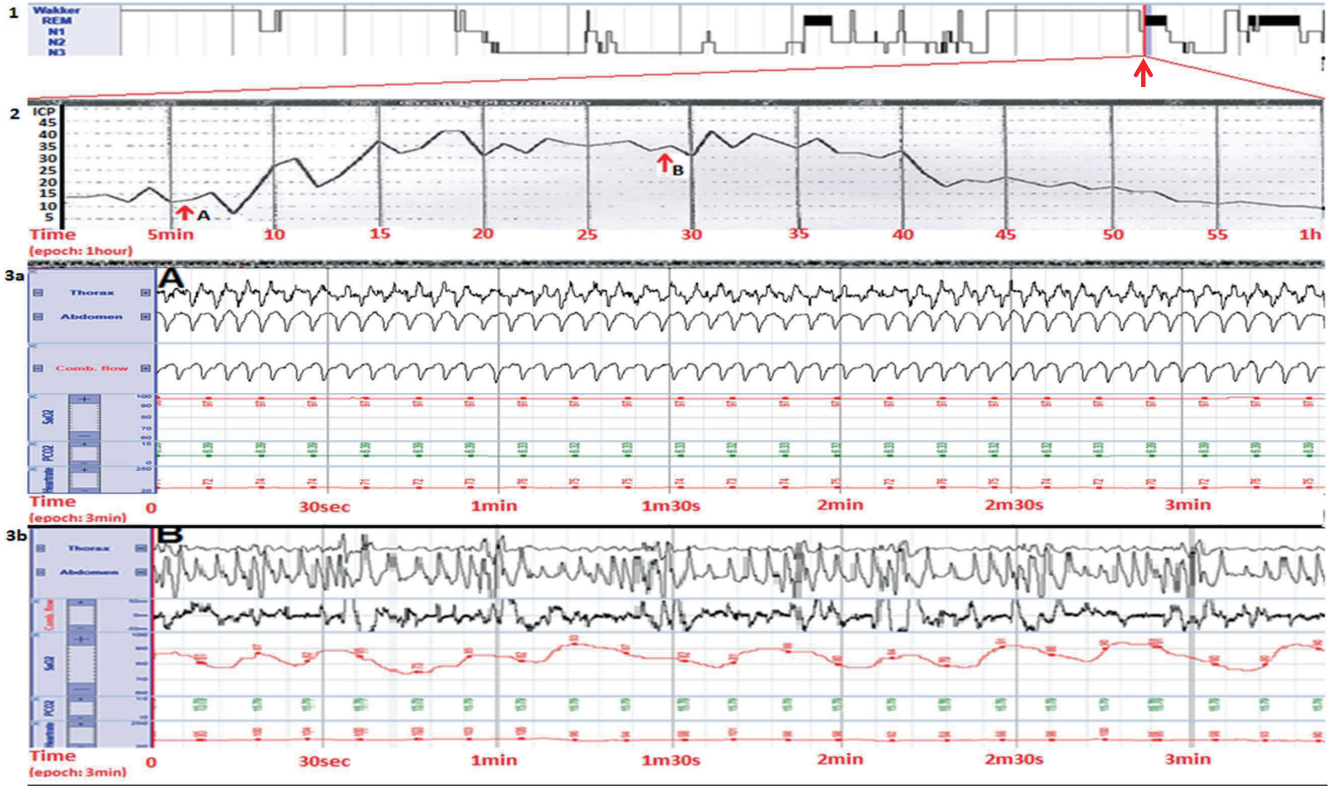
Figure 1: A unifying theory for craniosynostosis



OSA may lead, via precipitating cerebral hypoperfusion stimuli (e.g., hypercapnia), to reduced cerebral perfusion and autoregulatory responsivity, resulting in raised ICP. This vicious cycle can only be broken by a RERA, which leads to disturbed sleep architecture with a decrease in REM sleep.

Red font indicates updates of the original theory from Hayward, R. Venous hypertension and craniosynostosis. *Childs Nerv Syst* 2005;21(10):880-8

Supplemental Digital Content: A 4-year-old boy with Crouzon syndrome underwent simultaneous polysomnography and ICP monitoring



The arrow in the hypnogram indicates that the ICP-plateau occurs in REM sleep. Duration of the plateau is +/- 30 minutes, height >35 mmHg. Polysomnography during raised ICP (B) is clearly disturbed with the presence of frequent obstructive apnea/hypopnea and large fluctuations of the saturation profile.

CHAPTER 4

Upper airway endoscopy to optimize obstructive sleep apnea treatment in Apert and Crouzon syndromes

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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 multi-level 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.

Methods

Patients

In January 2006 a prospective observational cohort study started at the Dutch Craniofacial Center, Erasmus University Medical Center – 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 to 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 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 Bachar et al.[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 distribution 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 *pCO2*, 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 minutes, 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 multi-level obstruction. All but one patient with a multi-level 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).

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.

Discussion

This study about upper airway endoscopy in children with Apert or Crouzon syndrome has three key findings: 1.) OSA is often caused by multi-level 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 multi-level. 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 level of obstruction is not first identified with upper airway endoscopy.

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.

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 LeFort 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 inter-observer 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 afterwards.

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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Table 1: Patient characteristics

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

Values represent absolute numbers

†Mean (range)

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†	2	0	1	0	0	3
20	severe	Apert‡	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

†Patient with tracheal cannula due to severe OSA; ‡Due to severe OSA, one patient would later receive a tracheal cannula

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

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

		Pre-operative				**Post-operative**		
		Obstruction	SI	OSA	Surgery	Obstruction	SI	OSA
Patient								
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	LeFort II + BSSO	T1	1	no
7†	Crouzon	N2T1	3	severe	Monobloc	N1T1	2	mild
8†	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

†Patient with tracheal cannula due to severe OSA

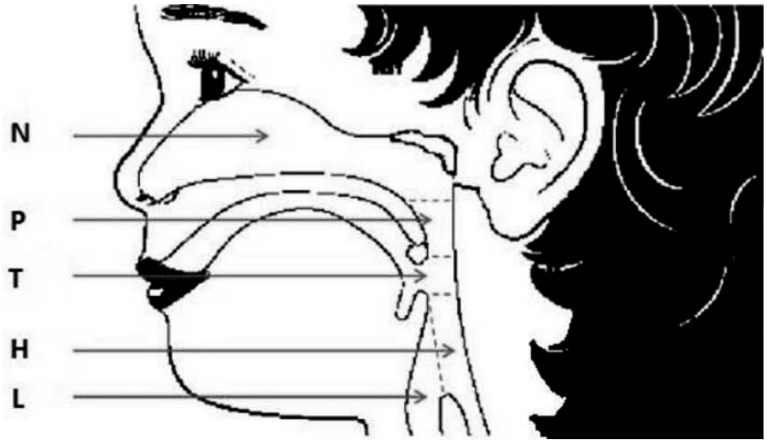

Figure 1: Levels of the upper respiratory tract used by Bachar et al.

N: nose and nasopharynx, P: uvulopalatine plane, T: tongue base, H: hypopharynx, L: larynx

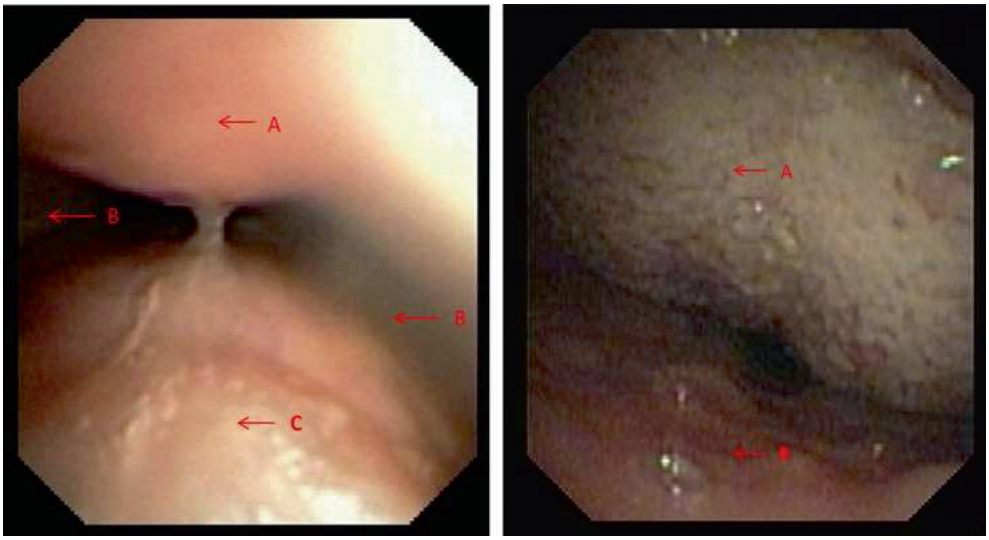

Figure 2: Endoscopic footage of obstructions at the level of the uvulopalatine plane and tongue base

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.

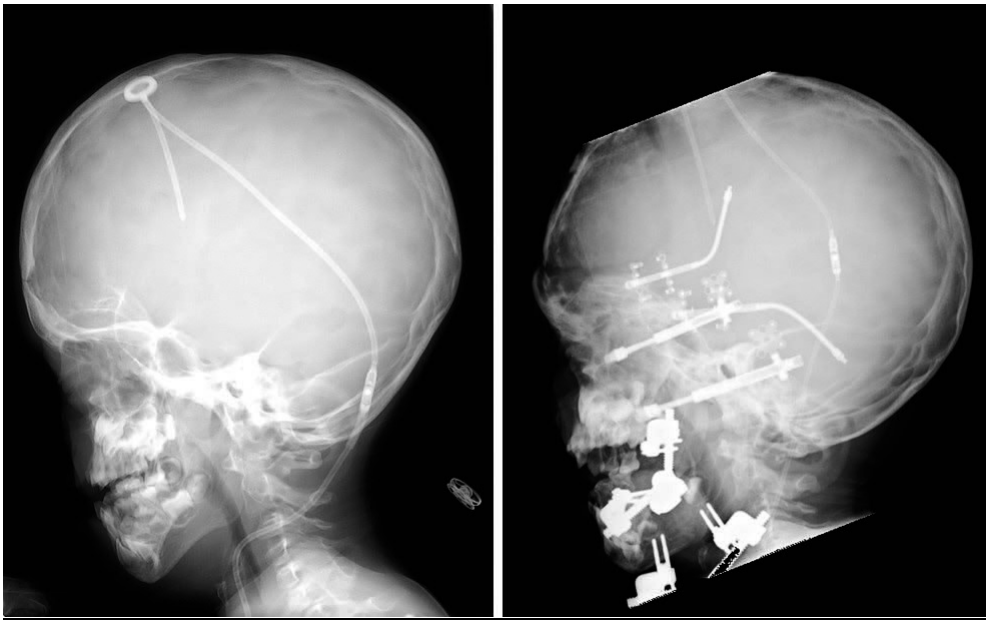

Figure 3: X-ray of a patient with midface and mandibular hypoplasia: a) pre-operatively; b) monobloc and mandibular advancement, during distraction

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.

CHAPTER 5

Abnormal transcranial Doppler cerebral blood flow velocity and blood pressure profiles in children with syndromic craniosynostosis and papilledema

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Abstract

Objective: Children with syndromic craniosynostosis are at risk of intracranial hypertension. This study aims to examine patient profiles of transcranial Doppler (TCD) cerebral blood flow velocity (CBFv) and systemic blood pressure (BP) in subjects with and without papilledema at the time of surgery, and subsequent effect of cranial vault expansion.

Methods: Prospective study of patients treated at a national referral center. Patients underwent TCD of the middle cerebral artery 1 day before and 3 weeks after surgery. Measurements included mean CBFv, peak systolic velocity, and end diastolic velocity; age-corrected resistive index (RI) was calculated. Systemic BP was recorded. Papilledema was used to indicate intracranial hypertension.

Results: Twelve patients (mean age 3.1 years, range 0.4-9.5) underwent TCD; 6 subjects had papilledema. Pre-operatively, patients with papilledema, in comparison to those without, had higher TCD values, RI, and BP (all $p=0.04$); post-operatively, the distinction regarding BP remained ($p=0.04$). There is a significant effect of time following vault surgery with a fall in RI ($p<0.01$).

Conclusion: Patients with syndromic craniosynostosis who have papilledema have a different TCD profile with raised BP. Vault surgery results in increased CBFv and fall in RI, however the associated systemic BP response to intracranial hypertension remained at short-term follow-up.

Introduction

Syndromic craniosynostosis is a congenital disorder characterized by the premature fusion of the skull sutures, facial anomalies, and malformations of the hands or feet.[1] Children with syndromic craniosynostosis are at risk of intracranial hypertension.[2] Prolonged intracranial hypertension can impair development of the central nervous system, potentially leading to behavioral disturbances, developmental delay, learning disabilities and visual loss by optic nerve atrophy.[3]

These patients usually receive cranial vault expansion within the first year of life in order to prevent or treat intracranial hypertension, by increasing intracranial volume, and decreasing venous hypertension.[4] Transcranial Doppler ultrasound (TCD) is an accurate, rapid, noninvasive technique that measures cerebral blood flow velocity (CBFv) dynamics.[5] TCD performed on the middle cerebral artery is able to measure changes in CBFv, but in the absence of an accurate measure of vessel diameter absolute changes in regional cerebral blood flow (CBF) can only be inferred.[6-8] Derived variables and calculations from the TCD signal are associated with changes in intracranial pressure (ICP).[9-13] For example, intracranial hypertension resulting from increased cerebrovascular resistance (CVR), leads to a decrease in CBFv.[14-16] To date, TCD study in craniosynostosis has so far mainly focused on its use as an alternative to invasive ICP monitoring.[5, 17]

The aims of this study are: 1) to use TCD in patients with syndromic craniosynostosis exhibiting papilledema, or not, in order to assess for difference in intracranial hemodynamics; and 2) to study the effect of vault expansion on these parameters.

Material and Methods

Patients

A prospective observational study was performed at the Dutch Craniofacial Center (Sophia Children's Hospital – Erasmus University Medical Center [MC], Rotterdam, the Netherlands), for which approval was given by the Ethics Committee of the Erasmus MC (MEC-2005-273). Children with syndromic (i.e., Apert, Crouzon, Saethre-Chotzen syndromes, based on genetic analysis) or complex craniosynostosis (defined as multiple suture synostoses in which no genetic cause is found yet) scheduled for vault expansion, who underwent TCD before and after surgery were included in the study. Parents of all subjects provided written informed consent.

Three patients were excluded. One patient underwent TCD only pre-operatively without any follow-up. In the other two patients, reliable measurements could not be made.

Transcranial Doppler

TCD was performed using a 2 MHz probe (Pioneer TC8080 system, Viasys Neurocare, Madison, WI). The middle cerebral artery was insonated via the transtemporal window (depth 44-54mm). Measurements included: Vmean, mean velocity (cm/sec); PSV, peak systolic velocity (cm/sec); and, EDV, end diastolic velocity (cm/sec). The *resistive index* (RI) is derived from these TCD variables[18], where RI equals [PSV-EDV] ÷ PSV). The RI was corrected for age RI, using normative values of the mean for age given by Bode et al.[19] We used the age-adjusted RI in the analysis.

Patients underwent TCD the day before surgery and 3 weeks after surgery, because at this point in time all patients returned to the outpatient clinic according to protocol for routine post-operative review. The examination took place with the child awake and in the supine position. At the time of TCD, blood pressure (BP) and hemoglobin concentration ([Hb]) were determined. No child had an elevated body temperature during the examination.

Surgical protocol

Our standardized treatment protocol includes vault expansion within the first year of life, or shortly after referral if the child was older at first presentation. The type of first craniofacial surgery performed depended on the diagnosis, for Apert and Crouzon syndromes occipital expansion (with springs), for Saethre-Chotzen syndrome fronto-orbital advancement, and for complex craniosynostosis it was based on the sutures involved. The only exception was when a patient suffered from severe obstructive sleep apnea and/or severe exorbitism, in that case a monobloc (midface advancement) was performed. In the event of recurrent intracranial

hypertension, the choice for the type of surgery was made individually per patient, based on, amongst others, age, additional symptoms, and type of prior surgery. Some children with Apert and Crouzon syndromes underwent midface advancement between 7 to 9 years, because of relative indications such as midface retrusion with malocclusion, exorbitism, lagophthalmus or psychosocial problems.

Fundoscopy

The presence of papilledema was used to indicate the presence of intracranial hypertension. All children underwent fundoscopy by an ophthalmologist prior to TCD to identify papilledema.

Statistical analysis

A spearman correlation of the values obtained on the left and right side of the skull was calculated. Since these correlations were significant (all $p<0.01$), this allowed for the use of one combined value for each variable. The significant correlation also allowed for the inclusion of two patients for whom only unilateral measurements were available.

Reference values of healthy controls described by Bode et al. were used for comparison with the values obtained in our craniosynostosis patients.[19] BP values were converted into z-scores (corrected for age and sex) using national norms for systolic and diastolic pressure, sBP-z and dBP-z respectively.[20] [Hb] was measured in the hospital hematology laboratory, which is accredited and approved to perform such analysis for clinical use.

We used multivariate analysis of variance (MANOVA) to compare the papilledema and non-papilledema group, before and after surgery. Analysis of variance (ANOVA) was used to compare the RI of craniosynostosis patients with those of healthy controls. Finally, a repeated measures model MANOVA was used to analyze time series (pre- to post-operative) for the age-adjusted RI (RI-index: RI derived/ RI reference). Statistical significance was defined as a p-value <0.05.

Results

TCD was performed in 12 children (8 boys), including cases of Apert (n=2), Crouzon (n=6), Saethre-Chotzen (n=1) and complex craniosynostosis (n=3), see table 1. One patient with Crouzon syndrome underwent surgery twice and also had TCD twice, with an interval of more than a year, leading to a total of 13 TCDs. Fundoscopy performed before TCD assessment showed papilledema on 6 occasions, and no papilledema on the other 7 occasions. Mean age at time of first TCD (i.e., 1 day before surgery) was 3.1 years (range: 0.4 – 9.5).

