OBSTRUCTIVE SLEEP APNEA IN CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS

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OBSTRUCTIVE SLEEP APNEA IN CHILDREN WITH SYNDROMIC CRANIOSYNOSTOSIS

OBSTRUCTIEF SLAAP APNEU SYNDROOM BIJ KINDEREN MET EEN SYNDROMALE CRANIOSYNOSTOSE

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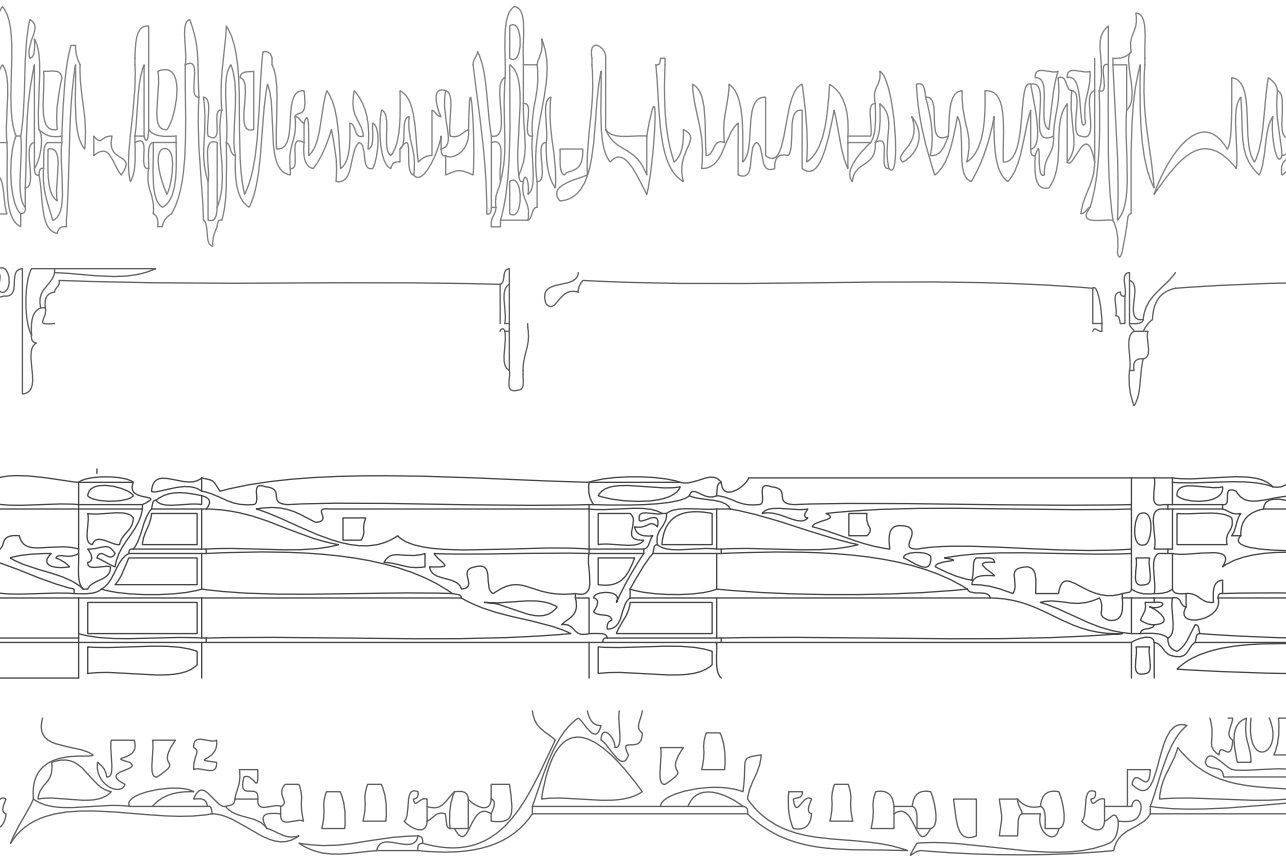
Part I

Introduction






Chapter 1

General introduction

INTRODUCTION

In the Netherlands between 179.000 and 204.000 children were born annually during the last ten years. Congenital anomalies occur in 1 in 33 births. The most frequent anomaly involves the heart with a prevalence of 1 in 150 births (66.7 per 10.000 births). The ventricular septal defects occur the most frequent (30.0 per 10.000 births) (Central Bureau of Statistics Netherlands, European Registration of Congenital Anomalies, National Neonatology Registration). A rare congenital anomaly is craniosynostosis, affecting 1 in 2.500 births.

The newborns cranial vault is composed of seven individual bones separated by sutures. This arrangement accommodates transient skull distortion during birth and permits future growth of the brain, the volume of which quadruples during the first two years of life. There are six major cranial sutures: the metopic, two coronal, the sagittal, and two lambdoid sutures. Six additional sutures are considered minor: two frontonasal, two temporosquamosal, and two frontosphenoidal. At the anterior of the skull, the sagittal, coronal, and metopic sutures meet to form the anterior fontanelle. The posterior fontanelle is formed by the intersection of the sagittal and lambdoid sutures. The sutures function as growth centres. In the center of a suture lie undifferentiated, proliferating cells. A part of these cells undergo osteogenic differentiation and migrate to the borders of the bone sheets. After differentiation in osteoblasts growth of the sheets occurs by apposition[1].

At two months of age, the posterior fontanelle closes, followed by anterior fontanelle closure at approximately two years of age[2]. While the metopic suture typically closes within the first year of age, all remaining cranial sutures close in adulthood, although they are no longer involved in skull growth after approximately the age of six. Then skull growth takes place by apposition of bone at the outer side of the skull and resorption at the inner side.

SYNDROMIC CRANIOSYNOSTOSIS

Craniosynostosis is characterized by the premature fusion or agenesis of calvarial sutures, which usually happens at 15 weeks of gestation for the metopic suture, at 16 weeks for the coronal and lambdoid sutures and at 18 weeks for the sagittal suture[3]. Due to the craniosynostosis normal growth of the skull related to the affected suture is restricted. In order to accommodate the growing brain, compensatory skull growth occurs in the other directions resulting in cranial deformation: this is categorized as scaphocephaly in case of involvement of the sagittal suture, as frontal plagiocephaly in case of one coronal suture, as brachycephaly in case of both coronal sutures, as trigonocephaly in case of the metopic suture, and as pachycephaly in case of synostosis of one lambdoid suture. In about 40%

of the cases (1:6.250) the craniosynostosis is part of a syndrome, such as Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome[4].