Pre-operative

Patients with papilledema have higher values for the TCD variables (Vmean, PSV, EDV) than patients without papilledema (whole model F: 4.23, df: 3, p=0.04), and the main effect is the difference in PSV (F: 7.2, df: 1, p=0.02). Patients with papilledema also have higher sBP-z and dBP-z (whole model F: 4.37, df: 2, p=0.04). The increase in BP is, on average, toward the upper limit of the normal range. See table 2.

Post-operative

Patients with papilledema have similar values for the TCD variables as those in patients without papilledema, with none of the individual variables reaching significance. However, the distinction between the groups when examining the respective z-scores for BP remains (whole model F: 4.66, df: 2, p=0.04). See table 3.

Over the course of the pre- to post-operative period there was a fall in [Hb] of 2.5g/dL, which may confound some of the TCD results. An additional follow-up TCD after three months, at a time when post-operative drop in [Hb] had likely returned to baseline, yielded similar TCD profile (whole model F: 6.90, df: 3, p=0.13) compared to the standard examination three weeks post-operative, suggesting that pre- to post-operative changes in [Hb] were of limited influence on the variables.

Time series for RI

Patients with papilledema have, before surgery, a higher RI compared to both those without papilledema as well as healthy control subjects (F: 4.99, df: 1, p=0.047, and F: 7.25, df: 1, p=0.02, respectively). After surgery, there is no significant difference between groups.

Overall, there is a significant effect of time (pre- to post-operative) with a fall in RI (F: 10.90, df: 1, $p<0.01$), which was not any greater in the papilledema group (i.e., no interaction between time and presence or absence of papilledema). See table 4.

Discussion

In this study of TCD assessment in children with syndromic craniosynostosis we have made three major observations. First, pre-operatively, subjects with papilledema, in comparison to those without, have higher values for the TCD measurements when considered together (most marked is the PSV) and higher sBP-z and dBP-z that are close to the upper limit of normal range. Second, pre-operative patients with papilledema have an increased RI, compared to patients without papilledema and to healthy control subjects. Third, over time (pre- to post-operative) both papilledema and non-papilledema groups have a fall in RI following cranial vault surgery; however, raised BP remains present in the short-term in subjects presenting with papilledema.

Pre-operative patients with papilledema have a different TCD profile and raised BP when compared with non-papilledema patients. This suggests that by the time papilledema develops in craniosynostosis there is already an associated systemic vascular response. Presumably, the adaptation to intracranial hypertension with evident papilledema includes a vascular component to maintain cerebral perfusion pressure. This response appears to be chronic (due to possible resetting or vascular remodeling) since it had not resolved by the time of post-operative follow-up.

The papilledema group also has a raised RI compared to healthy controls, suggesting abnormal brain hemodynamics with “downstream resistance” in the craniosynostosis subjects. This is likely caused by the presence of intracranial hypertension since our approach (i.e., patients examined while awake and in supine position without any symptoms of other disease) minimizes the role of other factors responsible for increased RI. These include extracranial factors (e.g., hypocapnia, hyperoxia, blood hyperviscosity, increased hematocrit, hypotension) and, most importantly, an intracranial factor—hydrocephalus—that was not present in any of our patients.

If we consider that a fall in RI reflects decrease in intracranial hypertension, then it would appear that at the time of surgery all subjects with craniosynostosis are on a spectrum of having intracranial hypertension, and it is just a question of degree in these two groups. It is possible that the non-papilledema group has a mild version of intracranial hypertension, with no evidence of effects on the eyes or any adaptive BP changes. The difference in the papilledema group is that their severity of intracranial hypertension was such that they developed papilledema and a vascular response that still had not resolved by the time of follow-up. The confounding factor is that the [Hb] fell during the pre- to post-operative interval, which might account for part of the elevated RI pre-operatively and the drop post-operatively in all patients. However, we consider this unlikely in view of the findings in three subjects that were followed-up for three months.

This study has the most homogeneous patient group compared to earlier studies of TCD in craniosynostosis, i.e., children with Apert, Crouzon and complex craniosynostosis who have the highest risk of intracranial hypertension. The patients with papilledema in our study have

TCD parameters consistent with what others have observed in intracranial hypertension, the added component is that our patients also have evidence of a systemic vascular response with hypertension. Rifkinson-Mann et al. used an elevated RI as indication for presence of intracranial hypertension in mainly scaphocephaly patients, and found this to be the case in a remarkably high percentage of 71% of their patients.[5] Similar to our results, Wang et al. found in one child with Apert syndrome an increase in CBFv and decrease in pulsatility index (PI) after surgery, and Govender et al. found in 6 of 7 syndromic patients after surgery a decreased PI.[17, 21] The PI is mathematically coupled to RI, where PI = [RI x PSV] ÷ mean CBFv. Iqbal et al., however, found in 4 patients with syndromic or complex craniosynostosis a more or less stable CBFv and increased PI after surgery[22], i.e., a reversed pattern compared to the other studies, for which no explanation was found.

We consider CBFv, and changes in CBFv, to be representative of CBF.[6-8] From first principles, CBFv is equal to (BP – ICP) / CVR, and a vault expansion reduces ICP by creating more intracranial volume. Craniosynostosis patients with papilledema have intracranial hypertension that is the result of a gradual process, with ICP in most cases 15-20 mmHg or slightly higher. Figure 1 outlines the processes at work in these subjects, based on our observations of BP, ICP (i.e., papilledema), and CVR (i.e., RI), leading to a post-operative rise in CBFv. In another intracranial pathophysiological setting—traumatic brain injury—TCD has likewise shown to be a valuable tool in identifying those at risk of intracranial hypertension.[15, 23-25] These patients have intracranial hypertension resulting from an acute insult, with ICP often >20 mmHg. Cerebral autoregulation is often impaired[26], and edema and hemorrhage raise ICP to pressures outside the limits of normal autoregulation, leading to a steep decrease in cerebral perfusion pressure, and with the normal dynamic compensation mechanism failing a decrease in CBF follows. An alteration in CBF is known to be a major determinant of survival, and in trauma it is due to cerebral ischemia.[27] In craniosynostosis our findings suggest a more indolent course with a component of systemic vascular adaptation.

Despite the above findings, there are some issues in this study that need to be reviewed closely. First, we consider CBFv to reflect CBF, which is likely but the latter has not been measured. The unknown hemodynamic factor is cerebral blood volume, of which we do not have any measure of its capacity or change after vault expansion; this change could either increase or decrease, while cerebral autoregulation ensures constant CBF. Second, three of our patients had unilateral synostosis. David et al. described asymmetrically decreased CBF ranging 0-30% in areas compressed secondary to the prematurely fused sutures.[28] We, however, observed similar bilateral values in our subjects; furthermore, the potential influence of this effect was addressed by using a combined left/right value for each variable. We also observed comparable post-operative results between patients who underwent frontal versus occipital surgery. Third, we are aware that several factors can influence cerebral hemodynamics but in our view our approach addresses most of these factors: a comfortable setting in the outpatient clinic (e.g., stable mental/emotional activity and heart rate), three weeks after surgery (e.g., no surgery related

stress or pain, no effect of anesthesia on blood gases and viscosity).[22] Cerebrovascular anatomy including the circle of Willis and collateral blood supply plays a role as well, and venous anomalies may be present in children with syndromic craniosynostosis.[29-31] The advantages of TCD is that it is an accurate, rapid, non-invasive, inexpensive, real-time monitor of CBFv and related parameters.

This study indicates that TCD measurements in combination with BP assessment are potentially useful in the clinical preoperative workup of children with syndromic craniosynostosis. Children with syndromic craniosynostosis should routinely undergo cranial vault expansion within the first year of life. TCD has potential as screening tool to identify patients at risk of (recurrent) intracranial hypertension, whereas BP provides insight into hemodynamic adaptation. We also believe that TCD could be an alternative for invasive ICP monitoring in patients without papilledema who are nevertheless suspected of intracranial hypertension, since papilledema might be a 'late' feature of intracranial TCD findings suggestive of intracranial hypertension. Finally, TCD can be used during follow-up to evaluate the effect of surgery, since effective vault expansion results in increased CBFv and fall in RI; persistent abnormalities might point to the presence of causal factors of intracranial hypertension that are not treated by a standard vault expansion and we, like others, speculate that obstructive sleep apnea may be responsible.[32-34]

Conclusion

Patients with syndromic craniosynostosis who have papilledema have a different TCD profile with raised BP when compared to patients presenting without papilledema. Vault surgery results in increased CBFv and fall in RI, however the associated systemic BP response to intracranial hypertension remained at short-term follow-up.

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Table 1: Patient characteristics

Patient	Diagnosis	Sex	Age (years)	Synostosis	Surgery	Papilledema
1	Apert	Male	0.4	Metopic + bicoronal	Monobloc	Yes
2	Apert	Female	9.5	Bicoronal	Monobloc	No
3	Crouzon	Male	3.4	Bicoronal	Occipital expansion (springs)	Yes
4	Crouzon	Male	3.8	Bicoronal + right lambdoid	Biparietal widening	Yes
5 A	Crouzon	Male	0.5	Bicoronal	Fronto-orbital advancement	No
B			1.7		Occipital expansion (springs)	Yes
6	Crouzon	Female	0.8	Bicoronal	Occipital expansion (springs)	No
7	Crouzon	Male	7.9	Pansynostosis	Monobloc	No
8	Crouzon	Female	6.9	Pansynostosis	Monobloc	No
9	Saethre-Chotzen	Female	1.9	Bicoronal	Fronto-orbital advancement	No
10	Complex	Male	0.5	Bicoronal	Occipital expansion (springs)	Yes
11	Complex	Male	1.7	Left coronal + sagittal + bi-lambdoid	Occipital expansion (springs) and fronto-orbital remodellation	Yes
12	Complex	Male	0.7	Right coronal + sagittal	Fronto-biparietal correction	No

Table 2: Pre-operative results, divided by papilledema and non-papilledema groups

	Vmean (cm/sec)	**PSV** (cm/sec)	**EDV** (cm/sec)	**sBP** (mmHg)	**dBP** (mmHg)	**sBP-z**	**dBP-z**	**Hb** (g/dL)
Non-papilledema	59.4 ± 5.6	91.6 ± 4.9	41.1 ± 5.8	92 ± 3	52 ± 2	0.11 ± 0.41	0.40 ± 0.28	12.0 ± 0.2
Papilledema	77.1 ± 10.5	125.9 ± 12.7	44.9 ± 7.1	103 ± 3	61 ± 6	1.58 ± 0.35	1.70 ± 0.48	11.7 ± 0.8

Mean ± SEM

Table 3: Post-operative results, divided by papilledema and non-papilledema groups

	Vmean (cm/sec)	**PSV** (cm/sec)	**EDV** (cm/sec)	**sBP** (mmHg)	**dBP** (mmHg)	**sBP-z**	**dBP-z**	**Hb** (g/dL)
Non-papilledema	78.2 ± 6.7	116.1 ± 8.0	56.3 ± 6.7	101 ± 3	58 ± 4	0.97 ± 0.32	0.94 ± 0.32	9.1 ± 0.5
Papilledema	86.9 ± 11.4	138.8 ± 16.6	59.0 ± 9.3	108 ± 3	66 ± 4	1.95 ± 0.35	2.17 ± 0.21	9.6 ± 0.2

Mean ± SEM

Table 4: Time series for resistive index, divided by papilledema and non-papilledema groups

	RI† (pre-operative)	**RI**† (post-operative)
Non-papilledema	1.01 ± 0.07	0.95 ± 0.06
Papilledema	1.18 ± 0.05	1.06 ± 0.04

Mean ± SEM

†The RI was corrected for age

Figure 1: Overview of the potential hemodynamic processes at work in craniosynostosis, with hypotheses divided by papilledema and non-papilledema groups.

CBFv ≈ CBF

CBFv = [BP – ICP] / CVR

Pre- to post-operative for non-papilledema:

PRE: ➔CBFv = [➔BP - ↑ICP] / ➔CVR

POST: ↑CBFv = [➔BP - ➔ICP] /↓CVR

Pre- to post-operative for papilledema:

PRE: ↑CBFv = [↑↑↑BP - ↑↑ICP] / ➔CVR

POST: ↑↑CBFv = [↑↑↑BP - ➔ICP] / ↓CVR

We consider CBFv to reflect CBF (➔ = normal, ↑ = increased, and ↓ = decreased)

PART IV
-
MANAGEMENT OF CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS

CHAPTER 6

Algorithm for the management of intracranial hypertension in children with syndromic craniosynostosis

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Abstract

Background: To examine the relationship between head growth, obstructive sleep apnea (OSA) and intracranial hypertension in patients with syndromic or complex craniosynostosis, and to evaluate our standardized treatment protocol for the management of intracranial hypertension in these patients.

Methods: Prospective observational cohort study of patients with syndromic craniosynostosis at a national referral center, treated according to a standardized protocol. Measurements: occipital-frontal head circumference (OFC), with growth arrest defined as downward deflection in OFC trajectory ≥0.5 SD fall from baseline over 2 years, or lack of change in OFC growth curve; sleep studies, with results dichotomized into no/mild versus moderate/severe OSA; fundoscopy to indicate papilledema, supplemented by optical coherence tomography and/or intracranial pressure monitoring to identify intracranial hypertension.

Results: We included 62 patients, of whom 21 (33.9%) had intracranial hypertension, 39 (62.9%) OSA, and 20 (32.3%) OFC growth arrest during the study. Age at which intracranial hypertension first occurred was 2.0 years (range: 0.4-6.0). Pre-operatively 13 (21.0%) patients had intracranial hypertension, which was only associated with moderate/severe OSA (P=0.012). In the first year after surgery, intracranial hypertension was particularly related to OFC growth arrest (P=0.006). Beyond a year after surgery, intracranial hypertension was associated with a combination of OFC growth arrest (P<0.001) and moderate/severe OSA (P=0.007).

Conclusions: Children with syndromic craniosynostosis are at risk of intracranial hypertension. The major determinant of this after vault expansion is impaired head growth, which may occur at varying age. Presence of moderate/severe OSA also significantly increases the risk of intracranial hypertension.

Introduction

Syndromic craniosynostosis is a congenital disorder present in 1-in-8400 births, characterized by premature fusion of skull sutures and additional congenital anomalies.[1]

Patients with craniosynostosis are at risk of intracranial hypertension because of cranio-cerebral disproportion, obstructive sleep apnea (OSA), hydrocephalus and venous outflow obstruction.[2-4] Intracranial pressure (ICP) represents the net effect of intracranial volume and content, brain compliance and cerebrospinal fluid dynamics.[5] Previous studies have shown the risk of intracranial hypertension prior to cranial vault expansion to be related to the suture(s) affected as well as the underlying syndrome (e.g. trigonocephaly 8%, scaphocephaly 13%, frontal plagiocephaly 16%, brachycephaly 31%, Apert 45%, Crouzon 63%, Muenke 0%, Saethre-Chotzen 29%, complex 47%).[6-9] Prolonged intracranial hypertension can have significant impact on development, behavior, learning, and may ultimately lead to irreversible visual loss caused by optic nerve atrophy.[10] Unfortunately, the recognition of intracranial hypertension is difficult because symptoms develop gradually and are non-specific.[11] Therefore, one option for early identification of elevated ICP is to undertake diagnostic invasive ICP monitoring.[12, 13] However, this investigation requires a surgical procedure and hospital admission, which is not feasible for routine screening. Hence, in a clinical setting, fundoscopy is being used to screen for intracranial hypertension, since papilledema is a sign of elevated ICP.

This study has two main objectives: first, to examine the relationship between head growth, OSA and intracranial hypertension; second, to evaluate our standardized treatment protocol for the management of intracranial hypertension in patients with syndromic craniosynostosis.

Methods

Patients

A prospective observational cohort study (recruitment January 2007 to December 2012), including all patients with syndromic (i.e. Apert, Crouzon, Muenke, Saethre-Chotzen, based on genetic analysis) or complex craniosynostosis (multiple suture synostoses in which no genetic cause is identified) treated at the Dutch Craniofacial Center (Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands). Inclusion criteria were age 3 years or younger at time of presentation, and follow-up of at least 1 year after referral. Exclusion criterion was vault surgery before referral. The Institutional Human Research Ethics Board approved this research (Erasmus MC, MEC-2005-273) and in all patients, parents provided written-informed consent.

Occipital Frontal Head Circumference (OFC)

OFC was measured during each visit to the clinic. These measurements were assessed in relation to National Standards in the Netherlands.[14] Downward deflection in the OFC trajectory from serial measurements over time was defined as follows: ≥0.5 standard deviation (SD) fall from baseline over 2 years, or lack of change in OFC growth curve.

Sleep study

Patients underwent sleep studies pre-operatively, post-operatively and annually until the age of 6 years, and once every 3 years thereafter. An additional sleep study was performed when OSA was suspected.

Our standardized clinical protocol involves sleep studies in the hospital or at home. A hospital sleep study (level I polysomnography) was carried out in cases of positive Brouillette score[15], or other signs of OSA. During the sleep studies a variety of cardiorespiratory variables were assessed, including nasal airflow, chest and abdominal wall motion and arterial oxygen-hemoglobin saturation using pulse oximetry (SpO_2).

A successful sleep study was defined as providing at least 360 minutes of data free of artifacts. The following summary statistics and events were defined and scored[16]:

1) Total sleep time defined as duration of total sleep time based on the period during which breathing was regular.
2) Apnea and hypopnea defined as a reduction in nasal airflow of ≥80% (apnea) or 50-80% (hypopnea) for the length of at least two breaths, with hypopnea only included if subsequent SpO_2 desaturation of at least 4% from baseline occurred. Thoracic and

abdominal breathing movement could be present (obstruction) or absent (central). A mixed apnea is a combination of an obstructive and a central apnea.

3) Obstructive apnea-hypopnea index (oAHI) defined as number of obstructive apneas, mixed apneas and obstructive hypopneas with SpO_2 desaturation, indexed by the total sleep time.
4) OSA was defined as an oAHI ≥1 per hour. Patients were subsequently subdivided as either mild OSA (oAHI ≥1 and <5), or moderate OSA (oAHI ≥5 and <24), or severe OSA (oAHI ≥25).[17-19]

Fundoscopy

The presence of papilledema was used to indicate intracranial hypertension, and therefore elevated ICP. All patients underwent fundoscopy by an ophthalmologist at set time points: pre-operative, 1 day before surgery, 3 months after surgery, from the age of 1 year every 6 months until aged 4 years, and then annually. After the age of 6 years, patients were seen annually and fundoscopy was performed only if presenting symptoms were indicative for intracranial hypertension. In the event of papilledema, additional fundoscopy was carried out within 4-6 weeks to confirm its presence.

Optical coherence tomography (OCT)

OCT was performed to calculate the total retinal thickness (TRT) by centralizing the patient's optic nerve head using a fixation light[20], in patients where intracranial hypertension was suspected but papilledema was absent. OCT makes use of broad-band near-infrared light sources, which have a considerable penetration of up to 3 mm into tissue and can therefore provide detailed information of the retina when applied through the eye.[20-22] OCT has shown that the retinal nerve fiber layer is thicker when papilledema is present[23, 24], while thereafter progressive thinning occurs in the event of optic nerve atrophy.[25]

ICP monitoring

Invasive ICP monitoring was used for 24 hours, in patients where intracranial hypertension was suspected but papilledema was absent and retinal thickness was normal. In this assessment we made the following evaluations:

1) *Baseline ICP value during day and overnight:* <10mmHg, normal; 10-15mmHg, borderline abnormal (see below since number, height and duration of plateau waves are

decisive); >15mmHg, abnormal; additionally, values at the beginning and end of the night were compared to check for any overnight increase in ICP.

2) *Number of abnormal plateau waves:* based on the height (<25mmHg normal, 25-35mmHg borderline, >35mmHg abnormal); and duration (<10 minutes normal, 10-20 minutes borderline, >20 minutes abnormal).

Standard treatment protocol for syndromic craniosynostosis in our hospital

Patients underwent OFC measurement and fundoscopy during initial assessment, and were scheduled for a sleep study, skull imaging (3D-computed tomography scan) and brain imaging using magnetic resonance imaging (MRI). Subsequently, they were scheduled for vault expansion within the first year, or shortly after referral if the child was older at first presentation. After surgery, patients had frequent routine follow-up appointments, eventually extended to at least annually, to screen for intracranial hypertension. These reviews included assessment of headaches, behavioral changes, frequent awakenings during the night, or deterioration of vision, OFC measurement and fundoscopy. When intracranial hypertension was suspected, but papilledema was absent, additional tests were performed: repeat fundoscopy 6 weeks later, a sleep study, an MRI, an OCT, and in some cases ICP monitoring.

In the event of identifying intracranial hypertension after vault expansion, an analysis of the available data was done and treatment was aimed at the causal factor. For example, growth arrest was treated by a second vault expansion. Presence of significant OSA could first be treated with nasal steroids, adenotonsillectomy, nocturnal oxygen, continuous positive airway pressure or midface advancement. A ventriculoperitoneal(VP) shunt was generally not preferable, since it reduces the intrinsic growth impulse of the brain on the skull and renders the patient dependent on its function; some patients may however ultimately need a VP-shunt, such as those with progressive hydrocephalus after vault expansion.

Intracranial hypertension is expected to lessen within 3 months following treatment, and when persistent, additional tests such as OCT and/or ICP monitoring were undertaken and visual acuity monitored repeatedly.

Statistical analysis

Analyses were performed using IBM SPSS and R software.[26] Continuous variables are expressed as mean (95% confidence interval) unless stated otherwise, and an independent T-test was used to compare continuous variables. Categorical variables are expressed as number (percentage), and comparisons were made using either a Chi-square test, or a Fisher's exact test when the expected value in any of the cells of the 2x2 contingency table was below 5.

Patients with papilledema, or without papilledema but with abnormally increased TRT or elevated ICP, were all considered to have intracranial hypertension.

Analyses were undertaken in 3 time frames:1) pre-operative; 2) 1 year after vault surgery; and 3) >1 year after vault surgery. For each patient an analysis was made of the OFC growth curve, sleep study result and intracranial hypertension status that were closest in time to each other, with a maximum interval of three months. Since some patients did not have a sleep study in each time frame, for reasons that could be related to the outcome, we used an available case analysis (i.e. missing at random analysis). This approach evaluates the relation between head growth, OSA and intracranial hypertension, and preserves the longitudinal design of the study.

As a preliminary test, we determined whether mild OSA (versus no OSA) was associated with intracranial hypertension. Since the test showed no significant association in any of the time frames, which is in-keeping with the literature, we dichotomized the sleep study results into no/mild OSA and moderate/severe OSA, where the former served as reference group for further analyses. Subsequently, the association between moderate/severe OSA and intracranial hypertension was tested.

Significance was defined as $P<0.05$. However, for the main analyses within the 3 time frames (i.e., association of OFC and moderate/severe OSA with intracranial hypertension) Bonferroni correction for multiple testing was applied for these analyses with significance defined as $P<0.017$.

Results

We included 62 patients (32 boys, 51.6%) with syndromic or complex craniosynostosis, including Apert (n=10), Crouzon (n=11), Muenke (n=9), Saethre-Chotzen (n=6) and complex craniosynostosis (n=26). Age at time of most recent follow-up was 6.0 years (5.5-6.5) (table 1).

Figure 1 is a flowchart summarizing all results, including the treatments prescribed. Tables 2 and 3 give an of the OFC growth curve trajectory and OSA data.

All patients underwent fundoscopy, and 14 underwent OCT and 5 ICP monitoring; 18 patients had papilledema, while 2 had abnormal TRT and 1 had elevated ICP, despite not having papilledema. Combined, 21 (33.9%) patients had intracranial hypertension, 39 (62.9%) patients had OSA, and 20 (32.3%) had a falling-off in OFC growth curve trajectory at least once during the study. Age at which intracranial hypertension first occurred was 2.0 years (range: 0.4-6.0).

Head growth, OSA and intracranial hypertension

Before vault surgery

At presentation, 13 (21.0%) patients had intracranial hypertension. Age at first presentation was no different between patients with or without intracranial hypertension (mean and range 0.6 years [0.0-2.5] versus 0.4 years [0.1-2.9], P=0.417), nor was age at time of surgery (mean and range 0.9 years [0.4-2.7] versus 0.8 years [0.4-3.2], P=0.499).

The OFC was no different between patients with or without intracranial hypertension (OFC-SD score -0.41 SD [-1.22-0.39] versus -0.28 SD [-0.75-0.19], P=0.774), nor was there any difference during subsequent follow-up. Intracranial hypertension was not associated with falling-off in OFC growth curve trajectory (P=0.378), but it was associated with moderate/severe OSA (P=0.012).

1 Year after vault surgery

At 1 year after surgery, 5 (8.1%) patients had intracranial hypertension, which was associated with falling-off in OFC growth curve trajectory (P=0.006), but not associated with moderate/severe OSA (P=0.116).

>1 Year after vault surgery

At >1 year after surgery, 13 (21.0%) patients had intracranial hypertension (i.e. 3 relapse, 3 persistent and 7 new cases). Age of occurrence of intracranial hypertension in the patients with relapse or new intracranial hypertension was 3.5 years (range: 1.6-6.0) which, 6 months earlier at 3.0 years (range: 1.5-6.0), was preceded by falling-off in OFC growth curve trajectory (0.9 SD [0.8-1.0], see figure 2). Intracranial hypertension in this time frame was associated with a combination of falling-off in OFC growth curve trajectory ($P<0.001$) and moderate/severe OSA ($P=0.007$).

Discussion

We have identified three key findings in this prospective cohort study of children with syndromic or complex craniosynostosis that will influence future clinical practice. First, at the time of presentation to a national referral center we have found a high prevalence (21%) of intracranial hypertension. Vault surgery has a major impact on this pathophysiology in that within a year of surgery only 8% of subjects had evidence of intracranial hypertension. However, the prevalence of intracranial hypertension subsequently returned to a high level (21%). Second, a significant proportion (63%) of our patients had OSA at some time during follow-up. Third, after vault expansion, there appears to be an important interaction between head growth, OSA, and intracranial hypertension. In particular, a falling-off in OFC growth curve trajectory is associated with the development of intracranial hypertension. Overall, moderate/severe OSA has a lower prevalence, but also significantly increased the risk of intracranial hypertension.

Pre-operatively, we found a high prevalence of intracranial hypertension, which was not related to age at time of referral, indicating that patients with intracranial hypertension were not referred too late nor were they operated upon later. We did however find an association between intracranial hypertension and moderate/severe OSA, suggesting that it is this severity of OSA that exposes the young pre-surgical patient, and makes them worse. This observation confirms two previous findings in untreated patients: Renier et al.[27] were the first to address the correlation between sleep and elevated ICP; Gonsalez et al.[2] demonstrated that apneic episodes resulted in an increased ICP-baseline, and that during rapid eye movement (REM) sleep ICP became elevated.

Vault surgery has a major impact and reduces the presence of intracranial hypertension. One year after vault expansion, there were few patients (8%) with intracranial hypertension, which emphasizes the advantage of routine surgery within the first year of life, compared to monitoring for intracranial hypertension and only perform surgery when this has been diagnosed; a majority of 83% of Apert syndrome patients managed according to the latter approach developed intracranial hypertension (average age: 18 months), requiring vault expansion and/or other treatment.[28] However, also in our study there were still some patients with intracranial hypertension, which indicates some other causal factor present that is not treated by surgery. Vault expansion is effective treatment for most factors contributing to the development of intracranial hypertension, including cranio-cerebral disproportion, most cases of hydrocephalus and venous outflow obstruction. OSA is the only factor not addressed by standard surgery and, in our practice, we consider the possibility of this diagnosis. It is therefore interesting that in our series all patients with persistent intracranial hypertension had persistent OSA.

During late follow-up, the prevalence of intracranial hypertension rises again to pre-surgical levels. Here we found an interaction between head growth, OSA and intracranial hypertension. Whereas initially after surgery only a falling-off in OFC growth curve trajectory was associated with intracranial hypertension, at >1 year after surgery, at an age when most

sutural growth is close to completion, we also found an association with moderate/severe OSA. We believe that this is the first study evaluating head growth, OSA and intracranial hypertension all together, while at the same time confirming the findings of previous studies.[3, 8, 29-31] However, regarding the relationship between OSA and intracranial hypertension, the underlying mechanism is not fully understood. It is often difficult to determine whether a patient is affected by OSA and intracranial hypertension together (e.g. more severe phenotype), or whether a patient has intracranial hypertension secondary to OSA. Our hypothesis is that during REM-sleep, when brain activity and perfusion peak, nasopharyngeal atonia and airway collapsibility increases leading to obstructive apnea. Apnea may cause hypoxia, hypercapnia and reactive cerebral vasodilatation, thereby increasing cerebral blood flow leading to a rise in ICP. Subsequent decrease in cerebral perfusion pressure may lead to compensatory vasodilatation and a further rise in ICP. This vicious cycle during sleep – OSA leading to decrease in cerebral perfusion and intracranial hypertension – can be broken by arousal and correction of blood gas homeostasis.

Despite the above findings, there are limitations that need to be considered. Primarily, we use the presence of papilledema to indicate intracranial hypertension. Fundoscopy is not only practical, but also a useful and clinically relevant assessment in patients with craniosynostosis because: a) the development of intracranial hypertension in patients with craniosynostosis is a gradual and chronic process, which is likely to result in papilledema; and b) the main risk for craniosynostosis patients is irreversible visual loss caused by optic nerve atrophy, affecting the optic nerve head. Taken together, this approach (combined with additional OCT and/or ICP monitoring when necessary) is, in our view, the most feasible in patients with craniosynostosis. In theory, there may be patients with elevated ICP who do not have any symptoms or papilledema, but this constellation is probably not clinically relevant, and also rare. We are especially alert in non-standard patients, including patients with severe optic atrophy where fundoscopy (and OCT) might not be reliable, which means that when intracranial hypertension is suspected there might be an earlier indication for ICP monitoring. Finally, we have focused on just the main factors contributing to intracranial hypertension in craniosynostosis. We are currently working on a model which incorporates all identifiable risk factors – head growth, OSA, hydrocephalus, venous hypertension, intracranial volume, Chiari I malformation, vault surgery and other treatments (e.g. OSA-treatment or VP-shunt) – to determine their contribution and complex interaction in the development of intracranial hypertension.

The central clinical message from our study of craniosynostosis patients is that intracranial hypertension is an important finding and early referral for multidisciplinary treatment is warranted. In our clinical algorithm patients should receive specialist follow-up after vault expansion. This follow-up includes symptom review, assessment for OFC growth arrest, and screening fundoscopy in all cases. When intracranial hypertension is evident or suspected, the potential influence of moderate/severe OSA should be considered as a contributory factor.

Conclusion

Children with syndromic or complex craniosynostosis are at risk of intracranial hypertension, because of a complex interaction between head growth, timing in relation to surgery (pre-operative, early- and late-postoperative period), and moderate/severe OSA. The major determinant of intracranial hypertension after vault expansion is impaired head growth, which may occur at varying age. Presence of moderate/severe OSA also significantly increases the risk of intracranial hypertension.

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Table 1: General characteristics of the patient population

	Intracranial hypertension	
	Present (n=21)	Absent (n=41)
Age at presentation (years)[a]	0.6 (0.0 – 2.5)	0.4 (0.1 – 2.9)
Age at surgery (years)[a]	0.9 (0.4 – 2.7)	0.8 (0.4 – 3.2)
Age at time of most recent follow-up (years)[b]	6.3 (5.4 – 7.3)	5.8 (5.2 – 6.4)
Gender (male)	11	21
Apert	5	5
Crouzon	6	5
Muenke	1	8
Saethre-Chotzen	2	4
Complex	7	19
OSA		
Patients with OSA (at least once during the study)	15	24
Head growth		
Patients with OFC growth arrest (at least once during the study)	13	7

Values represent absolute patient numbers, unless stated otherwise.

[a]Mean (range). [b]Mean (95% confidence interval).

Table 2: Analysis OFC growth curve trajectory data per time-frame: 1) before vault surgery, 2) 1 year after vault surgery, 3) >1 year after vault surgery

Prior to vault expansion (n=62)			
	Intracranial hypertension (n=13)	No intracranial hypertension (n=49)	
OFC (SD)[a]	-0.41 (-1.22 – 0.39)	-0.28 (-0.75 – 0.19)	P=0.774
Patients with falling-off OFC growth curve	1	1	P=0.378
1 Year after vault expansion (n=60)[†]			
	Intracranial hypertension (n=5)	No intracranial hypertension (n=55)	Total
OFC (SD)[a]	1.29 (0.01 – 2.58)	0.64 (0.22 – 1.07)	P=0.353
Patients with falling-off OFC growth curve	2	0	P=0.006*
>1 Year after vault expansion (n=60)[†]			
	Intracranial hypertension (n=13)	No intracranial hypertension (n=47)	Total
OFC (SD)[a]	0.03 (-0.88 – 0.95)	0.00 (-0.38 – 0.38)	P=0.937
Patients with falling-off OFC growth curve	12	7	P<0.001*

Values represent absolute patient numbers, unless stated otherwise.

[a]Mean (95% confidence interval). [†]Post-surgery, 2 patients were excluded from the analysis since they did not receive a vault expansion.

*Statistically significant after Bonferroni correction, P<0.017.

Table 3: Analysis of OSA data per time-frame: 1) before vault surgery, 2) 1 year after vault surgery, 3) >1 year after vault surgery

Prior to vault expansion (n=62)			
	Intracranial hypertension (n=13)	No intracranial hypertension (n=49)	
No + mild OSA	7	31	
Moderate + severe OSA	4	1	P=0.012*
1 Year after vault expansion (n=60)†			
	Intracranial hypertension (n=5)	No intracranial hypertension (n=55)	
No + mild OSA	4	38	
Moderate + severe OSA	1	0	P=0.116
>1 Year after vault expansion (n=60)†			
	Intracranial hypertension (n=13)	No intracranial hypertension (n=47)	
No + mild OSA	9	45	
Moderate + severe OSA	4	1	P=0.007*

Values represent absolute patient numbers.

†Post-surgery, 2 patients were excluded from the analysis since they did not receive a vault expansion.

*Statistically significant after Bonferroni correction, P<0.017.