Apert syndrome is an autosomal dominant syndrome caused in >98% of the cases by one of the two FGFR (fibroblast growth factor receptor) 2 mutations on chromosome 10, S252W and P253R with full penetrance[5, 6], very rare is S252F[4]. Recently, two rare mutations were found, a partial large FGFR 2 gene deletion and an Alu element insertion into the FGFR 2 gene[5]. The syndrome is characterized by symmetric complex syndactyly (involving both soft tissues and bone) of hands and feet, bicoronal synostosis, exorbitism, hypertelorism and midface hypoplasia. The intelligence varies from near normal to mentally retarded with a mean IQ of 62 to 74[7-9]. Apert is the most severe type of syndromic craniosynostosis.

Crouzon syndrome occurs in 1 in 25.000 births and is an autosomal dominant syndrome predominantly caused by mutations in FGFR 2 on chromosome 10 with variable expression[10], but the FGFR 3 mutation, A391E has also been reported in individuals with Crouzon syndrome and acanthosis nigricans[11]. Crouzon syndrome is characterized by midface hypoplasia, exorbitism and various forms of craniosynostosis, which may have a postnatal onset. The intelligence of patients with Crouzon syndrome is overall significantly better than the intelligence of patients with Apert syndrome, with an average IQ of 84 to 92[9, 12].

Pfeiffer syndrome is an autosomal dominant syndrome but most cases are sporadic. The syndrome is mainly caused by mutations in FGFR 2 on chromosome 10, but the P252R mutation in the FGFR 1 gene on chromosome 8 have also been described incidentally[4, 13, 14]. The phenotype of this syndrome is characterized by craniosynostosis (bilateral coronal or pansynostosis), midface hypoplasia and broad thumbs and great toes. With the discovery of the genetic background in syndromic craniosynostosis the same genotype in Pfeiffer syndrome was found as in Crouzon syndrome. The clinical presentation is also very similar to Crouzon syndrome besides the characteristically hand and foot anomalies. So there is an overlap between both syndromes and they can be considered as phenotypic variations of the same genetic defect[15].

Muenke syndrome is an autosomal dominant disorder with incomplete penetrance, caused by the P250R mutation of the FGFR 3 gene on chromosome 4, discovered in 1997[16]. It is one of the most commonly found mutations in the human genome, but does not always result in craniosynostosis[17]. The phenotype associated with this syndrome incorporates macrocephaly, uni- or bilateral coronal synostosis, hearing loss and developmental and language delay[18, 19]. The cognitive function seems to be normal with a mean IQ of 93[20].

Saethre-Chotzen syndrome is an autosomal dominant syndrome with incomplete penetrance, predominantly caused by mutations or deletions in the TWIST gene on chromosome 7. The syndrome is characterized by coronal synostosis, upper eyelid ptosis, external ear anomalies and limb abnormalities, such as brachydactyly, syndactyly, clinodactyly or broad halluces. Most patients with Saethre-Chotzen have a normal intelligence[21, 22], with the exception of patients with TWIST deletions who have a higher frequency of mental retardation[23].

In a significant number of patients one of the above-mentioned genetic mutations is found. FGFR's and their ligands the fibroblast growth factors (FGF's), play a central role in the growth and differentiation of mesenchymal and neuroectodermal cells[21, 24]. FGFR binds FGF and plays a substantial role in signal transduction. FGFR's regulate cell proliferation and differentiation and are thus involved in cranial suture fusion[24-26]. Also the TWIST gene encodes for a basic transcription factor that is responsible for mesenchymal cell development during cranial neuralization[18].

But not in all patients with a phenotypically syndromic craniosynostosis a mutation can be found. **Complex craniosynostosis** is defined as fusion of two or more cranial sutures without known FGFR or TWIST mutation[4, 18]. In the future new mutations are likely to be found in this group of patients with complex craniosynostosis[27].

INTRACRANIAL PRESSURE

Pathophysiology

The skull protects the intracranial compartment consisting of brain parenchyma (80%), cerebrospinal fluid (10%) and blood (10%). Because of the rigid structure of the skull with a fixed internal volume once growth is completed, intracranial pressure (ICP) is a function of the volume and the compliance of each component of the intracranial compartment. An increase in the volume of one component or the presence of pathologic components results in displacement of other structures, an increase in ICP, or both. In severe cases it can diminish the cerebral blood flow resulting in ischemia, cell injury and death[28]. The relationship between intracranial volume and pressure is not linear. An initial increase in volume results in a small increase in ICP due to compensation, but once the compensation mechanism is overcome, a further increase in volume results in a steep rise in ICP[29].

Factors involved in elevated intracranial pressure

Traumatic brain injury is the most common risk factor to develop elevated ICP. A brain tumour, hematoma or hydrocephalus can result in elevated ICP, just as cerebral edema due to an infection, tumour, head injury or stroke.

Patients with syndromic craniosynostosis are at risk for elevated ICP. Factors suggested to contribute to elevated intracranial pressure in craniosynostosis are craniocerebral disproportion, ventriculomegaly or hydrocephalus, venous hypertension and obstructive sleep apnea.

a. Craniocerebral disproportion

Due to premature fusion of calvarial sutures, the intracranial pressure may be elevated if the brain grows more rapidly than the skull[30]. In healthy children the intracranial volume does not increase linear with age. The growth is most rapid in the first 5 years of life; by the age of 2 years 77% of the intracranial volume observed at the age of 15 is reached and by 5 years 90% of the volume[31]. In children with syndromic craniosynostosis the intracranial volumes seem to be significantly smaller at birth with an increase to the normal growth curve before the age of one[32]. Except for Apert syndrome, in these children the intracranial volume is in the normal range at birth, but at 6 months of age much higher than the norm[32-36]. The explanation remains unclear. In Apert syndrome this increased intracranial volume was not related to cranial decompression or ventriculomegaly[35]. Posnick et al.[36] also found greater intracranial volumes than the mean in patients with Crouzon syndrome in contrast with Gault et al.[34].

Children with elevated ICP, due to their craniosynostosis, also had a significantly lower intracranial volume, but a lower intracranial volume did not result in elevated ICP in each case[37]. However, in a study from London no relationship between elevated intracranial pressure and decreased intracranial volume was found in children with craniosynostosis[38].

b. Ventriculomegaly or hydrocephalus

Ventricular dilatation is a common finding in patients with syndromic craniosynostosis. The increase in ventricular size can result in elevated ICP due to an increase in cerebrospinal fluid volume. Enlarged ventricles are defined as hydrocephalus when the condition is progressive and as ventriculomegaly when it is non-progressive[39]. Ventricular dilatation of either origin is reported in 30 to 70% of the patients with Crouzon or Pfeiffer syndrome with frequently true hydrocephalus and in 40 to 90% of the patients with Apert syndrome, which mainly concerns ventriculomegaly. In Muenke and Saethre-Chotzen syndrome ventricular dilatation is rare, but specific literature for these syndromes is rare[39].

In craniosynostosis, hydrocephalus can hypothetically result from cerebrospinal fluid outflow obstruction due to constriction of the posterior fossa, malabsorption due to venous sinus hypertension[39] or increased cerebrospinal fluid production[40]. Ventriculomegaly

seemed to be associated with primary brain maldevelopment or sometimes with secondary brain atrophy. Other less common causes of hydrocephalus are basilar invagination, aqueductal stenosis and compression by the midline occipital bone crest[41].

c. Venous hypertension

Venous hypertension is also common in syndromic craniosynostosis and another factor contributing to elevated ICP[30, 42]. It can be caused by anomalous venous drainage and anatomical vascular variations resulting in development of collateral veins[30, 43]. Abnormal intracranial venous drainage seems to be present in patients with severe stenosis of the sigmoid sinus- jugular bulb and jugular segment (intraosseous part of the jugular sinus) complex. These patients are more likely to show earlier signs of elevated ICP, mostly before the age of 3. Presence of elevated ICP due to the effects of venous hypertension is unusual after six. After this age the collateral venous drainage will likely become sufficient to allow the ICP to normalize[43].

Early fusion of the lambdoid sutures in combination with the petro-occipital synchondroses can be associated with stenosis of the jugular foramen[41]. And in presence of a small posterior fossa this stenosis is possibly related to venous hypertension[39, 41, 44]. Jugular foramen stenosis is suggested to result in a rise of the sagittal sinus pressure, which increases the cerebrospinal fluid pressure[44].

d. Obstructive sleep apnea

Forty percent of the patients with syndromic craniosynostosis will develop obstructive sleep apnea[45]. During invasive ICP monitoring, plateau waves of elevated ICP are recognized to be associated with obstructive apneas and desaturations. Obstructive sleep apnea results in hypoxia and hypercapnia with subsequent vasodilatation and an increase of the cerebral blood flow resulting in elevated ICP[42]. In the next part of this introduction obstructive sleep apnea will be discussed extensively.

Prevalence of elevated intracranial pressure

In isolated, single-suture craniosynostosis the frequency of elevated ICP before vault expansion differs for the various types of craniosynostosis[46-48]. In patients with syndromic craniosynostosis, either Apert or Crouzon syndrome, elevated ICP before vault expansion is seen in 45% and 63% respectively[7,49]. Regular screening with visual evoked potentials (VEP) for signs of elevated ICP prior to vault expansion, demonstrated an incidence of elevated ICP of 83% in children with Apert syndrome with a mean age of 18 months (range 1 month- 4 years 5 months)[50]. In the different types of craniosynostosis the frequencies of elevated ICP (≥ 15 mm Hg), invasively measured before surgery, are shown in table 1[7, 18, 37, 46-49, 51, 52].

Table 1: Frequencies of elevated intracranial pressure per type of craniosynostosis

Type of craniosynostosis	Frequency of elevated ICP (range, %)
Trigonocephaly	0-33
Scaphocephaly	13-24
Frontal plagiocephaly	6-22
Brachycephaly	31-50
Complex craniosynostosis	47-64
Apert syndrome	39-50
Crouzon/ Pfeiffer syndrome	63-65
Muenke syndrome	0
Saethre-Chotzen syndrome	29-43

Recurrent elevated intacranial pressure

Despite early treatment elevated ICP may still reoccur or persist after early cranial expansion[43, 53]. Late-presenting children with a smaller intracranial volume than normal have a higher chance to develop recurrent elevated ICP due to craniocerebral disproportion with a need for reoperation[32]. Information on the frequency of this problem, however, is limited[54]. In Saethre-Chotzen syndrome the postsurgical rate of elevated ICP raised to 42% after 5 years of follow-up[53]. In Apert syndrome 35% will develop a second episode of elevated ICP on average 3 years and 4 months after vault expansion[50].

Diagnostic methods

Elevated ICP can be diagnosed in different ways, either through direct measurement or through indirect methods. The classic clinical symptoms of acute elevated intracranial pressure are headache, vomiting and disturbed consciousness. Gradually development of elevated ICP seen in craniosynostosis is difficult to recognize with more subtle features as deterioration in schoolwork and sight, and change in behavior[29].

The 'gold standard' for measuring ICP is an invasive overnight measurement during at least 12 hours with direct monitoring of the intracranial pressure. An intraparenchymal device is most commonly used in daily practice. A drawback of the ICP monitoring is the need for a surgical procedure, hospital admittance and the risk of complications such as haemorrhage, cerebrospinal fluid leak and infection[29, 54].

The analysis of ICP measurements includes the identification of the baseline ICP and the presence of wave patterns. There are three waveforms. C-waves are a normal variation in ICP related to the cardiac cycle. B-waves are rises in pressure to a level between 20 and 50 mm Hg during 5 to 10 minutes with decline to the baseline afterwards. They can be normal, especially during sleep. A-waves are abnormal plateau waves present in the acute phase of elevated ICP due to traumatic brain injury for example. Loss of cerebral autoregulation results in these waves with a sudden rise in pressure above 50 mm Hg during at least 20 minutes without recurrence to the baseline[29].