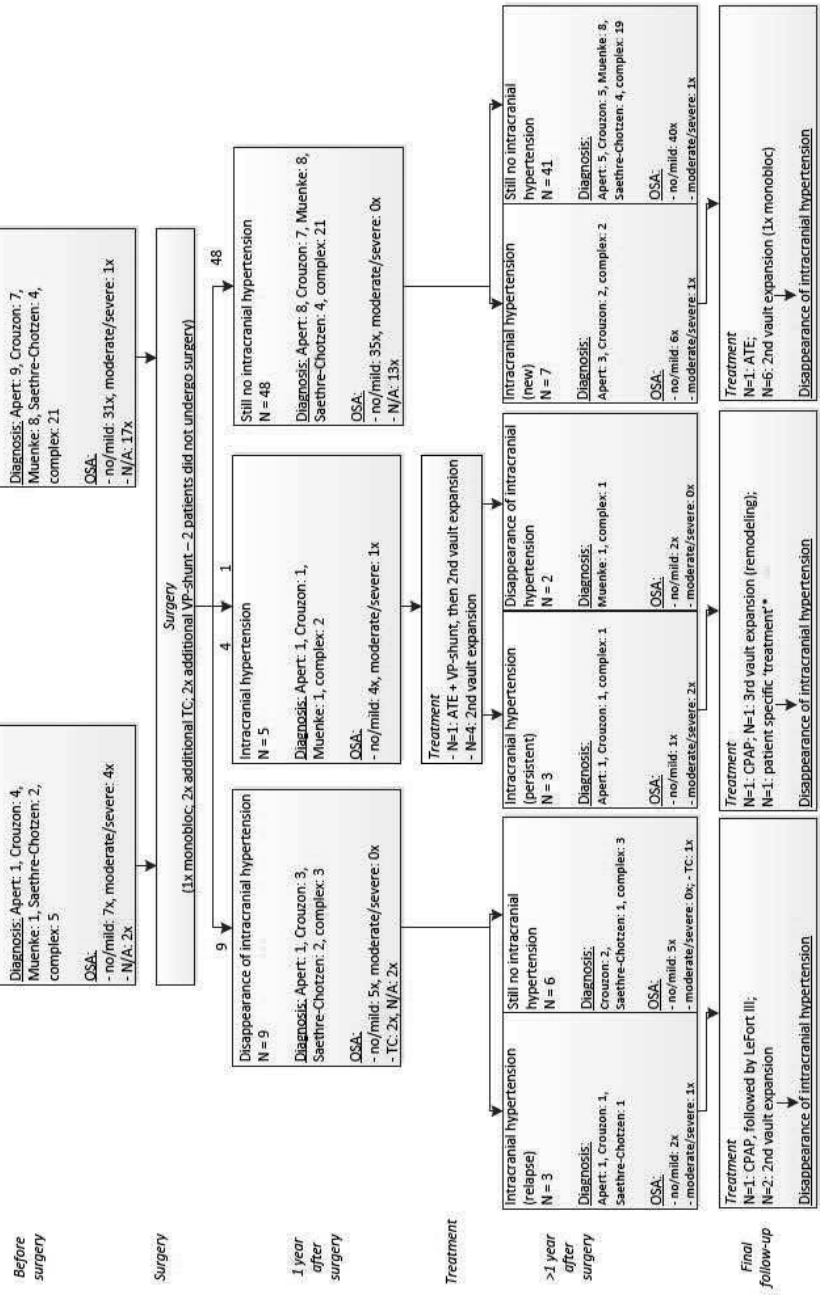
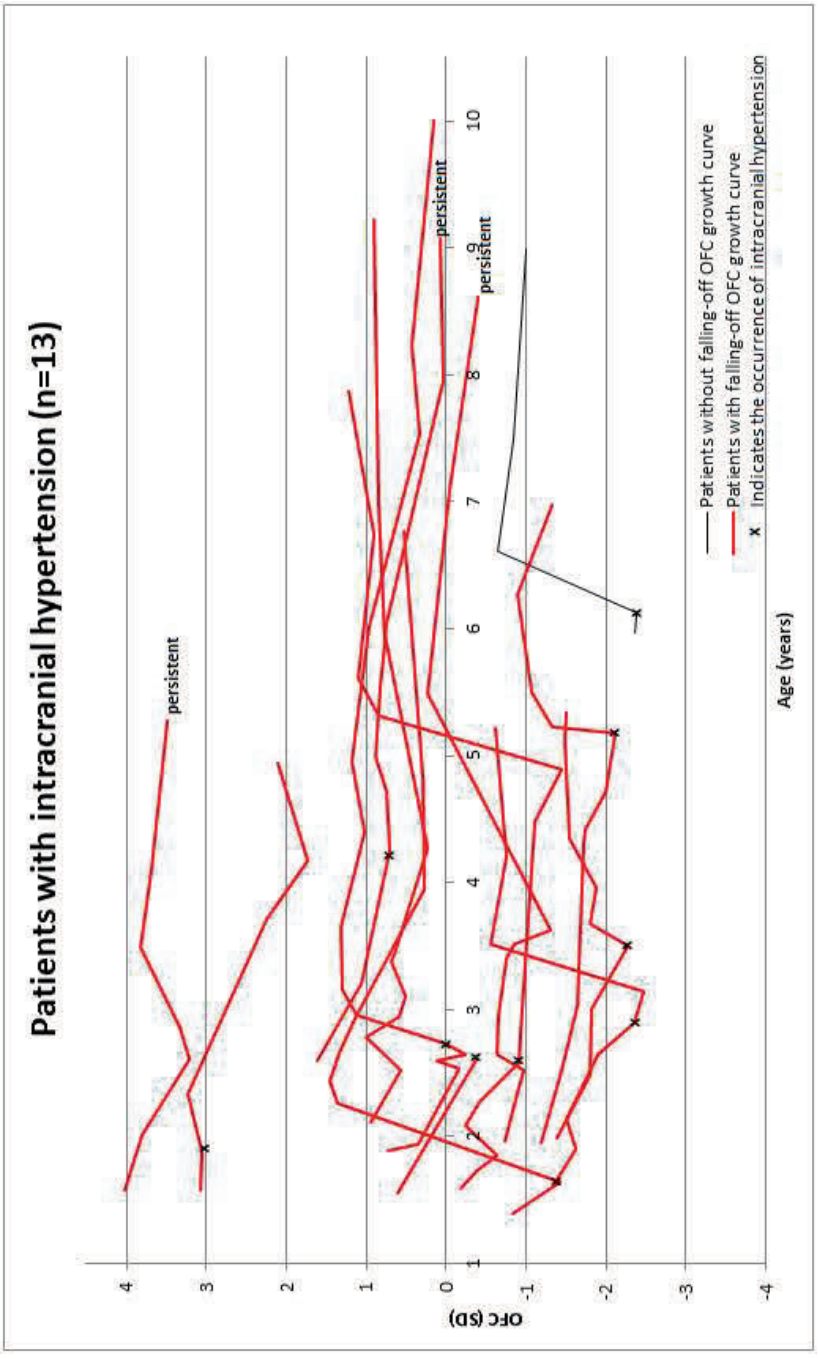


Figure 1: Flowchart of the patients in the study

Apert and Crouzon: occipital surgery; Muenke and Saethre-Chotzen: frontal surgery; complex craniosynostosis: type of surgery depending on sutures involved; in case of significant OSA: monobloc. Two patients did not undergo early surgery because they had no premature closure of skull sutures and no signs of intracranial hypertension at first presentation or during follow-up. Hydrocephalus was present in 4 patients, all with intracranial hypertension, 3 of whom ultimately received a VP-shunt.

Abbreviations: N/A: sleep study was not available; TC: tracheal cannula; ATE: adenotonsillectomy; VP-shunt: ventriculoperitoneal shunt; CPAP: continuous positive airway pressure.

*A patient with only mild papilledema (i.e. subtle blurring of the margins of the optic disk), with psychomotor retardation but without symptoms of intracranial hypertension and normal OCT and ICP monitoring, where in consultation with the parents a 'watchful waiting' period was applied and no treatment was prescribed.


Patients with intracranial hypertension (n=13)
persistent
persistent
persistent
OFC (SD)
Age (years)
Patients without falling-off OFC growth curve
Patients with falling-off OFC growth curve
Indicates the occurrence of intracranial hypertension

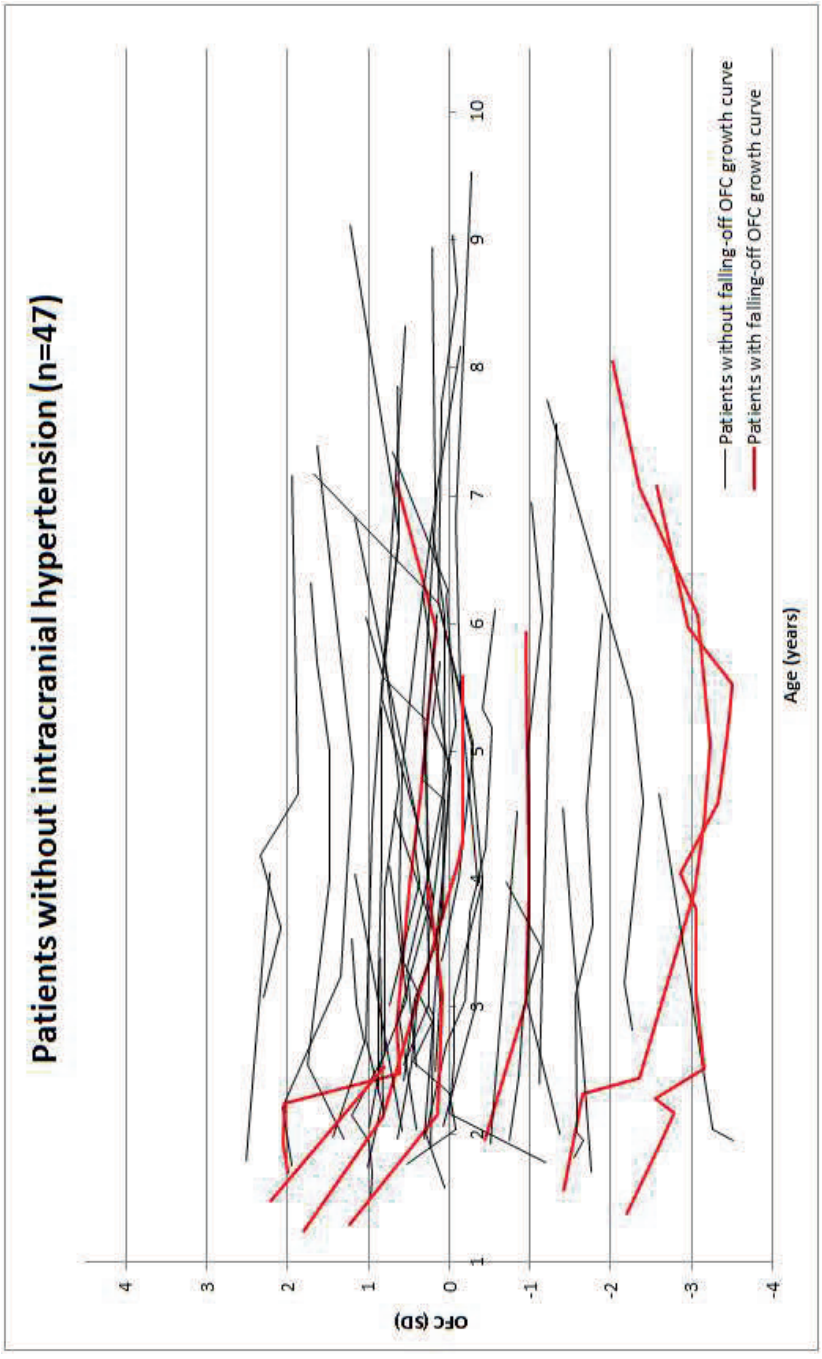


Figure 2: OFC growth curve trajectories >1 year after vault expansion, for patients A) with papilledema and B) without papilledema

CHAPTER 7

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

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Abstract

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

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

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

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

Introduction

Apert and Crouzon-Pfeiffer syndromes are congenital disorders characterized by the premature fusion of skull sutures and facial anomalies. They are associated with a significant risk of developing intracranial hypertension, mainly in the first six years of life.[1] In Apert syndrome, the incidence of intracranial hypertension before cranial vault expansion is 45%; in Crouzon-Pfeiffer syndrome it is 63%.[2, 3] One sign of intracranial hypertension is papilledema, which, in a clinical setting, is screened using fundoscopy.[4] Prolonged intracranial hypertension can impair neuropsychological development, cause behavioral disturbances, and may ultimately lead to optic nerve atrophy with visual loss.[5] Many patients, especially those with Crouzon-Pfeiffer syndrome, also develop tonsillar herniation, which is associated with the presence of intracranial hypertension.[6]

To prevent or treat episodes of intracranial hypertension, patients routinely undergo vault expansion within their first year of life. Until 2005, the first choice of treatment in our hospital—the Netherlands' only national referral center for syndromic craniosynostosis—was fronto-orbital advancement (FOA). After a presentation by Professor Hayward during a consensus meeting[7], the protocol was changed to occipital expansion as the first operation for Apert and Crouzon-Pfeiffer syndromes. By creating a larger intracranial volume than FOA, this was expected to prevent or treat intracranial hypertension more effectively.

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

Methods

Patients

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

Cranial vault expansion

Our treatment protocol includes vault expansion within the first year of life, or shortly after referral if the child is older at first presentation. The choice of the type of surgery performed had been based solely on the protocol that had applied at that time, with a change from FOA to occipital expansion in 2005. The only exception covered patients who suffered from severe obstructive sleep apnea and/or severe exorbitism: a monobloc was then performed.

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

Occipital expansion (conventional method)[11]: The occipital bone is removed in one piece with the horizontal osteotomies situated cranially just behind the coronal sutures and caudally just above the torcula. From the most anterior part of the bone flap a bandeau is taken out. The bandeau is placed horizontally, just above the occipital osteotomy. The remaining bone flap is rotated 180 degrees, remodeled and fixed to the bandeau. Bone grafts are positioned in between

the parietal bone and the replaced bone flap to secure the level of expansion. Fixation is usually done with resorbable plates and screws, or resorbable sutures. The expansion achieved by conventional occipital expansion is approximately 3.0–3.5 cm, depending on the stretch that the skin of the scalp allows.

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

Skull growth

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

Neuroimaging

MR scan imaging data were acquired using a 1.5 Tesla MR Unit (GE Healthcare, MR signa excite HD); the imaging protocol included a 3D SPGR T1-weighted MR sequence, with a slice thickness of 2 mm without slice gap, FOV= 22.4 cm, matrix size= 224*224, in plane resolution of 1 mm, TE= 3.1 ms and TR= 9.9 ms. If no MR scan was available, the CT-scan was evaluated. These CT data were acquired using a multi-detector CT scanner (Siemens, Erlangen, Germany); scans had a slice thickness of 1.25 mm (H10s kernel). All MR and CT scans were reviewed in a 3D reformatting platform (AquariusNET; TeraRecon, Inc., Melbourne, Victoria, Australia), in which scans were aligned in the sagittal, coronal and transvers planes to optimize the examination. The presence and degree of cerebellar tonsillar herniation was examined in midsagittal and adjacent scan slices. Patients were divided into three groups: (1) those with no tonsillar herniation; (2) those with herniation of less than 5 mm below the foramen magnum; and (3) those with herniation of 5 mm and more below the foramen magnum (classic definition of Chiari type I malformation[13]).

Fundoscopy

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

Visual acuity testing

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

Statistical analysis

Since our protocol had changed from FOA to occipital expansion in 2005, the FOA group had a longer follow-up time. To account for this, we determined the latest available follow-up in the occipital expansion group, and applied the same follow-up time to the FOA group.

Continuous variables are expressed as the mean (95% confidence interval), and an independent sample T-test was used for comparisons. Since the expected value in one of the cells of the 2x2 contingency table was below 5, categorical variables were compared using the Fisher exact test. Statistical significance was defined as a P-value of <0.05.

Results

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

Before surgery

The OFC was similar between children who had been scheduled for FOA (OFC-SD score: -0.28 [-0.96 – 0.40]) and occipital expansion (-0.04 [-0.77 – 0.68]), P=0.62. The prevalence of papilledema was 35.1%. Regarding the presence of tonsillar herniation or papilledema, there was no difference between the two groups; see table 3.

After surgery

Occipital-frontal head circumference

OFC in the overall Apert and Crouzon-Pfeiffer group increased more after occipital expansion than after FOA (OFC-SD score: +1.09 versus +0.32, P=0.03), especially in patients with Apert syndrome (OFC-SD score: +1.17 versus -0.14, P=0.04). See table 3.

Tonsillar herniation

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

Papilledema

In the overall group, fewer patients who had undergone occipital expansion had papilledema (4 patients of 19) than those who had undergone FOA (11 patients of 18); P=0.02, table 3. This association was particularly prominent in patients with Crouzon-Pfeiffer syndrome: P=0.02.

Visual acuity

After FOA and occipital expansion, the visual acuity of the eye with greatest vision was similar not only in the overall group (0.09 and 0.13 logMAR respectively, P=0.28; see table 3), but also for Apert and Crouzon-Pfeiffer syndromes separately. In the occipital expansion group, three patients had a visual acuity of 0.30 logMAR; one of these patients also had papilledema.

Follow-up

Follow-up after primary vault expansion showed that papilledema could, post-operatively, occur for the first time (FOA: n=6, occipital: n=3), re-occur (FOA: n=2, occipital: 1), or persist (FOA: n=3, occipital: n=0). The mean age at occurrence/re-occurrence in the overall group was 3.5 years (range: 1.5 – 4.8 years), which was similar for FOA and occipital expansion. Subsequent treatment was initiated, and all patients had normalization of intracranial hypertension within 3-6 months of final treatment. A flowchart of the patients with papilledema is shown in figure 2, the details of the follow-up and the initiated treatments are given in table 4.

Discussion

This study indicates that occipital expansion is preferred as the initial type of surgery in patients with Apert and Crouzon-Pfeiffer syndromes. After occipital expansion, the increase in OFC—a strong predictor of intracranial volume in these children[12]—was greater in these patients than in those who had undergone FOA. Subsequently, after occipital expansion, fewer patients had tonsillar herniation and papilledema. This was particularly the case in patients with Crouzon-Pfeiffer syndrome, probably because the prevalence of tonsillar herniation and papilledema is intrinsically higher than in Apert syndrome. Since tonsillar herniation and papilledema are both indirect signs of intracranial hypertension[4, 6], our findings confirm the superiority of occipital expansion in the treatment of intracranial hypertension as the first craniofacial procedure.

During follow-up after vault expansion, cranio-cerebral disproportion is one of the main contributors to the development of intracranial hypertension.[15] Here, we show that occipital expansion leads to a greater increase in OFC-SD score than FOA does, even at five years after surgery. We hypothesize that, due to the smaller increase in intracranial volume after FOA, patients are less able to compensate for any other risk factors for intracranial hypertension that are present (e.g., hydrocephalus, venous outflow obstruction or obstructive sleep apnea[16-19]); they are therefore at greater risk of developing intracranial hypertension, which is confirmed by the higher incidences of tonsillar herniation and papilledema.

Tonsillar herniation is not present at birth in patients with craniosynostosis, but acquired during life. There are several theories to explain the mechanism by which it develops.[20-22] The ongoing debate focuses on whether it is a cause or consequence of intracranial hypertension.[6] In our view, it is likely that tonsillar herniation is secondary to prolonged intracranial hypertension. This is due to the facts that 1.) the incidences of tonsillar herniation and papilledema are both higher after FOA, and 2.) these two conditions tend to co-occur: in our study, 83% of the children who had tonsillar herniation also had papilledema.