In children, a baseline pressure below 10 mm Hg is considered as a normal ICP. An upper limit of the baseline pressure between 10 and 15 mm Hg is borderline elevated. A baseline pressure of 15 mm Hg or more and/ or at least four B-waves during at least 5 minutes during sleep is considered to be elevated[29, 49].

Indirect methods to screen for elevated ICP are palpation of the fontanelle in infants and measurement of the head circumference. The head circumference growth curve can form a notion of the growth of the skull, although it does not take growth in upward direction (turricephaly) into account. A decline of the curve can be associated with elevated ICP.

Radiological evaluation for screening on elevated ICP consists of a skull radiograph, a computed tomography (CT) angiography scan or magnetic resonance imaging (MRI) scan. A skull radiograph might demonstrate a beaten-copper pattern, also known as digital impressiones, which correspond to the gyral pattern of the underlying brain. These radiographic changes are visible as markings in the skull of the gyri in presence of elevated ICP. To screen for elevated ICP this method is insensitive[55]. A CT angiography scan of the brain can show ventricular dilatation or signs of venous hypertension[39, 55].

A reliable symptom of elevated ICP, although rather late in onset, is papilledema[56]. If fundoscopy reveals papilledema, it is a sure sign for elevated ICP after exclusion of hyperopia, which can resemble papilledema without being a sign of elevated ICP, so-called pseudopapilledema[57]. The specificity of papilledema is 98%, but the sensitivity is age-dependent. Above eight years the sensitivity is 100%, but in younger children absence of papilledema does not exclude the presence of elevated ICP and thus fundoscopy is likely to result in an underestimation of the incidence of elevated ICP[56]. Ocular coherence tomography can measure the retinal nerve fibre layer thickness. The thickness is increased if severe papilledema is present. But it is not effective to differentiate between mild papilledema and pseudopapilledema[58]. Visual evoked potentials (VEP) can be used if neurophysiologic expertise is available. Prolongation of the N2 wave latency period is correlated with elevated ICP[59].

Treatment of elevated intracranial pressure

Treatment of elevated ICP is dependent on the causal factor. In craniosynostosis the first treatment or prevention of elevated ICP is surgical decompression to expand the skull within the first year of life[48]. Other options can be the insertion of a ventriculoperitoneal shunt or treatment of obstructive sleep apnea.

Consequences of untreated elevated intracranial pressure

If left untreated, elevated ICP may lead to irreversible visual loss caused by optic nerve dysfunction, mental impairment or tonsillar herniation[41, 48, 60, 61]. Visual loss is a very rare, but severe complication. In our hospital visual loss is described in three cases with Crouzon and in one case with Apert syndrome in presence of papilledema but without other

symptoms of elevated ICP[60]. Renier et al.[48] mentioned an observed frequency of optic atrophy in 10% of the Crouzon cases and no optic atrophy was observed in the other syndromes. Regularly screening of sight and the presence of papilledema can possibly prevent these severe complications.

Vault expansion done after the age of 1 results in a higher risk to develop elevated ICP. The mental development seems to be better after early surgical treatment done before the age of 1[48]. Possibly there is an association between elevated ICP and the mental development. Another study found no correlation between the mental development and the age at surgery[8]. So, the association between craniosynostosis, age at surgery, untreated elevated ICP and mental impairment is not clear yet.

Elevated ICP appears to cause herniation of the cerebellar tonsils through the foramen magnum. More than one third of the patients with tonsillar herniation will develop symptoms or syringomyelic cavities, but in most craniosynostosis patients it remains asymptomatic. Chronic tonsillar herniation can cause suboccipital pain, compression of the lower brainstem and upper cervical spinal cord (respiratory problems) and deformation of the fourth ventricle[41].

Tonsillar herniation of the cerebellum is also known as Chiari malformation and is commonly observed in Crouzon and Pfeiffer syndrome (73%) and rarely in Apert syndrome (2%). In Crouzon syndrome 20% will develop symptoms of chronic tonsillar herniation before the age of 20. In these sydromes the herniation is not present at birth, but acquired after. It seems to be related to an abnormally small posterior fossa, in particular after fusion of the lambdoid sutures within the first two years of life[39, 41]. In Crouzon syndrome the sagittal and lambdoid sutures fuse significantly earlier than in Apert syndrome, which can explain the different occurrence. Another factor that may explain the difference is hydrocephalus. All patients with Crouzon syndrome and hydrocephalus show a Chiari malformation. Of the Crouzon patients with a Chiari malformation 53% do not have a hydrocephalus[41].

OBSTRUCTIVE SLEEP APNEA

Definition and pathophysiology

Obstructive sleep apnea (OSA) is a clinical syndrome due to partial or complete upper airway obstruction characterized by difficulties in breathing, snoring and apneas during sleep resulting in sleep fragmentation, hypoxia and hypercapnia. Other features of OSA are restless sleep, mouth breathing, sweating, and daytime sleepiness[62, 63]. Between inspiration and expiration a substantial change in the size of the airway is shown, which is most apparent in the rhinopharynx[64]. Collapse occurs when the pressure surrounding the airway becomes greater than the pressure within the airway.

OSA can result in development of elevated ICP. The causal relationship and the exact underlying mechanism between airway obstruction and elevated ICP are not fully clear. A possible hypothesis is that the muscular tone of the pharyngeal dilators, who maintain the patency of the airway, reduces during active sleep. This causes accumulation of carbon dioxide and reactive vasodilatation, followed by a rise in ICP. With the elevated ICP the cerebral perfusion pressure decreases resulting in more vasodilatation. A vicious cycle exists, which can be broken by an arousal resulting in correction of the blood gases and the airway obstruction[30, 42, 65].

Causes of obstructive sleep apnea

The upper airway obstruction is due to an anatomically small upper airway and/ or to a decreased neuromuscular tone of the pharyngeal dilators during sleep. Anatomic factors along the upper airway, such as nasal obstruction, enlarged tonsils and adenoids, pharyngeal collapse or fat deposition by obesity can decrease the airway size or stability, and may therefore contribute to the development of OSA. Also endocrine disorders, such as hypothyroidy or acromegaly, and neuromuscular factors, such as hypotonia or hypertonia can result in OSA. Medicaments, such as analgesics or muscle relaxants can affect the neural control or collapsibility of the airway or reduce the size of the upper airway[66].

Also craniofacial anomalies, such as midface hypoplasia, retro- or micrognathia, skull base anomalies or a narrow maxillary arch can lead to a decrease in the size of the rhinopharynx, oropharynx, or hypopharynx, and can predispose to obstructive sleep apnea[67, 68].

Prevalence of obstructive sleep apnea

Obstructive sleep apnea exists in 2 to 5 percent of the healthy children, which can occur at any age with a peak incidence between three and six years of age[62]. At that age adenotonsillar hypertrophy is the major risk factor for development of OSA, because the tonsils and adenoid are the largest in relation to the oropharynx[62, 69].

The risk to develop OSA is 40% in children with Apert, Crouzon and Pfeiffer syndrome mainly during the first six years of life[45, 68, 70]. Beside the anatomical anomalies in these syndromes they also develop adenotonsillar hypertrophy. In Muenke and Saethre-Chotzen syndrome and complex craniosynostosis the incidence of OSA is unknown.

In 1982, Schafer described upper airway obstruction and sleep disorders in children with craniofacial anomalies[71]. Up till then, little attention was paid to respiratory difficulties in syndromic craniosynostosis. Only the severe OSA patients are recognized and the initial treatment was a tracheostomy[72]. However, in the last years due to the familiarity with the risk to develop OSA in presence of syndromic craniosynostosis also the moderate and mild cases are diagnosed.

Diagnostic methods

A questionnaire on presence of symptoms can be helpful to screen for obstructive sleep apnea. This questionnaire is developed and validated for normal, otherwise healthy children and consists of three questions about the presence of difficulty in breathing during sleep, observed apneas and snoring. From this questionnaire the Brouillette score is calculated which is related to the likelihood of having OSA[73].

Another tool to estimate the presence of OSA is observation of the child during sleep. The parents' observation includes different items: effort of respiration (difficulty in breathing), apneas during breathing, snoring, retractions, sleep position, hyperextension of the neck, restless sleep and mouth breathing.

The gold standard to diagnose presence and severity of OSA is polysomnography (PSG). Polysomnography can be done at the hospital or ambulatory at home. A lot of studies to diagnose OSA and to analyze PSG's are done in adults. Much fewer studies are performed in children and different definitions for duration and severity of OSA are used. The degree of OSA is expressed in an obstructive apnea hypopnea index (OAHI), the number of obstructive and mixed apneas and hypopneas followed by desaturation per hour. An OAHI ≥ 1 is defined as OSA. Also an oxygenation desaturation index (ODI) is measured by the number of desaturations ($\geq$ 4% decrease with respect to the baseline) per hour. A score < 1 is considered to be normal, between 1-5 is defined as mild OSA, between 6 and 25 as moderate OSA, and > 25 as severe OSA[62, 63, 74, 75].

Treatment of obstructive sleep apnea

According to its severity and cause or level of obstruction, OSA can be treated pharmacologically (e.g. with nasal corticosteroid spray or antibiotics), surgically (e.g. with adenotonsillectomy (ATE) or midface advancement), or non-surgically (e.g. with nocturnal oxygen or continuous or bi-level positive airway pressure (CPAP or BiPAP))[67, 69, 76].

Because of the associated midface hypoplasia in children with Apert, Crouzon or Pfeiffer syndrome, midface advancement appears to be the treatment of choice for OSA in syndromic craniosynostosis[77]. But on long-term mixed respiratory results of midface advancement in patients with syndromic craniosynostosis are reported[78]. It is unclear how long and to which level the improvement in breathing lasts, and which factors are predictors of respiratory outcome. It is known that growth of the maxilla in anterior direction is very limited in Apert, Crouzon and Pfeiffer syndrome, so if surgical advancement of the maxilla is performed at an early age further advancement at adult age will be needed[79, 80].

Consequences of untreated obstructive sleep apnea

If OSA is not treated sufficiently, disturbed sleep patterns may result in major physical and functional impairment, for instance failure to thrive, recurrent infections, feeding difficulties, disturbed cognitive functions, delayed development, cor pulmonale or sudden

death[81]. Because of the major consequences of untreated OSA early recognition is mandatory[70]. Specific attention for upper airway obstruction during follow-up is needed.

QUALITY OF LIFE AND BEHAVIOR

Quality of life

Quality of life is a method to describe the impact on daily functioning of a disorder. International standardised quality of life questionnaires are available and there are two different types of quality of life, the general health-related quality of life (Infant Toddler Quality of Life questionnaire (ITQoL) or Child Health Questionnaire (CHQ)) and the disease-specific (OSA-18)[82-85]. With the health-related quality of life questionnaires several domains are examined and a general reproduction of the impact of the sickness of the child is given on the physical and psychosocial aspects of the health of the child, parent and family. With the disease-specific questionnaire special domains associated with a disease are evaluated to show the impact of this specific disease.

In different fields the health-related quality of life is assessed, such as in children with cancer, meningococcal septic shock and cleft lip and palate[86-88]. For obstructive sleep apnea the OSA-18 survey is developed to use in healthy children with a history of snoring and disrupted sleep for three months or longer due to adenotonsillar hypertrophy. A significant correlation between the mean OSA-18 score and the severity of OSA is found[82].

Warschausky et al.[89] reported health-related quality of life in children with craniofacial anomalies. They compared 27 children with primary cleft lip and/ or palate with 28 children with other craniofacial diagnoses, including only 5 children with Apert, Crouzon or complex craniosynostosis. They found significant perceived general health concerns in the second group, but no specific physical or mental health concerns.

Health-related and disease-specific quality of life in a selected group of children with syndromic or complex craniosynostosis is not studied before.