The mean age at which papilledema occurred after surgery was 3.5 years; in most patients it occurred between 2 and 4.5 years. This confirms the observations of Marucci et al., who found that after an average period of 3 years and 4 months after vault expansion, 35% of patients with Apert syndrome developed a second period of intracranial hypertension.[23] Other authors have also stated that, despite early treatment, intracranial hypertension might still relapse or persist.[1, 5, 24, 25] Spruijt et al. demonstrated that a falling-off in the OFC growth curve is an important factor in the occurrence or re-occurrence of intracranial hypertension after surgery, as is obstructive sleep apnea during longer follow-up.[15] After the age of 6 years, the re-occurrence of papilledema is rare in these patients.[1, 15] At 5.7 years, the length of follow-up in our study can therefore be seen as sufficient.

Visual acuity—which might be affected by prolonged intracranial hypertension—was similar between the FOA and occipital expansion groups. Once intracranial hypertension has

been detected, treatment is quickly undertaken on the basis of assessment of the OFC growth curve, polysomnography and MR scan. Our visual acuity results seem to suggest that our protocol is effective in preventing visual loss: only one child with papilledema in the occipital expansion group—who also had psychomotor retardation—had a visual acuity of 0.30 logMAR, which is usually seen as the minimum for adequate functioning. However, visual acuity in these patients might also be affected by other disturbances, such as abnormalities of the optic nerve or visual pathways, and/or by the strabismus or amblyopia that can result from structural alterations or absence of the extraocular muscles.[26, 27] We should also add that visual loss is a severe complication, which might be too crude as study endpoint, as it only develops after prolonged intracranial hypertension.[5, 28]

The advancement/expansion achieved by vault expansion is greatest for the springs method, followed by conventional occipital expansion, and then by FOA. The significantly greater increase in OFC after occipital expansion compared to FOA indicates that, given the strong relationship between OFC and intracranial volume[12], the resulting greater increase in intracranial volume leads to lower incidences of tonsillar herniation and papilledema. An additional advantage is that the frontal-orbital area remains untouched, thereby facilitating a monobloc or facial bipartition procedure later in life. However, even after occipital expansion the prevalence of recurrent papilledema was 21%, although due to our center's preference in recent years for springs this percentage might fall further in the future.[11] This recurrence nevertheless highlights these patients' need for close follow-up by a multidisciplinary team. We use the presence of papilledema as the primary approach to indicate intracranial hypertension.[15] Screening for it by means of fundoscopy is not only practical, but also useful and clinically relevant. As a likely consequence of intracranial hypertension, papilledema is a sign that the optic nerve head is affected, and that the main risk for craniosynostosis patients—optic nerve atrophy and irreversible visual loss—may follow. However, we are aware that the sensitivity of papilledema might be suboptimal, and therefore we perform additional examinations such as optical coherence tomography and intracranial pressure monitoring when intracranial hypertension is suspected but papilledema absent.[29-31]

We recommend routine screening for intracranial hypertension after vault expansion: even when there are no signs or symptoms of intracranial hypertension, this should include assessment of symptoms (headaches, behavioral changes, frequent awakenings during the night), OFC measurement and fundoscopy.

Conclusion

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

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Table 1: Demographics

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

Numbers represent absolute patient numbers, unless stated otherwise.

Table 2: Patient characteristics: a) Apert syndrome; b) Crouzon-Pfeiffer syndrome

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

#	Diagnosis	Mutation		Synostosis	Surgery	Exorbitism	OSA	Tracheostomy
1	Crouzon	p.Q289P	*FGFR2*	Right coronal, metopic, sagittal, bi-lambdoid	FOA	Mild	Mild	No
2	Crouzon	p.S267P	*FGFR2*	bicoronal	FOA	Severe	No	No
3	Crouzon	p.C342W	*FGFR2*	Pansynostosis	FOA (monobloc)	Severe	Severe	Yes
4	Crouzon	p.C342Y	*FGFR2*	Pansynostosis	FOA	Severe	Moderate	No
5	Crouzon	p.C278F	*FGFR2*	Metopic, sagittal, bicoronal	FOA	Severe	Mild	No
6	Crouzon	p.S267P	*FGFR2*	Bicoronal	FOA	Mild	No	No
7	Crouzon	p.C342Y	*FGFR2*	Bicoronal, sagittal	FOA	Mild	Mild	No
8	Crouzon	p.C342Y	*FGFR2*	Bicoronal	FOA	Severe	Mild	No
9	Crouzon	p.S354C	*FGFR2*	Bicoronal	OE	Mild	No	No
10	Pfeiffer	c.1084+3 A>G	*FGFR2*	Pansynostosis	OE	No	No	No
11	Crouzon	p.W290R	*FGFR2*	Pansynostosis	OE	No	No	No
12	Crouzon	p.Y340H	*FGFR2*	Pansynostosis	OE	Mild	Mild	No
13	Crouzon	p.L327V	*FGFR2*	Pansynostosis	OE (springs)	Severe	Mild	No
14	Pfeiffer	p.W290C	*FGFR2*	Right coronal, metopic, sagittal, bi-lambdoid	OE (springs)	Severe	Severe	Yes
15	Pfeiffer	p.E565G	*FGFR2*	Pansynostosis	OE (springs)	Mild	Mild	No
16	Crouzon	p.C278F	*FGFR2*	Pansynostosis	OE	Severe	Mild	No
17	Pfeiffer	p.P252R	*FGFR1*	Bicoronal	OE (springs)	Mild	No	No
18	Crouzon	p.G338R	*FGFR2*	Sagittal, bi-lambdoid	OE	Mild	No	No
19	Crouzon	p.L357V	*FGFR2*	Bicoronal, right lambdoid	OE	Mild	No	No

[†]One patient with Apert syndrome did not undergo genetic analysis

Surgery: FOA: fronto-orbital advancement; OE: occipital expansion (with or without springs)

OSA: Obstructive sleep apnea, categorized based on the oAHI-index: mild (oAHI ≥1 and <5), moderate (oAHI ≥5 and <25) or severe OSA (oAHI ≥25)[32, 33]

Table 3: Occipital-frontal head circumference, tonsillar herniation, papilledema and visual acuity

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

Values represent absolute patient numbers, unless stated otherwise; PRE-OP: pre-operative; POST-OP: post-operative

P-value (PRE-OP): PRE-OP fronto-orbital advancement versus PRE-OP occipital expansion

P-value (POST-OP): POST-OP fronto-orbital advancement versus POST-OP occipital expansion

*Statistically significant, P-value <0.05

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

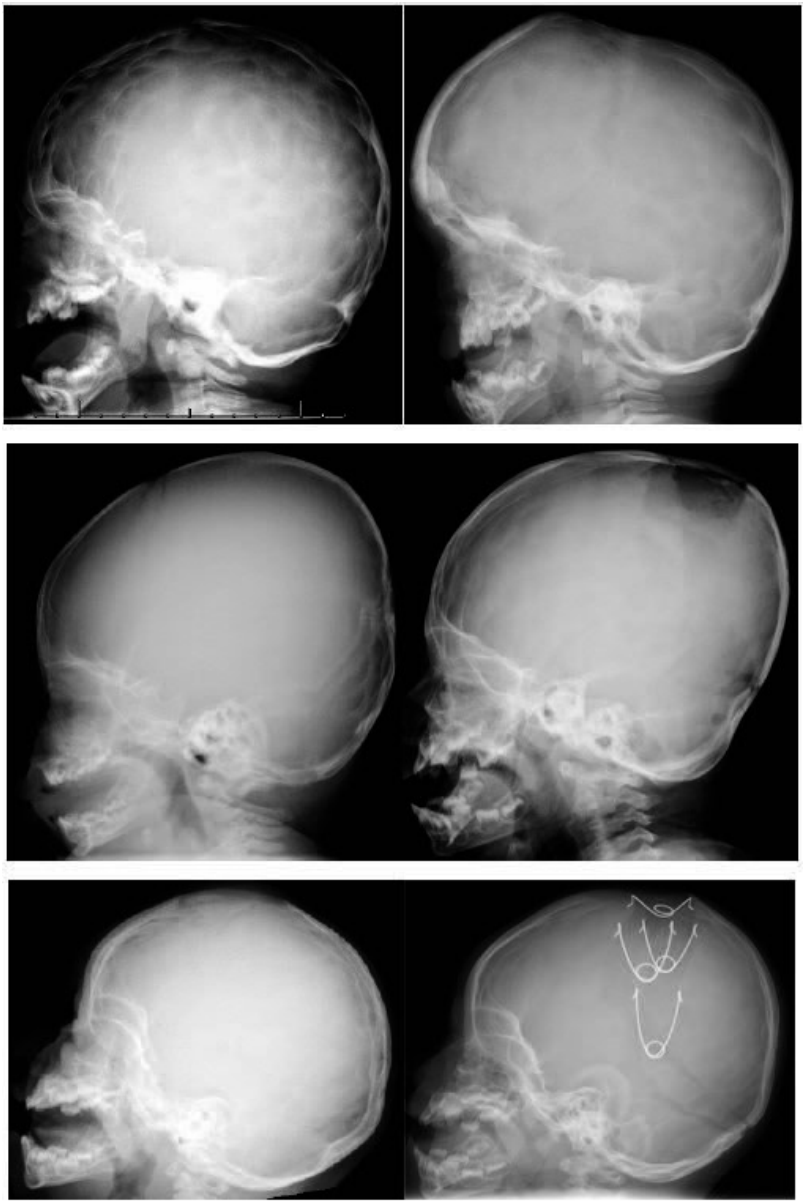
‡Values for visual acuity are expressed in logMAR. After FOA, 13 of 18 patients had their visual acuity measured (6 *Snellen Chart*, 5 *Tumbling E-chart*, 2 *APK*), 11 had strabismus, 2 of whom also had amblyopia. Following occipital expansion, 12 of 19 patients had their visual acuity measured (5 *Snellen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

Table 4: Follow-up after the primary vault expansion, for the patients who had papilledema post-operatively

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

Numbers represent absolute patient numbers, unless stated otherwise.

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

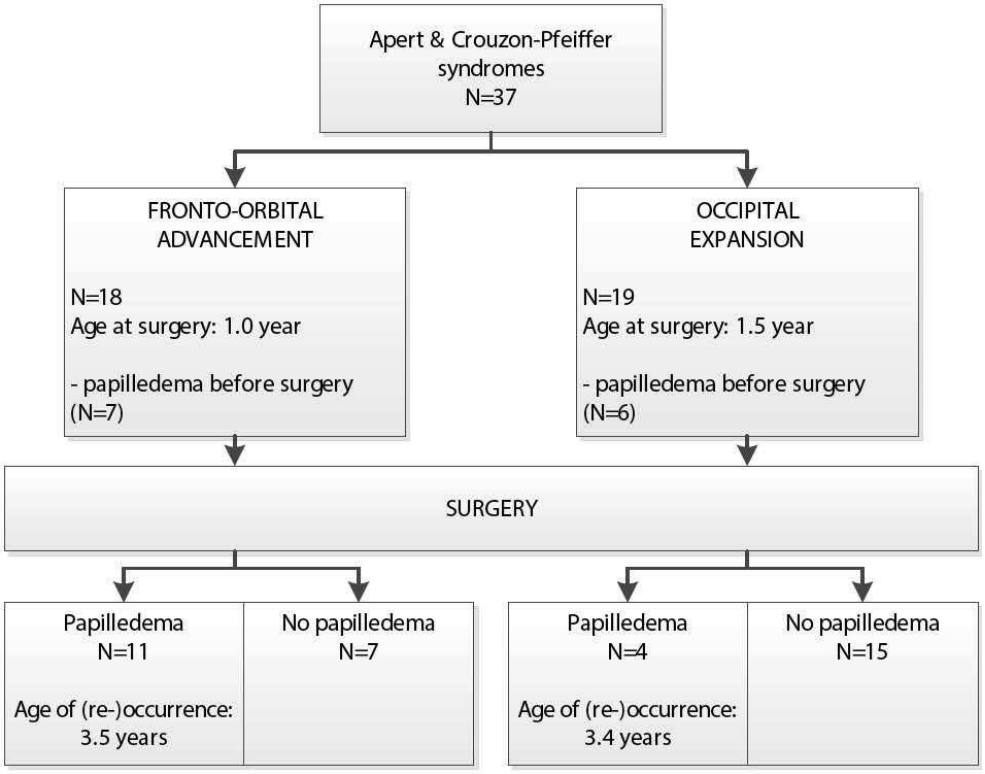


a. (FOA): After surgery the impressiones digitatae have decreased, although a vertex bulge has developed, which is a sign of lack of intracranial volume and possible intracranial hypertension.[34] Additionally, the facial profile is disturbed. The advancement achieved is approximately 1.5–2.0 cm.

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

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

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



PART V
-
SUMMARY
&
DISCUSSION AND FUTURE PERSPECTIVES

CHAPTER 8

Summary

Apert
syndromic craniosynostosis

- Patients can have atypical presentation of intracranial hypertension, which due to its multifactorial etiology necessitates multidisciplinary treatment.

Obstructive sleep apnea & intracranial hypertension

- A vicious cycle exists between OSA, cerebral hypoperfusion, cerebral autoregulatory responsivity, intracranial hypertension, and (REM) sleep.
- Assessment of intracranial hypertension is challenging. Screening should include: symptom review, occipital-frontal head circumference assessment, polysomnography to check for OSA, MR scan to check for hydrocephalus and/or cerebellar tonsillar herniation, and fundoscopy; if indicated, this is supplemented by optical coherence tomography and/or intracranial pressure monitoring.
- Patients with moderate/severe OSA have more respiratory effort related arousals, resulting in disturbed sleep architecture with a decrease in REM sleep (i.e., 'sleep quality').
- Upper airway endoscopy is an essential tool, in addition to polysomnography, to optimize OSA treatment.
- Children with papilledema have, compared to those without, increased cerebral blood flow and decreased cerebrovascular resistance; they also develop an associated systemic vascular response (i.e., raised blood pressure) that remains present at post-operative follow-up.

Management

- Children with syndromic craniosynostosis are at high risk of obstructive sleep apnea [OSA] and intracranial hypertension, the latter of which can re-occur after vault surgery.
- The preferred type of first craniofacial procedure in Apert and Crouzon/Pfeiffer syndromes is occipital expansion. It leads, compared to fronto-orbital advancement, to a greater increase in occipital-frontal head circumference (and therefore intracranial volume), thereby reducing the incidences of cerebellar tonsillar herniation and papilledema.

The aim of this thesis is to unravel the topic of obstructive sleep apnea [OSA] in children with syndromic craniosynostosis, and especially to determine its contribution to the development of intracranial hypertension.

Part I (chapter 1) provides an introduction to craniosynostosis, OSA and intracranial hypertension. Craniosynostosis (1 : 2.100–2.500) is a rare congenital disorder characterized by premature fusion of skull suture(s) resulting in an abnormal skull shape. Syndromic craniosynostosis comprises 24% of all cases, and is associated with additional abnormalities such as facial anomalies and malformations of hands and feet. The main diagnoses include Apert, Crouzon/Pfeiffer, Muenke, and Saethre-Chotzen syndromes, and complex craniosynostosis. Anamnesis and physical examination are most valuable for making the diagnosis, which is confirmed by 3D-CT scan. OSA, a disorder of breathing during sleep, has a prevalence of 68% in these patients. The cause is often an abnormal anatomy leading to obstructions at multiple levels in the upper airway. Symptoms include apnea, snoring and difficulty in breathing during sleep; these can be used to calculate the Brouillette score, which is a valid screening tool for the presence of OSA in these patients. Definite diagnosis is made using polysomnography, which includes calculation of the obstructive apnea-hypopnea index to indicate the severity of OSA, while sleep pattern is evaluated as well. Treatment may consist of nasal corticosteroids, adenotonsillectomy, respiratory support (e.g., Optiflow, continuous positive airway pressure), midface advancement surgery, mandibular lengthening, or in severe cases a tracheal cannula. OSA is a risk factor (along with cranio-cerebral disproportion, venous hypertension, hydrocephalus and abnormal cerebral blood flow) for developing intracranial hypertension, and therefore raised intracranial pressure [ICP]. The prevalence of intracranial hypertension is related to the syndrome and the affected suture(s), and can be as high as 83% in Apert syndrome. Patients undergo routine vault surgery within the first year of life. Screening for intracranial hypertension during follow-up is done on the basis of a combination of examinations: symptom review (e.g., headaches, behavioral changes, frequent awakenings during the night, deterioration of vision), occipital-frontal head circumference [OFC] (to assess skull growth), polysomnography (to check for OSA), MR scan (to check for hydrocephalus and/or cerebellar tonsillar herniation), and fundoscopy, if indicated supplemented by optical coherence tomography [OCT] and/or ICP monitoring. Despite early vault expansion, intracranial hypertension might still persist or relapse. Subsequent treatment (e.g., 2nd vault expansion, OSA treatment, or ventriculoperitoneal shunt) is decided on by a multidisciplinary team. Ultimately, if not adequately treated, prolonged intracranial hypertension can lead to mental retardation, cerebellar tonsillar herniation and visual loss.

Part II (chapter 2): a newborn with Apert syndrome with atypical craniofacial presentation, as clinical illustration to the issues that can play a role in children with syndromic craniosynostosis.