Behavior

Behavior, attention and concentration are important aspects in the development of children. These aspects are possibly impaired in children with craniosynostosis that is associated with developmental delay and lower intelligence in some syndromes. Problems can be assessed with the Child Behavior Checklist (CBCL), a widely used norm-referenced measure[90, 91].

Boltshauser et al.[92] evaluated behavior and quality of life in 30 patients with isolated sagittal craniosynostosis. Parents reported the behavior of their children in the normal range and the health-related quality of life was comparable with the norms, except lower scores on positive emotional functioning.

The amount of behavioral and emotional problems in children with syndromic or complex craniosynostosis is unknown.

HYPOTHESIS AND OBJECTIVES

The aim of this thesis is to assess the importance and impact of obstructive sleep apnea in children with syndromic or complex craniosynostosis. The topics of interest are the prevalence, diagnostics and treatment outcome of obstructive sleep apnea and the influence on prevalence of papilledema, health-related quality of life and general behavior.

Hypothesis

Obstructive sleep apnea is an important feature in children with syndromic and complex craniosynostosis, which requires regular screening and affects daily functioning.

Objectives

The risk for developing obstructive sleep apnea in children with syndromic craniosynostosis is known for a few years, but the prevalence and consequences in these children are unknown. Diagnostic methods and treatment modalities need to be evaluated. The objectives of this thesis are:

1. To determine the prevalence, evaluate screening tools, diagnostic methods and determinants of obstructive sleep apnea in children with syndromic and complex craniosynostosis
2. To assess the respiratory outcome of midface advancement for treatment of obstructive sleep apnea and to determine the factors contributing to its efficacy
3. To describe the prevalence of functional problems in children with syndromic craniosynostosis
4. To assess the health-related and disease-specific quality of life and behavioral problems in these children.

REFERENCES

1. Merrill AE, Bochukova EG, Brugger SM, et al. Cell mixing at a neural crest-mesoderm boundary and deficient ephrin-Eph signaling in the pathogenesis of craniosynostosis. Human molecular genetics 2006;15:1319-1328.
2. Tunnessen WW, Jr. Persistent open anterior fontanelle. Jama 1990;264:2450.
3. Mathijssen IM, van Splunder J, Vermeij-Keers C, et al. Tracing craniosynostosis to its developmental stage through bone center displacement. Journal of craniofacial genetics and developmental biology 1999;19:57-63.
4. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet 2006;14:289-298.
5. Bochukova EG, Roscioli T, Hedges DJ, et al. Rare mutations of FGFR2 causing apert syndrome: identification of the first partial gene deletion, and an Alu element insertion from a new subfamily. Human mutation 2009;30:204-211.
6. Wilkie AO, Slaney SF, Oldridge M, et al. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nat Genet 1995;9:165-172.
7. Renier D, Arnaud E, Cinalli G, et al. Prognosis for mental function in Apert's syndrome. J Neurosurg 1996;85:66-72.
8. Yacubian-Fernandes A, Palhares A, Giglio A, et al. Apert syndrome: factors involved in the cognitive development. Arquivos de neuro-psiquiatria 2005;63:963-968.
9. Da Costa AC, Walters I, Savarirayan R, et al. Intellectual outcomes in children and adolescents with syndromic and nonsyndromic craniosynostosis. Plastic and reconstructive surgery 2006;118:175-181; discussion 182-173.
10. Reardon W, Winter RM, Rutland P, et al. Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. Nat Genet 1994;8:98-103.
11. Meyers GA, Orlow SJ, Munro IR, et al. Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 1995;11:462-464.
12. Yacubian-Fernandes A, Ducati LG, Silva MV, et al. [Crouzon syndrome: factors related to the neuropsychological development and to the quality of life]. Arquivos de neuro-psiquiatria 2007;65:467-471.
13. Cornejo-Roldan LR, Roessler E, Muenke M. Analysis of the mutational spectrum of the FGFR2 gene in Pfeiffer syndrome. Human genetics 1999;104:425-431.
14. Muenke M, Schell U, Hehr A, et al. A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome. Nat Genet 1994;8:269-274.
15. Rutland P, Pulleyn LJ, Reardon W, et al. Identical mutations in the FGFR2 gene cause both Pfeiffer and Crouzon syndrome phenotypes. Nat Genet 1995;9:173-176.
16. Muenke M, Gripp KW, McDonald-McGinn DM, et al. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. American journal of human genetics 1997;60:555-564.
17. Moloney DM, Wall SA, Ashworth GJ, et al. Prevalence of Pro250Arg mutation of fibroblast growth factor receptor 3 in coronal craniosynostosis. Lancet 1997;349:1059-1062.
18. Kress W, Schropp C, Lieb G, et al. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet 2006;14:39-48.
19. Doherty ES, Lacbawan F, Hadley DW, et al. Muenke syndrome (FGFR3-related craniosynostosis): expansion of the phenotype and review of the literature. American journal of medical genetics 2007;143A:3204-3215.

20. Arnaud E, Meneses P, Lajeunie E, et al. Postoperative mental and morphological outcome for nonsyndromic brachycephaly. Plastic and reconstructive surgery 2002;110:6-12; discussion 13.
21. Kimonis V, Gold JA, Hoffman TL, et al. Genetics of craniosynostosis. Seminars in pediatric neurology 2007;14:150-161.
22. Pantke OA, Cohen MM, Jr., Witkop CJ, Jr., et al. The Saethre-Chotzen syndrome. Birth defects original article series 1975;11:190-225.
23. de Heer IM, de Klein A, van den Ouweland AM, et al. Clinical and genetic analysis of patients with Saethre-Chotzen syndrome. Plastic and reconstructive surgery 2005;115:1894-1902; discussion 1903-1895.
24. Morriss-Kay GM, Wilkie AO. Growth of the normal skull vault and its alteration in craniosynostosis: insights from human genetics and experimental studies. J Anat 2005;207:637-653.
25. Lajeunie E, Catala M, Renier D. Craniosynostosis: from a clinical description to an understanding of bone formation of the skull. Childs Nerv Syst 1999;15:676-680.
26. Britto JA. Advances in the molecular pathogenesis of craniofacial conditions. Oral and maxillofacial surgery clinics of North America 2004;16:567-586.
27. Passos-Bueno MR, Serti Eacute AE, Jehee FS, et al. Genetics of craniosynostosis: genes, syndromes, mutations and genotype-phenotype correlations. Frontiers of oral biology 2008;12:107-143.
28. Allen CH, Ward JD. An evidence-based approach to management of increased intracranial pressure. Critical care clinics 1998;14:485-495.
29. Wiegand C, Richards P. Measurement of intracranial pressure in children: a critical review of current methods. Developmental medicine and child neurology 2007;49:935-941.
30. Hayward R. Venous hypertension and craniosynostosis. Childs Nerv Syst 2005;21:880-888.
31. Sgouros S, Goldin JH, Hockley AD, et al. Intracranial volume change in childhood. J Neurosurg 1999;91:610-616.
32. Sgouros S, Hockley AD, Goldin JH, et al. Intracranial volume change in craniosynostosis. J Neurosurg 1999;91:617-625.
33. Anderson PJ, Netherway DJ, Abbott AH, et al. Analysis of intracranial volume in apert syndrome genotypes. Pediatric neurosurgery 2004;40:161-164.
34. Gault DT, Renier D, Marchac D, et al. Intracranial volume in children with craniosynostosis. J Craniofac Surg 1990;1:1-3.
35. Gosain AK, McCarthy JG, Glatt P, et al. A study of intracranial volume in Apert syndrome. Plastic and reconstructive surgery 1995;95:284-295.
36. Posnick JC, Armstrong D, Bite U. Crouzon and Apert syndromes: intracranial volume measurements before and after cranio-orbital reshaping in childhood. Plastic and reconstructive surgery 1995;96:539-548.
37. Gault DT, Renier D, Marchac D, et al. Intracranial pressure and intracranial volume in children with craniosynostosis. Plastic and reconstructive surgery 1992;90:377-381.
38. Fok H, Jones BM, Gault DG, et al. Relationship between intracranial pressure and intracranial volume in craniosynostosis. British journal of plastic surgery 1992;45:394-397.
39. Collmann H, Sorensen N, Krauss J. Hydrocephalus in craniosynostosis: a review. Childs Nerv Syst 2005;21:902-912.
40. Reid S, Ferretti P. Differential expression of fibroblast growth factor receptors in the developing murine choroid plexus. Brain research 2003;141:15-24.
41. Cinalli G, Spennato P, Sainte-Rose C, et al. Chiari malformation in craniosynostosis. Childs Nerv Syst 2005;21:889-901.
42. Hayward R, Gonsalez S. How low can you go? Intracranial pressure, cerebral perfusion pressure, and respiratory obstruction in children with complex craniosynostosis. J Neurosurg 2005;102:16-22.