Part III focuses on OSA and intracranial hypertension in children with syndromic craniosynostosis. Chapter 3: a study that examines the role of OSA and puts it in the context of a

unifying model for children with syndromic craniosynostosis. Sleep architecture, the main outcome in this study, is in principle normal in these patients. The presence of intracranial hypertension leads to a slight increase in the number of respiratory effort related arousals [RERA], but sleep architecture remains intact. Patients with moderate/severe OSA have major abnormalities, as more RERAs lead to a disturbed sleep architecture with lower sleep efficiency and a decrease in REM sleep. Monobloc advancement reduces OSA (at the midface) and intracranial hypertension, thereby improving sleep architecture. Finally, a previously proposed unifying theory for craniosynostosis is updated: a vicious cycle of OSA, cerebral hypoperfusion, cerebral autoregulatory responsivity, and intracranial hypertension, resulting in disturbed (REM) sleep. Next, chapter 4: the use of upper airway endoscopy to optimize OSA treatment in children with Apert and Crouzon/Pfeiffer syndromes. OSA in these patients is often related to midface hypoplasia, although it is demonstrated that it is usually a multi-level problem with partial or complete obstruction(s) at the level(s) of the nose, uvulopalatine plane, tongue base, hypopharynx, and larynx. Additionally, the findings during endoscopy assessment are positively correlated with OSA severity. Midface advancement, combined with mandibular distraction if indicated, reduces upper airway obstruction(s), thereby resulting in a reduction of OSA. Children suffering from OSA should receive upper airway endoscopy assessment in addition to polysomnography as a guide to optimize treatment, since performing midface advancement as a matter of routine might be a suboptimal treatment choice. Next, chapter 5: patients' cerebral blood flow velocity [CBFv] profiles and the consequences of intracranial hypertension in children with syndromic craniosynostosis. Transcranial Doppler of the middle cerebral artery is performed 1 day before and 3 weeks after surgery, to measure CBFv and calculate the resistive index [RI]; systemic blood pressure is recorded as well. Pre-operatively, patients with papilledema, in comparison to those without, have higher CBFv, RI, and blood pressure. Vault surgery leads to increased CBFv and fall in RI. Patients with papilledema have intracranial hypertension of such severity that they develop an associated systemic vascular response resulting in raised blood pressure; this raised blood pressure remains present after surgery at (short-term) follow-up.

Part IV highlights the main aspects in the management of children with syndromic craniosynostosis. Chapter 6: a prospective observational cohort study about an algorithm for the management of intracranial hypertension in children with syndromic craniosynostosis. The focus is on the evaluation of the standardized treatment protocol of our craniofacial center, which includes routine vault expansion in the first year of life and multidisciplinary follow-up. Presence of papilledema, combined with positive OCT and/or ICP monitoring is used to indicate intracranial hypertension; a high percentage of children with intracranial hypertension during the study (34%) confirms the importance of this finding in these patients. They demonstrate a complex interaction among head growth, OSA, timing of surgery, and intracranial hypertension. The major determinant of intracranial hypertension after vault expansion is impaired head growth, which may occur at varying ages. Regarding OSA, this particularly has to be a point of attention in patients with persistent intracranial hypertension. During late follow-up,

moderate/severe OSA also increases the risk of developing intracranial hypertension. Next, chapter 7: a study determining the optimal type of first vault expansion in children with Apert and Crouzon/Pfeiffer syndromes. Fronto-orbital advancement was the standard treatment in our hospital in the past, but after an international consensus meeting the protocol was changed to occipital expansion. This study supports the preference for occipital expansion, since it leads to a greater increase in OFC (and therefore intracranial volume), which reduces the incidences of cerebellar tonsillar herniation and papilledema. Since cerebellar tonsillar herniation and papilledema are indirect signs of intracranial hypertension, these findings confirm the superiority of occipital expansion in the treatment of intracranial hypertension. Visual acuity is similar between both groups, and since only one child had a visual acuity of 0.30 logMAR that is considered as the minimum for adequate functioning, this further suggests our protocol is effective in preventing secondary visual loss.

Taken together, OSA is common in children with syndromic craniosynostosis and can through a complex vicious cycle result in intracranial hypertension. Early referral is warranted for routine vault surgery within the first year of life and further multidisciplinary treatment. During follow-up, the optimal procedure to screen for intracranial hypertension is challenging, although the current approach with papilledema at the center is both useful and clinically relevant. Intracranial hypertension is the consequence of a dynamic process in which multiple risk factors interact. A specialized craniofacial center is the optimal setting to ensure effective treatment for all patients, including those with the most severe presentation.

CHAPTER 9

Discussion

This thesis is a further step towards the goal of fully appreciating the topic of intracranial hypertension in children with syndromic craniosynostosis.

A hypothetical model is made for each patient (figure 1).

Obstructive sleep apnea

Obstructive sleep apnea [OSA] has always been one of the central topics in craniosynostosis research. OSA is proposed to be a significant risk factor[1-3], and the prospective study indeed shows a clear association between moderate/severe OSA and intracranial hypertension. The main hypothesis for this association is a vicious cycle during (REM) sleep[4]: apnea may cause hypoxia, hypercapnia, and reactive cerebral vasodilatation, thereby increasing cerebral blood flow [CBF], and leading to intracranial hypertension (i.e., intracranial pressure [ICP]). A subsequent decrease in cerebral perfusion pressure may lead via autoregulatory reflexes to more vasodilatation to preserve CBF, and a further rise in intracranial hypertension. An arousal will ultimately break the cycle (figure 2).

A striking example of a patient illustrating our theory is a 4-year-old boy with Crouzon syndrome (figure 3). He had persistent papilledema after first vault expansion. He was then treated by adenotonsillectomy (RE: severe OSA) and ventriculoperitoneal[VP] shunt (RE: hydrocephalus), followed by second vault expansion after which papilledema initially disappeared, but it relapsed after 8 months. He demonstrated a clearly disturbed polysomnography with frequent apneas/hypopneas with desaturations provoking the plateau of raised ICP. Overall, he had moderate OSA and a raised baseline ICP with seven abnormal ICP-plateaus >35 mmHg, all these plateaus occurring during REM sleep. Continuous positive airway pressure was started to treat OSA, after which intracranial hypertension disappeared.

One of the major advances in recent years is the standard use of level 1 polysomnography, i.e., polysomnography in the hospital including assessment of cardiorespiratory variables, electroencephalography [EEG], videotaping, and medical and technical support. The ambulatory sleep study is still useful for screening, but in case of a positive Brouillette score or an abnormal ambulatory sleep study, polysomnography in the hospital is recommended. This polysomnography is more reliable than a sleep study at home, but it especially allows for a more detailed evaluation of the child's situation. The main advantages are a more precise and extended measurement of (cardio-)respiratory variables, the use of EEG, and the availability of video which can provide important extra information to diagnose a patient. EEG allows for the scoring of respiratory effort related arousals [RERA] and the evaluation of the patient's sleep architecture. Normal sleep is characterized by both a regular sleep architecture, i.e., the distribution of the sleep stages which are divided into non-REM sleep (N1, N2, N3) and REM sleep, as well as proper transitions from one sleep stage to another. OSA and intracranial hypertension have both been suggested to be predominantly REM sleep

phenomena.[2, 3, 5] During REM sleep, when brain activity and perfusion peak[6], children with moderate/severe OSA have indeed more RERAs, which leads to disturbed sleep architecture. A consequent decrease in the percentage of REM sleep is clinically important since it might lead to a variety of symptoms, i.e., it is a decrease in 'sleep quality'.

OSA is still the main focus of attention when evaluating a polysomnography according to the criteria of the American Academy of Sleep Medicine.[7] Recently, these criteria were updated, but, based on a pilot study where polysomnography recordings were scored according to both the old and the new criteria, the effect on the obstructive apnea-hypopnea index [oAHI] appeared limited. However, in addition to OSA, the presence of upper airway resistance syndrome [UARS] should also be taken into consideration. Patients who suffer from UARS demonstrate signs of increased respiratory effort, such as inspiratory flow limitation with flattening of the tops and increased heart rate variability [HRV]; there are hardly any apneas, hypopneas, or desaturations. The oAHI in patients with UARS is therefore usually below 1[8], and the use of only the conventional indicators of sleep disordered breathing might lead to an underestimation of the severity of a child's condition. HRV has been particularly of interest in UARS-research, since it may be increased in patients with increased respiratory workload and might prove to be a potential noninvasive alternative to esophageal pressure monitoring in diagnosing UARS. In a pilot study, HRV analysis was able to distinguish patients with normal breathing from those with UARS, and from those with moderate/severe OSA; this demonstrates the validity of such analysis, although progress still needs to be made to turn it into a more practical, user friendly method. Additionally, UARS was found not to increase the risk of intracranial hypertension, which is in line with previous findings of this only being the case for moderate/severe OSA. The main question, however, is if the physician's clinical view of whether a patient suffers from UARS or not, corresponds with science. A physician's assessment based on, amongst others, nasal inspiratory flow limitation, HRV and patient specific information could indeed reliably predict which patient suffers from UARS.

Another development is the inclusion of upper airway endoscopy in the pre-operative work-up of patients with OSA. This makes it possible to determine precisely at which level(s) of the upper airway there is an obstruction, since it is often a multi-level problem in these patients.[9] The endoscopy findings are positively correlated with the polysomnography results that indicate the severity of OSA, and the combination of these tests can guide subsequent treatment. Children with Apert and Crouzon/Pfeiffer syndromes where midface hypoplasia is common are also the ones who most often have OSA that requires treatment, therefore midface advancement was usually performed as a matter of routine. However, without further examination of the cause, this can lead to undertreatment, or even mistreatment; for example, on the basis of the findings during endoscopy two of our patients underwent not only advancement of the midface, but also of the mandible. Therefore, in addition to polysomnography upper airway endoscopy is essential to optimize OSA treatment, which can reduce upper airway obstruction(s) and thereby reduce OSA.

Ultimately, it comes down to the question of which patient with sleep disordered breathing needs to be treated. This is one of the main challenges in clinical practice; it is evident that children with moderate/severe forms of OSA require treatment, not only because of the clinical discomfort which is usually present, but also because of the increased risk of developing intracranial hypertension. However, for subjects with UARS or mild OSA the indication for treatment is less clear. These patients might not have obvious symptoms, but are mostly identified as part of the screening protocol. Since these patients do not have an increased risk to develop intracranial hypertension, it seems justifiable to apply a wait and see approach. An exception is when a child has persistent intracranial hypertension. Patients with persistent intracranial hypertension frequently have persistent OSA as well, some of them the mild form. OSA is the only factor not addressed by standard vault surgery, and therefore it is essential to consider its potential influence as a contributory factor to intracranial hypertension.

Cranio-cerebral disproportion

A patient's brain may grow more rapidly than the skull, since the growth of the latter could be affected by premature fusion of the calvarial sutures.[10] In normal children, skull growth is greatest in the first years of life; at the age of 2 years 77%, and at age 5 years 90% of the total intracranial volume [ICV] is reached.[11] Patients with syndromic craniosynostosis have normal brain volume[12] and ICV[13, 14], although children with Apert syndrome have an ICV much higher than the norm.[15, 16]

Cranio-cerebral disproportion is an essential link in the pathophysiological mechanism resulting in intracranial hypertension. It is perhaps the most obvious contributing factor to intracranial hypertension, and has once been considered as such. However, it has been shown to vary greatly in its extent, and studies have shown that in isolation it is not a reliable predictor of intracranial hypertension.[17, 18] The key is, that it should not be evaluated as an absolute value at one point in time and compared to the reference of healthy children, but instead as a longitudinal within-patient analysis. During clinical practice, the occipital-frontal head circumference [OFC] is measured during each visit to the clinic and used to measure skull growth. OFC correlates with ICV in healthy individuals[11, 19, 20], and OFC is a reliable predictor of ICV in children with syndromic craniosynostosis as well.[21] Therefore, OFC is an accurate, feasible method to monitor skull growth within a patient during follow-up to evaluate whether cranio-cerebral disproportion is present.[21] For example, to illustrate that relative values over time are more important than one absolute value: one patient may have stable skull growth that follows the 0 SD (p50) growth curve, while another patient may have started at +2 SD and drop to +1 SD. One might argue that the latter patient despite having a downward deflection in his OFC growth curve still has a greater skull than the first patient in absolute terms; in our view, however, the relative change (i.e., equal 0 SD versus minus 1 SD) represents a greater risk of developing intracranial hypertension than the absolute skull size itself. Skull growth arrest before surgery is caused by

the synostotic sutures, however the exact mechanism of this phenomenon in the post-operative period is still unknown; since it occurs more often in particular syndromes, it is probably mostly related to the underlying genetic defect.

The studies are in agreement with the aforementioned hypothesis. After surgery, a downward deflection of a patient's OFC growth curve was the most important risk factor of intracranial hypertension while absolute skull size was not different between patients with and without intracranial hypertension. This association was present during both early and late post-operative periods, although it was most obvious during late follow-up. The falling-off in OFC growth curve took place six months before the occurrence of intracranial hypertension, clearly indicating a causal relationship; it should be noted, further contributing to our contention that multiple factors interact in the development of intracranial hypertension, that during late follow-up moderate/severe OSA was also identified as a significant risk factor.

Hydrocephalus

Cerebral ventricles are assessed using the frontal occipital horn ratio, preferably on MR scan.[22, 23] Cerebral ventricular dilatation is defined as ventriculomegaly when the condition is stable over time or as hydrocephalus when it is progressive.[24] The possible causes for the condition include increased cerebrospinal fluid [CSF] production by the choroid plexus, malabsorption due to venous hypertension, or CSF outflow obstruction to the spinal cord due to constriction of the posterior fossa or cerebellar tonsillar herniation.[24-26] Also, it may be associated with brain maldevelopment or brain atrophy.[24] Hydrocephalus is most frequently present in Crouzon/Pfeiffer syndrome with a reported prevalence of 30% (although this is difficult to determine based on the current literature since serial measurements are necessary), and the overall prevalence of ventricular dilatation is 30-70% in these patients[24, 27, 28]; in Apert syndrome ventriculomegaly is common (40-90%), whereas the condition is rare in Muenke and Saethre-Chotzen syndromes.[24] Ventricular volume is also larger in patients with a Chiari I malformation.[12]

Hydrocephalus, i.e., progressive ventriculomegaly, can lead to an increase in CSF volume resulting in intracranial hypertension and/or cerebellar tonsillar herniation.[24] Vault expansion is the preferred treatment option in the event of hydrocephalus with intracranial hypertension. A VP-shunt is counterproductive and generally not preferable, since it reduces the intrinsic growth impulse of the brain on the skull and renders the patient dependent on its function; some patients may nevertheless ultimately need it such as those with progressive hydrocephalus after vault expansion.[24, 26]

Venous hypertension

Venous outflow obstruction of the brain can be caused by abnormal anatomy, i.e., anomalous venous drainage.[10] A smaller jugular foramen particularly affecting the jugular/sigmoid sinus complex has been named as causal factor[29], the bony narrowing may constrict venous outflow pathways and subsequently lead to a raise in venous pressure, and CSF pressure.[10, 30, 31] This theory was later disputed, however, when jugular foraminal narrowing was shown to be common in these children, but irrespective of the presence of intracranial hypertension.[32] Other possible explanations include FGFR2 up-regulation causing premature vascular endothelial proliferation and differentiation resulting in a narrowed lumen, or persistence of the fetal pattern of intracranial venous drainage.[10] Collateral veins are also common.[10] These collaterals form especially occipitally, and indicate an abnormal drainage from intracranial to extracranial.[33] They are shown to be present already in very young patients, and equally frequently in patients with and without papilledema. Therefore, the anomalous venous drainage including collaterals likely implies an innate disorder of the venous system, rather than a compensating mechanism for intracranial hypertension. This inborn abnormal venous system may make these patients more prone to develop venous hypertension, and therefore intracranial hypertension.[32] Evaluation of the (abnormal) venous outflow pattern is especially important when planning for occipital vault surgery, since these veins may provide the only venous drainage and its division may have fatal consequences.[34]

At present, venous hypertension is not routinely assessed to the fullest for each child on clinical grounds (for example by MR venography[35]). One of the main reasons for this is that the treatment of choice for venous hypertension is the same as is already standard practice in these patients, namely vault expansion. However, the basic venous anatomical abnormalities naturally continue to exist after vault expansion and may affect CSF dynamics even more once the restricting effects of the skull have been removed, resulting in progressive hydrocephalus and/or cerebellar tonsillar herniation.[36] A more direct technique to evaluate this venous component would be Doppler ultrasound to measure blood flow velocities in the superior sagittal sinus; invasive measurement of the superior sagittal sinus venous pressure is the gold standard and has been done in the past[37], but due to ethical considerations this is not possible anymore nowadays.

Cerebral blood flow

Arterial CBF, and cerebral autoregulation, play a key role in the vicious cycle of OSA leading to intracranial hypertension. Transcranial Doppler [TCD] has been shown to be an accurate, rapid, noninvasive technique to evaluate the vascular component of intracranial physiology[38]; it measures cerebral blood flow velocity [CBFv] dynamics, which reliably represents CBF.[39, 40] TCD variables and its derivatives are associated with changes in intracranial hypertension.[41-43] TCD in craniosynostosis has so far mainly focused on its use as an alternative to ICP monitoring.[44-46]

Patients with intracranial hypertension have abnormal brain hemodynamics compared to both patients without intracranial hypertension and healthy controls. They have a higher CBFv and resistive index [RI], and an increase of the latter can be interpreted as indication for presence of intracranial hypertension. Subsequent vault surgery leads to an increase in CBFv and a fall in RI, and based on this it even appears that at time of surgery all patients are on a spectrum of having intracranial hypertension. Patients with papilledema have intracranial hypertension of such severity that besides the effect on the eyes, they have abnormal brain hemodynamics and they also develop an associated systemic vascular response, i.e., increased blood pressure. This is to maintain cerebral perfusion pressure, which is essential since its steep decrease can ultimately result in a deadly fall in CBF as is sometimes seen in brain trauma patients.[47-49]

CBF peaks around the age of 5 years[50], and it could be one of the reasons for the post-operative peak of re-occurrence of intracranial hypertension at this age. Additionally, CBF is an important link in the aforementioned dynamic vicious cycle, and previous reports have also described that OSA leads to an increase in CBFv.[51, 52] Potentially, CBFv can help determine which patients not only suffer from a severe phenotype, but in whom OSA truly is a contributing factor to intracranial hypertension.

Treatments

A routine first vault expansion is performed in the first year of the patient's life, or shortly after referral if the child is already older at first presentation; this is the standard in most craniofacial centers around the world.[53] Vault surgery has a major impact and reduces the presence of intracranial hypertension. This emphasizes the advantage of routine surgery, compared with monitoring for intracranial hypertension and only perform surgery when this has been diagnosed. A study of patients with Apert syndrome managed according to the latter approach showed that 83% of them developed intracranial hypertension as determined by fundoscopy, a deterioration in visual evoked potentials [VEP], or transcranial intracranial pressure monitoring (average age: 18 months, range: 1 month – 4 years, 5 months), which required vault expansion and/or other treatment.[54] VEP-scan might have an additional value in the screening of intracranial hypertension[55], but since only one center reports on this technique it is difficult to assess its reliability also because it has not been compared to ICP monitoring; moreover, the low number of patients who do not need vault surgery for intracranial hypertension does not seem to justify this approach.

OSA requires special attention, in that it is the only factor not addressed by standard surgery whereas vault expansion is effective treatment for most other factors contributing to intracranial hypertension. OSA management has been shown to be effective in our studies, reducing intracranial hypertension when previously raised. Monobloc surgery has the most substantial effect, although all types of airway improvement have beneficial effects and this

should not be pinned on monoblocs alone; moreover, for monobloc it is probably a combination since it also increases intracranial volume and, regardless of its effect on the airway, has the potential to directly reduce intracranial hypertension.

Cerebellar tonsillar herniation

Cerebellar tonsillar herniation, a caudal displacement of the cerebral tonsils through the foramen magnum, is classified into either herniation of less than 5mm below the foramen magnum (i.e., tonsillar herniation) or herniation of 5mm and more below the foramen magnum (i.e., classic Chiari type I malformation).[56] It is usually not present at birth in patients with craniosynostosis, but acquired during life.[57] Several theories have been proposed to explain the mechanism by which it develops, including anomalies of the cerebellum, an overcrowded posterior fossa due to bony underdevelopment or premature lambdoid suture synostosis, venous hypertension, hydrocephalus and/or intracranial hypertension.[26, 58-62] Patients with syndromic craniosynostosis have a smaller foramen magnum already at birth, probably caused by hypoplasia of the occipital bones and partially by premature closure of the intra-occipital synchondroses in Apert and Crouzon/Pfeiffer syndromes, although the latter is neither clearly related to hydrocephalus nor to the presence of cerebellar tonsillar herniation.[63] They also have an increased (cerebellar volume / posterior fossa volume)-ratio suggesting that the posterior fossa is indeed overcrowded, although the range of these ratios falls within the range of controls and therefore it can only be seen as a predisposing factor instead of being truly predictive for who is more prone to develop cerebellar tonsillar herniation.[64] Patients with Crouzon/Pfeiffer syndrome have an intrinsic prevalence of 32%, which is higher than other syndromes; a prevalence of 73% is even reported, although in this study an MR scan was not standard practice but only performed in case of clinical signs.[12, 58] Despite that progression may occur over time, possibly compressing the brain stem, cranial nerves and upper spinal cord, it is often asymptomatic in children with syndromic craniosynostosis.[65, 66] As long as a child is asymptomatic, a conservative approach is advocated with regular neurosurgical follow-up and if indicated MR scanning. Routine foramen magnum decompression is neither indicated nor effective, but does carry risks.[34, 67, 68] Surgical treatment is only indicated if the child is symptomatic. However, neurosurgical follow-up is important, since some patients may eventually still develop neurological symptoms, central sleep apnea and/or syrinx.[62, 69]

The main relevance, however, is that cerebellar tonsillar herniation likely develops secondary to prolonged intracranial hypertension.[57] Hence, it is likely to be the consequence, rather than a cause of intracranial hypertension. There are several indications for this, for example patients with Apert and Crouzon/Pfeiffer syndromes who underwent FOA instead of occipital expansion had higher incidences of papilledema as well as cerebellar tonsillar herniation; those two conditions often co-occurred, namely 83% of the patients with papilledema also had cerebellar tonsillar herniation; and, cerebellar tonsillar herniation was usually identified

after the occurrence of intracranial hypertension. Regarding the latter, since due to practical reasons an MR scan is not available at each point in time, it is sometimes difficult to determine exactly when cerebellar tonsillar herniation is present for the first time or when deterioration takes place. Nevertheless, an improvement in the status of cerebellar tonsillar herniation is rarely observed, but rather a deterioration from tonsillar herniation to Chiari type I malformation usually after a period of intracranial hypertension.

Intracranial hypertension

A standardized protocol to screen for intracranial hypertension is applied. This includes anamnesis/symptom review (e.g., headaches, behavioral changes, frequent awakenings during the night, deterioration of vision), OFC assessment, and fundoscopy. If indicated, i.e., when papilledema is absent but intracranial hypertension nevertheless suspected, additional examinations such as optical coherence tomography and/or ICP monitoring are performed. This seems a practical, useful and clinically relevant approach to identify intracranial hypertension in children with syndromic craniosynostosis. A future study could further assess the reliability of papilledema as indicator of intracranial hypertension in comparison with the gold standard of ICP monitoring, and subsequently determine whether the current approach is indeed the most optimal or whether there is a possibility for improvement.

After vault expansion, patients are still at risk of intracranial hypertension.[31, 70-72] Patients with Apert, Crouzon/Pfeiffer, and Saethre-Chotzen syndromes are mostly involved, and it occurs in 35-43% of the subjects. In Muenke syndrome, the risk of intracranial hypertension appears to be relatively low and for these patients a more syndrome-specific treatment protocol may be preferred. The peak of re-occurrence is between ages 2-4 years whereas after the age of 6 years it is rare. The main known risk factors for this are skull growth arrest, possibly the peak in CBF, and, in the long-term, OSA.

There are several possible consequences of intracranial hypertension, including mental impairment, a systemic vascular response leading to raised blood pressure, disturbed sleep architecture resulting in a decrease in sleep quality, cerebellar tonsillar herniation, and visual loss secondary to optic nerve atrophy.[51, 57, 73, 74] Mental impairment, however, can also be caused intrinsically due to the genetic mutation, nevertheless early vault surgery before the age of 1 year seems to be beneficial for the mental development.[71] Our clinical algorithm seems to be effective in preventing those severe complications, reducing cerebellar tonsillar herniation, but especially by preventing visual loss.

Future perspectives

Children with syndromic craniosynostosis are at risk of intracranial hypertension (see figure 4). The aforementioned risk factors all contribute to its development, although usually not in isolation but in a complex interaction and therefore a child's ICP is the result of a dynamic process to which all these factors contribute. This perhaps more than anything highlights these patients' need for multidisciplinary follow-up.

One of the main challenges in these patients is that they can present with a severe phenotype. Patients with Crouzon/Pfeiffer syndrome, for example, have different craniofacial outcomes compared to the other syndromes which is probably largely caused by the specific genetic mutation; they might present with one or several of the aforementioned risk factor(s) as well as intracranial hypertension. In these cases, it might be difficult to determine whether a patient is affected by a risk factor and intracranial hypertension together, or whether the risk factor has led to secondary intracranial hypertension. Naturally, the more severe a patient's phenotype, the more difficult it is to determine which of the factors has the most crucial role, although—in line with our hypothesis—it is probably more a case of 'a straw that breaks the camel's back'. A patient might be affected by a certain risk factor, and consequently be less able to compensate for any other risk factors that are present; they are therefore at greater risk of developing intracranial hypertension.

Future research should focus on this dynamic process that ultimately results in intracranial hypertension. The aims should be to determine:

1.) The (relative) importance of each individual risk factor
    - OSA, the most important risk factor for intracranial hypertension?
2.) The sequence of occurrence of the risk factors and intracranial hypertension
    - Does one risk factor usually precede another risk factor, is there a pattern in occurrence?

The prospective cohort study (chapter 6) is a first step towards this goal. This can be further improved upon by creating a more sophisticated model, i.e., figure 1. Next, a specialist from the field should interpreted this figure(s), to determine the focus, identify patterns, and provide a clinical perspective of the data thereby guiding subsequent statistical analysis. A user-friendly format needs to be provided for the physician, but the widespread use of smartphones in healthcare settings offers opportunities to implement even a complex model 'at the bedside'. Ultimately, a prediction model for intracranial hypertension in children with syndromic craniosynostosis might be developed with the child's characteristics being entered on a smartphone (for example: a boy with Apert syndrome, 1-year-old, OSA +, CBFv ↑, skull growth arrest –, hydrocephalus –, signs of venous hypertension –, cerebellar tonsillar herniation +), to support clinicians and guide therapeutic decisions.

We believe this is feasible in the foreseeable future. For each individual patient, all the data concerning the risk factors are available as is their intracranial hypertension status. Currently, the limiting factor is the huge number of patients necessary for such analysis, but this will only be a question of time. A national referral center for syndromic craniosynostosis is the ideal setting to perform such research, but such a hospital is even more important to be able to provide optimal quality of care.[75] The Dutch Craniofacial Center has all the necessary expertise to ensure effective multidisciplinary treatment for patients today, whilst at the same time it strives to prolong its status as one of the world's leading craniofacial centers.

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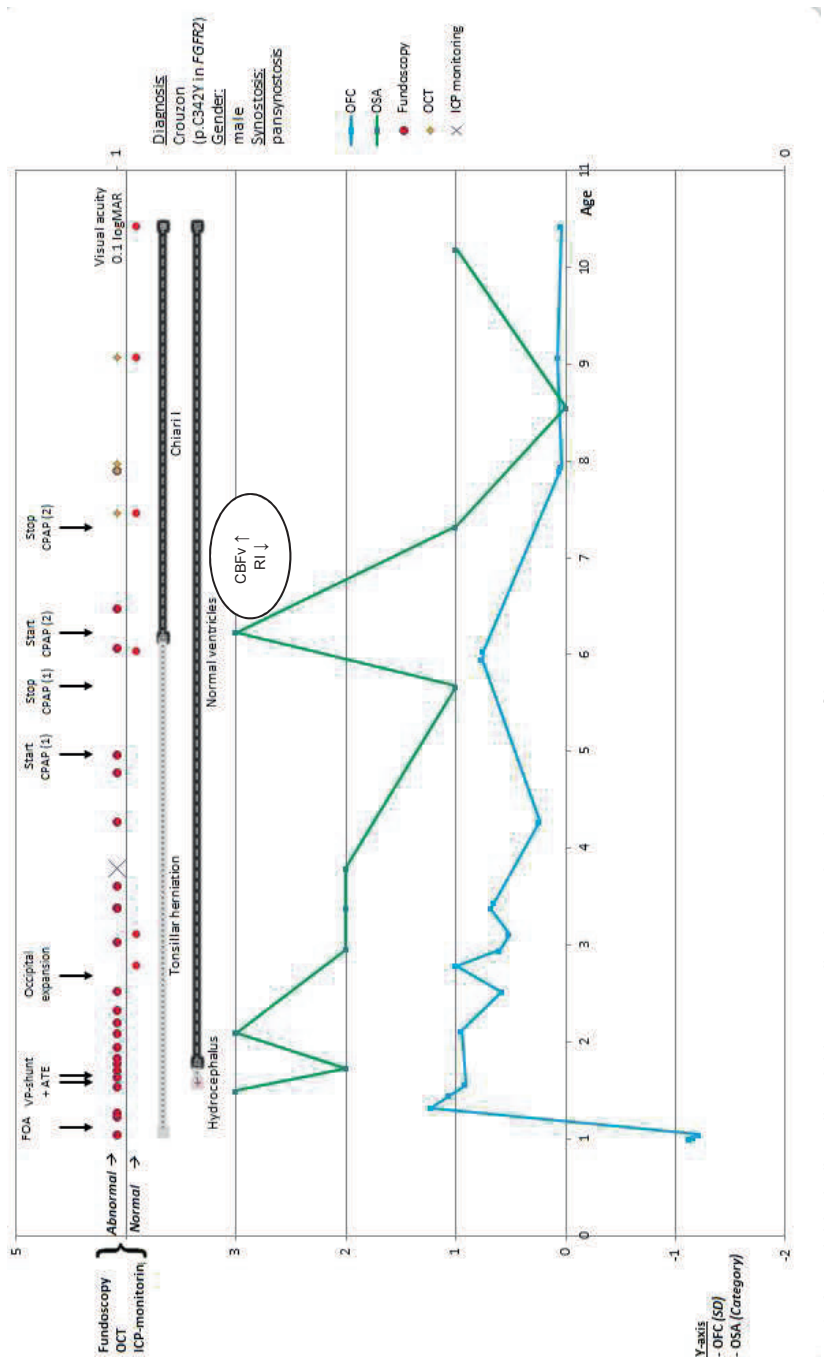

Figure 1: A model including all variables contributing to the development of intracranial hypertension.

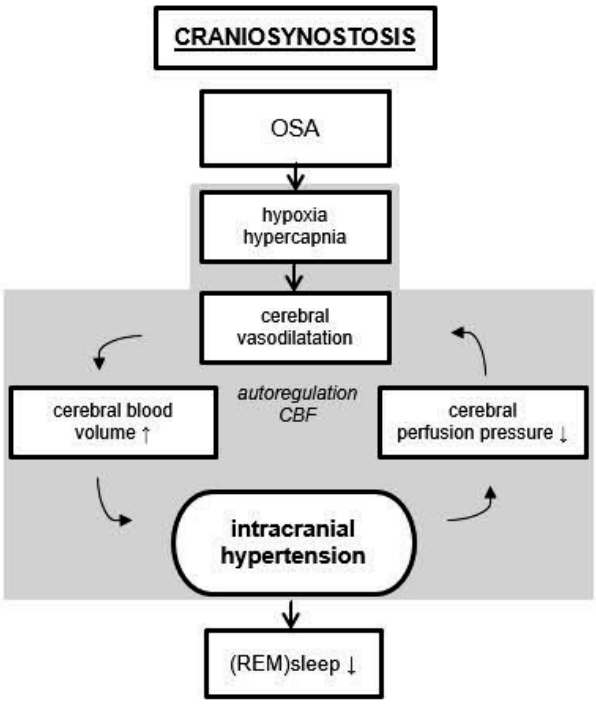

Figure 2: The vicious cycle of OSA, cerebral hypoperfusion, intracranial hypertension, and (REM)sleep.

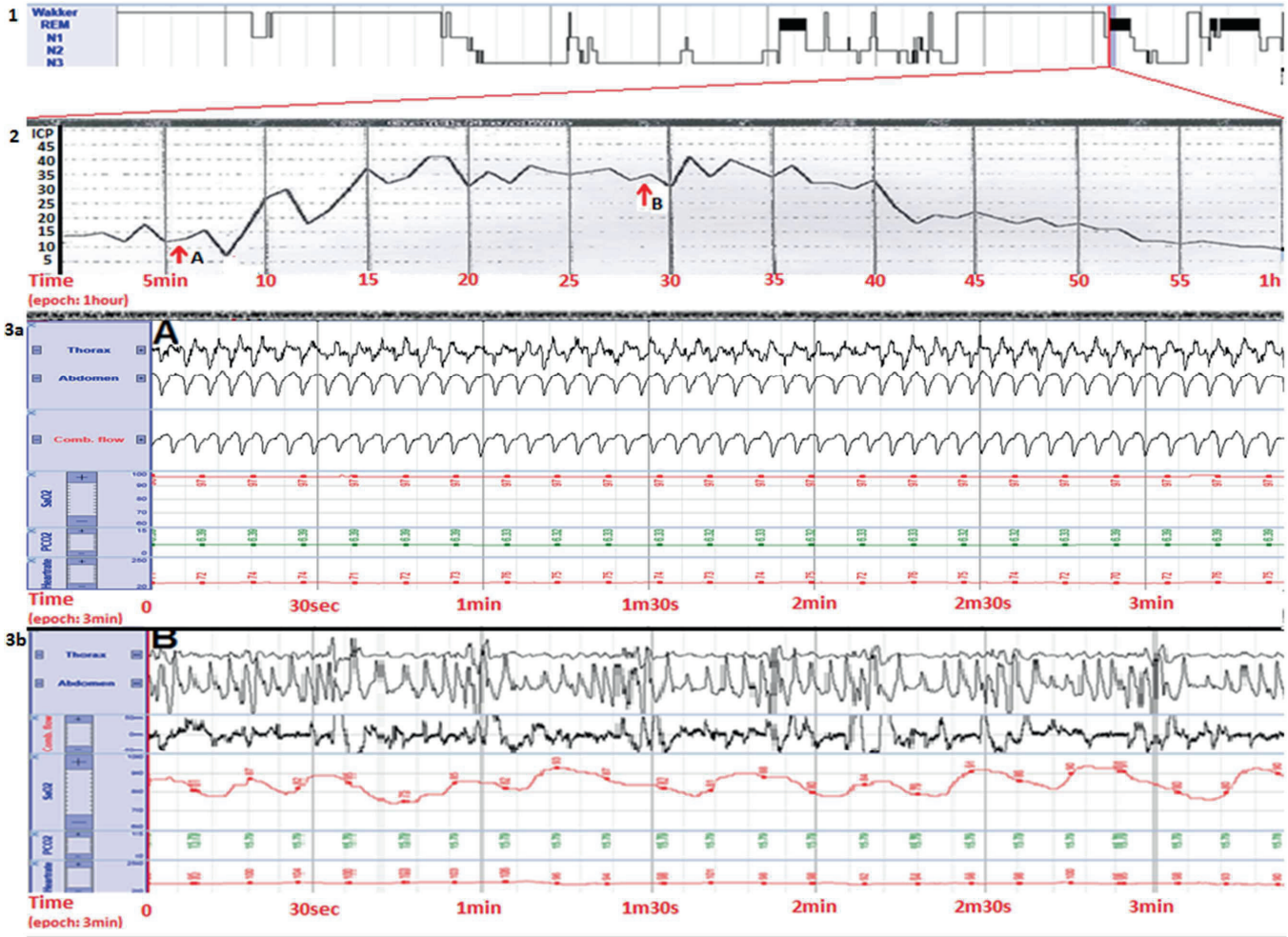

Figure 3: A patient with Crouzon syndrome, shown are his polysomnography recording and simultaneous ICP monitoring result.

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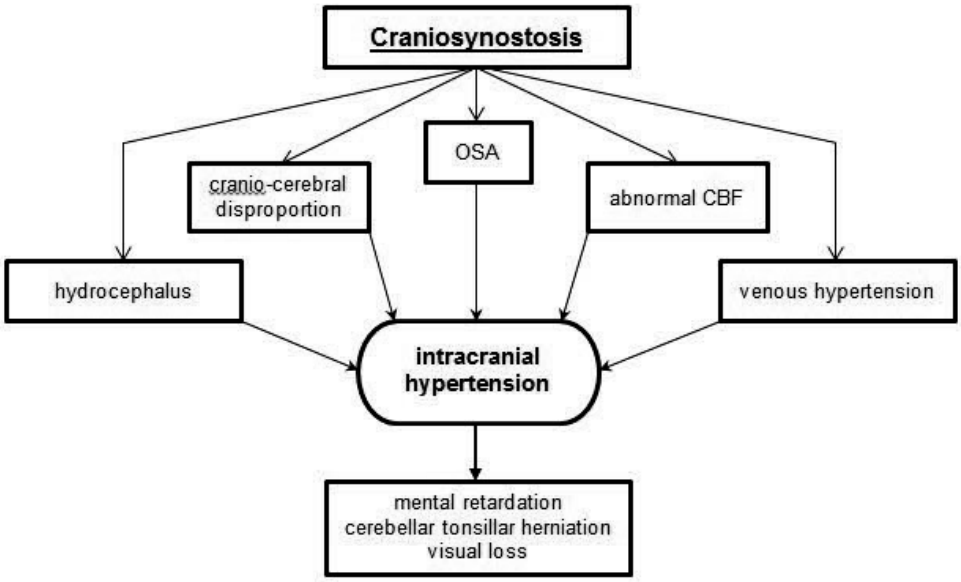

Figure 4: An overview of the risk factors for intracranial hypertension in children with syndromic craniosynostosis, and the subsequent possible consequences.

CHAPTER 10

Nederlandse samenvatting

Dit proefschrift heeft als doel het analyseren van het onderwerp obstructief slaap apneu [OSA] in kinderen met syndromale craniosynostose, en in het bijzonder de bijdrage hiervan te bepalen aan het ontwikkelen van verhoogde hersendruk.

Deel I (hoofdstuk 1) geeft een introductie van craniosynostose, OSA, en verhoogde hersendruk. Craniosynostose (1 : 2.100-2.500) is een zeldzame congenitale aandoening gekenmerkt door een voortijdige sluiting van schedelna(a)d(en) wat resulteert in een afwijkende schedelvorm. Syndromale craniosynostose beslaat 24% van de patiënten, en is geassocieerd met bijkomende abnormaliteiten zoals gezichtsafwijkingen en malformaties van de handen en voeten. De voornaamste diagnoses zijn Apert, Crouzon/Pfeiffer, Muenke, en Saethre-Chotzen syndroom, en complexe craniosynostose. Anamnese en lichamelijk onderzoek zijn het belangrijkste voor het stellen van de diagnose, die daarna bevestigd wordt middels een 3D-CT scan. OSA, een stoornis van de ademhaling tijdens slaap, heeft een prevalentie van 68% in deze patiënten. De oorzaak is vaak een abnormale anatomie die leidt tot obstructies op verschillende niveaus in de bovenste luchtwegen. Apneus, snurken en moeilijkheden met de ademhaling tijdens slaap zijn veel voorkomende symptomen; deze kunnen worden gebruikt om de Brouillette score te berekenen, wat een gevalideerde screeningsmethode is voor de aanwezigheid van OSA in deze patiënten. De definitieve diagnose wordt gesteld met polysomnografie, waarbij de obstructieve apneu-hypopneu index wordt berekend om de ernst van OSA aan te geven, en waarbij tevens het slaappatroon wordt beoordeeld. De behandeling kan bestaan uit nasale corticosteroïden, adenotonsillectomie, ademhalingsondersteuning (bijv. Optiflow, continuous positive airway pressure), midface advancement chirurgie, mandibula verlenging, of in ernstige gevallen een trachea canule. OSA is een risicofactor (tezamen met cranio-cerebrale disproportie, veneuze hypertensie, hydrocephalus en abnormale cerebrale bloedflow) voor het ontwikkelen van verhoogde hersendruk. De prevalentie van verhoogde hersendruk is afhankelijk van het syndroom en van de aangedane schedelna(a)d(en), en kan oplopen tot 83% bij het syndroom van Apert. Patiënten ondergaan routinematig een schedeloperatie in het eerste levensjaar. Screening voor verhoogde hersendruk gedurende follow-up wordt gedaan op basis van een combinatie van onderzoeken: anamnese (bijv. hoofdpijn, gedragsveranderingen, frequente awakenings 's nachts, visusvermindering), de schedelomtrek [OFC] (ter beoordeling van de schedelgroei), polysomnografie (evaluatie van OSA), MRI scan (evaluatie van hydrocephalus en/of cerebellaire tonsillare herniatie), en fundoscopie, op indicatie aangevuld met optical coherence tomography [OCT] en/of een ICP meting. Ondanks schedelexpansie, kan verhoogde hersendruk persisteren of recidiveren. De vervolgbehandeling (bijv. 2^{e} schedelexpansie, OSA behandeling, of ventriculoperitoneale shunt) wordt bepaald door een multidisciplinair team. Verhoogde hersendruk kan uiteindelijk, indien niet adequaat behandeld, resulteren in mentale retardatie, cerebellaire tonsillaire herniatie en visusvermindering.

Deel II (hoofdstuk 2): een pasgeborene met Apert syndroom met een atypische craniofaciale presentatie, als klinische illustratie van de problematiek die een rol kan spelen bij kinderen met syndromale craniosynostose.

Deel III focust op OSA en verhoogde hersendruk in kinderen met syndromale craniosynostose. Hoofdstuk 3: een studie die de rol van OSA onderzoekt en dit plaatst in de context van een alomvattend model voor kinderen met syndromale craniosynostose. Slaap architectuur, de belangrijkste uitkomstmaat in deze studie, is in principe normaal in deze patiënten. De aanwezigheid van verhoogde hersendruk leidt tot een lichte toename in het aantal respiratoir gerelateerde arousals [RERA], maar de slaaparchitectuur blijft intact. Patiënten met matig/ernstig OSA hebben substantiële afwijkingen, aangezien meer RERAs leiden tot een verstoorde slaaparchitectuur met een verminderde slaapefficiëntie en een afname in REM slaap. Monobloc advancement reduceert OSA (op midface-niveau) en verhoogde hersendruk, en verbetert zodoende de slaaparchitectuur. Tenslotte, een eerder voorgestelde samenvattende theorie voor craniosynostose wordt geüpdatet: een vicieuze cirkel van OSA, cerebrale hypoperfusie, cerebrale autoregulatie, en verhoogde hersendruk, resulterend in een verstoorde (REM) slaap. Vervolgens, hoofdstuk 4: het gebruik van endoscopie van de bovenste luchtwegen ter optimalisering van OSA behandeling in kinderen met Apert en Crouzon/Pfeiffer syndroom. OSA in deze patiënten is vaak gerelateerd aan midface hypoplasie, echter het wordt aangetoond dat het doorgaans een multi-level probleem is met partiële of complete obstructie(s) op de niveau(s) van de neus, palatum, tongbasis, hypopharynx, en larynx. Daarnaast zijn de endoscopie bevindingen positief gecorreleerd met de ernst van OSA. Midface advancement, op indicatie gecombineerd met mandibula distractie, reduceert de bovenste luchtweg obstructie(s), dat resulteert in een vermindering van de OSA. Kinderen die lijden aan OSA zouden een endoscopie van de bovenste luchtwegen moeten ondergaan in aanvulling op polysomnografie als een leidraad ter optimalisering van de behandeling, aangezien het verrichten van een midface advancement als een kwestie van routine een suboptimale behandelkeuze zou kunnen zijn. Vervolgens, hoofdstuk 5: de patiënten hun cerebrale bloedflow snelheid [CFBv] profielen en de consequenties van verhoogde hersendruk in kinderen met syndromale craniosynostose. Transcraniële Doppler van de arteria cerebri media wordt verricht 1 dag voor en 3 weken na operatie, om de CBFv en de resistive index [RI] te bepalen; de bloeddruk wordt ook gemeten. Pre-operatief hebben patiënten met papiloedeem, in vergelijking met degenen zonder, een hogere CBFv, RI en bloeddruk. Een schedeloperatie leidt tot een toename in CBFv en een afname van de RI. Patiënten met papiloedeem hebben verhoogde hersendruk in een dermate ernstige vorm dat ze een systemische vasculaire response ontwikkelen wat resulteert in verhoogde bloeddruk; deze verhoogde bloeddruk blijft bestaan na operatie gedurende (korte-termijn) follow-up.

Deel IV belicht de belangrijkste aspecten in het management van kinderen met syndromale craniosynostose. Hoofdstuk 6: een prospectief observationele cohort studie betreffende een algoritme voor het management van verhoogde hersendruk in kinderen met syndromale craniosynostose. De focus ligt op het evalueren van het gestandaardiseerde behandelprotocol van ons craniofaciale centrum, wat bestaat uit een routinematige schedelexpansie in het eerste levensjaar en multidisciplinaire follow-up. De aanwezigheid van papiloedeem, gecombineerd met positieve OCT en/of ICP meting wordt gebruikt om verhoogde hersendruk aan te tonen; een hoog percentage kinderen met verhoogde hersendruk gedurende de

studie (34%) bevestigt het belang van deze bevinding bij deze patiënten. Zij vertonen een complexe interactie tussen schedelgroei, OSA, moment van de operatie, en verhoogde hersendruk. De belangrijkste determinant van verhoogde hersendruk na schedelexpansie is een afbuigende schedelgroei, wat kan optreden op variërende leeftijd. Wat betreft OSA, dit moet vooral een aandachtspunt zijn bij patiënten met persisterend verhoogde hersendruk. Tijdens late follow-up, verhoogd ook matig/ernstig OSA het risico op het ontwikkelen van verhoogde hersendruk. Vervolgens, hoofdstuk 7: een studie die het optimale type schedelexpansie in kinderen met Apert en Crouzon/Pfeiffer syndroom onderzoekt. Een fronto-orbitale advancement was de standaard behandeling in ons ziekenhuis in het verleden, echter na een internationale consensus meeting werd het protocol aangepast naar een occipitale expansie. Deze studie ondersteunt de voorkeur voor occipitale expansie, omdat het leidt tot een grotere toename in OFC (en daarom intracranieel volume), wat resulteert in een reductie van de incidenties van cerebellaire tonsillaire herniatie en papiloedeem. Aangezien cerebellaire tonsillaire herniatie en papiloedeem indirecte tekenen van verhoogde hersendruk zijn, bevestigen deze bevindingen de superioriteit van een occipitale expansie in de behandeling van verhoogde hersendruk. De visus is vergelijkbaar tussen de beide groepen, en aangezien slechts één kind een visus van 0.30 logMAR had wat wordt beschouwd als het minimum voor adequaat functioneren, is dit een verdere aanwijzing dat ons protocol effectief is in het voorkomen van secundaire visusvermindering.

Concluderend, OSA is veel voorkomend in kinderen met syndromale craniosynostose en kan, via een complexe vicieuze cirkel, resulteren in verhoogde hersendruk. Vroege verwijzing is noodzakelijk voor een routinematige schedeloperatie in het eerst levensjaar en verdere multidisciplinaire behandeling. Gedurende follow-up, is de optimale procedure voor het screenen op verhoogde hersendruk een uitdaging, hoewel de huidige benadering met papiloedeem in het middelpunt zowel bruikbaar als klinisch relevant is. Verhoogde hersendruk is het gevolg van een dynamisch proces waarin verschillende risicofactoren op elkaar inwerken. Een gespecialiseerd craniofaciaal centrum is de optimale setting om een effectieve behandeling voor alle patiënten te garanderen, inclusief degenen met de meest ernstige presentatie.

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PART VI
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APPENDIX

CURRICULUM VITAE

Bart Spruijt was born on the 4th of July, 1988 in Voorthuizen, Gelderland, the Netherlands. He attended the Dr. W. van den Berghschool and did his Atheneum at the Johannes Fontanus College, after which he moved to Rotterdam to study medicine at the Erasmus MC. During his first years as medical student, his passion for paediatrics became apparent and he started the Master of Science (NIHES) - Health Sciences in this field. He got in touch with his mentor Prof. dr. Henriëtte A. Moll, and, following his graduation as MD, he performed monthly weekend shifts at the emergency department of the Sophia Children's Hospital – Erasmus MC. Subsequently, he also started his PhD at the Dutch Craniofacial Center (promotor: Prof. dr. Irene M.J. Mathijssen): all has culminated into this thesis.

PhD PORTFOLIO

Name PhD student:	Bart Spruijt
Erasmus MC department:	Dutch Craniofacial Center (pediatrics / plastic surgery)
PhD period:	01-01-2013 – 31-10-2015
Promotor:	Prof. Dr. I.M.J. Mathijssen
Co-promotor:	Dr. K.F.M. Joosten

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
Master of Science (NIHES): Health Sciences	2008-2011	-
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2013	40/1.4
Research Integrity	2014	8/0.3
Biomedical English Writing and Communication	2015	84/3
Specific courses		
Sleep Scoring – Dutch Sleep Institute	2013	8/0.3
Seminars and workshops		
Grand Round (pediatrics)	2013-2015	56/2
ICK-KNF PSG demo meetings	2013-2015	56/2
Presentations		
Craniofacial research meeting *(Rotterdam, the Netherlands)*	2013	28/1
Scientific meeting plastic surgery *(Rotterdam, the Netherlands)*	2014	28/1
Sophia research day *(Rotterdam, the Netherlands)*	2014	28/1
European Sleep Research Society [1] *(Tallinn, Estonia)*	2014	28/1
European Sleep Research Society [2] *(Tallinn, Estonia)*	2014	28/1
Craniofacial research meeting *(Rotterdam, the Netherlands)*	2014	28/1
Laposa - Patients Association *(Nijkerk, the Netherlands)*	2015	28/1
Algorithm for the management of intracranial hypertension in syndromic craniosynostosis - European Society of Craniofacial Surgery *(Paris, France)*	2014	28/1

(Inter)national conferences		
Symposium on schisis and craniofacial anomalies *(Rotterdam, the Netherlands)*	2013	8/0.3
Sleep and Breathing *(Berlin, Germany)*	2013	24/0.9
Sophia research day *(Rotterdam, the Netherlands)*	2013	8/0.3
PhD-day *(Rotterdam, the Netherlands)*	2013	8/0.3
Jubilee congress - Sophia 150 years *(Rotterdam, the Netherlands)*	2013	8/0.3
Craniofacial research meeting *(Rotterdam, the Netherlands)*	2013	8/0.3
Symposium on schisis and craniofacial anomalies *(Rotterdam, the Netherlands)*	2014	8/0.3
Sophia research day *(Rotterdam, the Netherlands)*	2014	8/0.3
PhD-day *(Rotterdam, the Netherlands)*	2014	8/0.3
European Sleep Research Society *(Tallinn, Estonia)*	2014	24/0.9
European Society of Craniofacial Surgery *(Paris, France)*	2014	28/1
Craniofacial research meeting *(Rotterdam, the Netherlands)*	2014	8/0.3
Laposa - Patients Association *(Nijkerk, the Netherlands)*	2015	8/0.3
PhD-day *(Rotterdam, the Netherlands)*	2015	8/0.3
Other		
MD pediatrics – weekend shifts at the emergency department of the Sophia Children's Hospital – Erasmus MC	2013-2014	56/2

2. Teaching

	Year	Workload (Hours/ECTS)
Supervising		
Bianca den Ottelander	2015	1
Lecturing		
Sophia Onderzoekers Vertegenwoordiging – Educational Committee	2014-2015	56/2
"Dysmorfologie & syndroomdiagnostiek"	2014-2015	56/2
Supervising practicals and excursions, tutoring		
Tutor: 1st year medical students	2014-2015	84/3
Other		
NVSCA Congress (organizing committee)	2014	56/2
PhD-day 2015 (organizing committee)	2015	28/1
		> 30 ECTS

PUBLICATIONS

1. Spruijt B*, Rijken BF*, Joosten KF, Bredero-Boelhouwer HH, Pullens B, Lequin MH, Wolvius EB, van Veelen – Vincent ML, Mathijssen IM. Atypical presentation of a newborn with Apert syndrome. *Childs Nerv Syst. 2015 Mar;31(3):481-6.*

2. Spruijt B, Joosten KF, Driessen C, Rizopoulos D, Naus NC, van der Schroeff MP, Wolvius EB, van Veelen ML, Tasker RC, Mathijssen IM. Algorithm for the management of intracranial hypertension in children with syndromic craniosynostosis. *Plast Reconstr Surg. 2015 Aug;136(2):331-40.*

3. Spruijt B, Rijken BF, den Ottelander BK, Joosten KF, Lequin MH, Loudon SE, van Veelen ML, Mathijssen IM. First vault expansion in Apert and Crouzon-Pfeiffer syndromes: front or back? *Plast Reconstr Surg. 2016 Jan;137(1):112e-21e.*

4. Spruijt B, Tasker RC, Driessen C, Lequin MH, van Veelen ML, Mathijssen IM, Joosten KF. Abnormal transcranial Doppler cerebral blood flow velocity and blood pressure profiles in children with syndromic craniosynostosis and papilledema. *J Craniomaxillofac Surg. 2016 Jan 11. pii: S1010-5182(16)00006-8.*

5. Spruijt B, Mathijssen IM, Bredero-Boelhouwer HH, Cherian PJ, Corel LJ, van Veelen ML, Hayward RD, Tasker RC, Joosten KF. Sleep architecture linked to airway obstruction and intracranial hypertension in children with syndromic craniosynostosis. *Accepted: Plast Reconstr Surg.*

6. Doerga PN, Spruijt B, Mathijssen IM, Wolvius EB, Joosten KF, van der Schroeff MP. Upper airway endoscopy to optimize obstructive sleep apnea treatment in Apert and Crouzon syndromes. *J Craniomaxillofac Surg. 2016 Feb;44(2):191-6.*

7. Spruijt B, Vergouwe Y, Nijman RG, Thompson M, Oostenbrink R. Vital signs should be maintained as continuous variables when predicting bacterial infections in febrile children. *J Clin Epidemiol. 2013 Apr;66(4):453-7.*

*These authors contributed equally to this work

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Ik draag dit proefschrift op aan mijn maatje

Bart