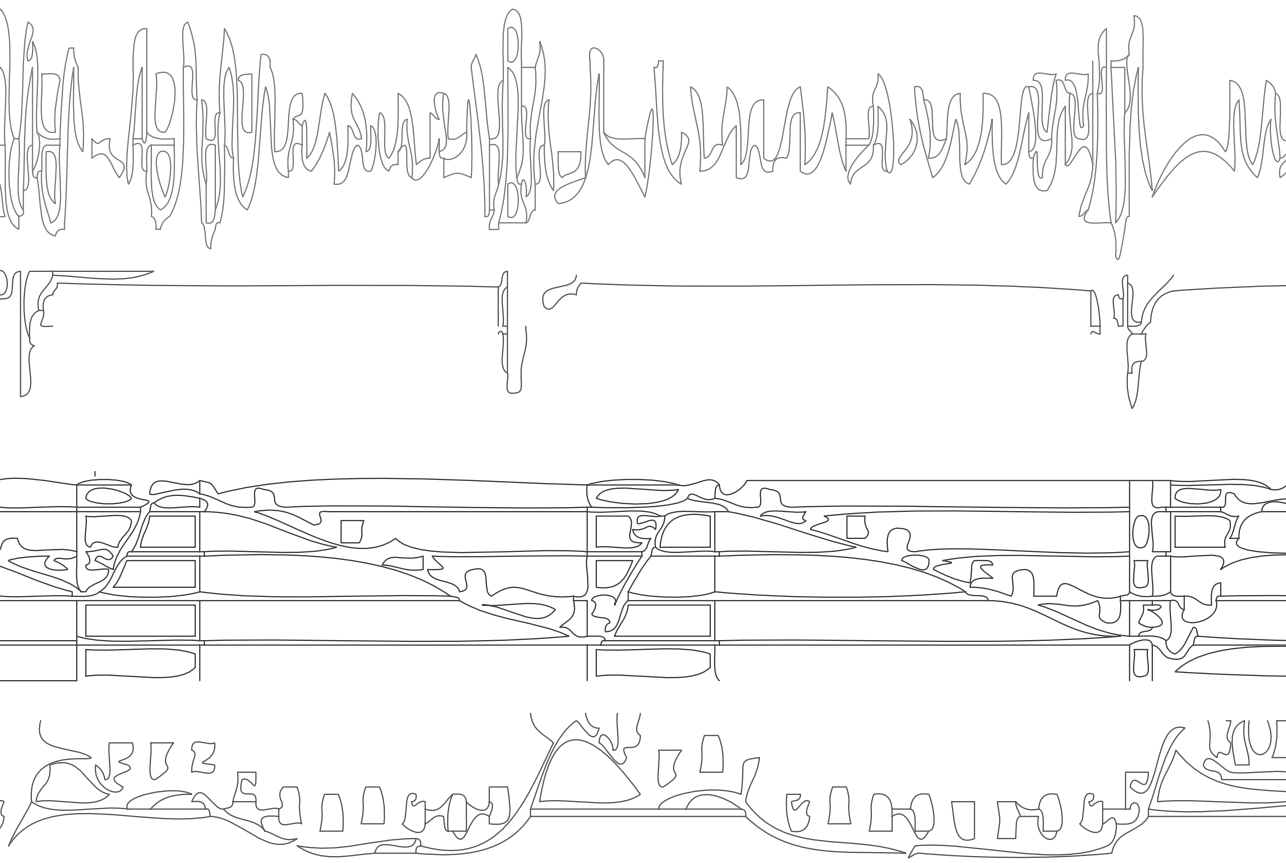
43. Taylor WJ, Hayward RD, Lasjaunias P, et al. Enigma of raised intracranial pressure in patients with complex craniosynostosis: the role of abnormal intracranial venous drainage. J Neurosurg 2001;94:377-385.
44. Rich PM, Cox TC, Hayward RD. The jugular foramen in complex and syndromic craniosynostosis and its relationship to raised intracranial pressure. AJNR Am J Neuroradiol 2003;24:45-51.
45. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 2004;15:670-674.
46. Arnaud E, Renier D, Marchac D. Prognosis for mental function in scaphocephaly. J Neurosurg 1995;83:476-479.
47. Mathijssen I, Arnaud E, Lajeunie E, et al. Postoperative cognitive outcome for synostotic frontal plagiocephaly. J Neurosurg 2006;105:16-20.
48. Renier D, Lajeunie E, Arnaud E, et al. Management of craniosynostoses. Childs Nerv Syst 2000;16:645-658.
49. Renier D, Sainte-Rose C, Marchac D, et al. Intracranial pressure in craniostenosis. J Neurosurg 1982;57:370-377.
50. Marucci DD, Dunaway DJ, Jones BM, et al. Raised intracranial pressure in Apert syndrome. Plastic and reconstructive surgery 2008;122:1162-1168; discussion 1169-1170.
51. Thompson DN, Harkness W, Jones B, et al. Subdural intracranial pressure monitoring in craniosynostosis: its role in surgical management. Childs Nerv Syst 1995;11:269-275.
52. Thompson DN, Malcolm GP, Jones BM, et al. Intracranial pressure in single-suture craniosynostosis. Pediatric neurosurgery 1995;22:235-240.
53. Woods RH, Ul-Haq E, Wilkie AO, et al. Reoperation for intracranial hypertension in TWIST1-confirmed Saethre-Chotzen syndrome: a 15-year review. Plastic and reconstructive surgery 2009;123:1801-1810.
54. Tamburrini G, Caldarelli M, Massimi L, et al. Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Childs Nerv Syst 2005;21:913-921.
55. Tuite GF, Evanson J, Chong WK, et al. The beaten copper cranium: a correlation between intracranial pressure, cranial radiographs, and computed tomographic scans in children with craniosynostosis. Neurosurgery 1996;39:691-699.
56. Tuite GF, Chong WK, Evanson J, et al. The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. Neurosurgery 1996;38:272-278.
57. Fried M, Meyer-Schwickerath G, Koch A. Excessive hypermetropia: review and case report documented by echography. Annals of ophthalmology 1982;14:15-19.
58. Karam EZ, Hedges TR. Optical coherence tomography of the retinal nerve fibre layer in mild papilloedema and pseudopapilloedema. The British journal of ophthalmology 2005;89:294-298.
59. Desch LW. Longitudinal stability of visual evoked potentials in children and adolescents with hydrocephalus. Developmental medicine and child neurology 2001;43:113-117.
60. Bartels MC, Vaandrager JM, de Jong TH, et al. Visual loss in syndromic craniosynostosis with papilledema but without other symptoms of intracranial hypertension. J Craniofac Surg 2004;15:1019-1022; discussion 1023-1014.
61. Stavrou P, Sgouros S, Willshaw HE, et al. Visual failure caused by raised intracranial pressure in craniosynostosis. Childs Nerv Syst 1997;13:64-67.
62. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
63. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Arch Pediatr Adolesc Med 2005;159:775-785.

64. Arens R, Sin S, McDonough JM, et al. Changes in upper airway size during tidal breathing in children with obstructive sleep apnea syndrome. American journal of respiratory and critical care medicine 2005;171:1298-1304.
65. Gonsalez S, Hayward R, Jones B, et al. Upper airway obstruction and raised intracranial pressure in children with craniosynostosis. Eur Respir J 1997;10:367-375.
66. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. Progress in cardiovascular diseases 2009;51:285-293.
67. Hoeve HL, Joosten KF, van den Berg S. Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol 1999;49 Suppl 1:S59-61.
68. Lo LJ, Chen YR. Airway obstruction in severe syndromic craniosynostosis. Ann Plast Surg 1999;43:258-264.
69. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;109:704-712.
70. Hoeve LJ, Pijpers M, Joosten KF. OSAS in craniofacial syndromes: an unsolved problem. Int J Pediatr Otorhinolaryngol 2003;67 Suppl 1:S111-113.
71. Schafer ME. Upper airway obstruction and sleep disorders in children with craniofacial anomalies. Clinics in plastic surgery 1982;9:555-567.
72. Lauritzen C, Lilja J, Jarlstedt J. Airway obstruction and sleep apnea in children with craniofacial anomalies. Plastic and reconstructive surgery 1986;77:1-6.
73. Brouilette R, Hanson D, David R, et al. A diagnostic approach to suspected obstructive sleep apnea in children. J Pediatr 1984;105:10-14.
74. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
75. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
76. Goldstein NA, Fatima M, Campbell TF, et al. Child behavior and quality of life before and after tonsillectomy and adenoidectomy. Arch Otolaryngol Head Neck Surg 2002;128:770-775.
77. Nout E, Cesteleyn LL, van der Wal KG, et al. Advancement of the midface, from conventional Le Fort III osteotomy to Le Fort III distraction: review of the literature. Int J Oral Maxillofac Surg 2008
78. Nelson TE, Mulliken JB, Padwa BL. Effect of midfacial distraction on the obstructed airway in patients with syndromic bilateral coronal synostosis. J Oral Maxillofac Surg 2008;66:2318-2321.
79. Bachmayer DI, Ross RB, Munro IR. Maxillary growth following LeFort III advancement surgery in Crouzon, Apert, and Pfeiffer syndromes. Am J Orthod Dentofacial Orthop 1986;90:420-430.
80. Meazzini MC, Mazzoleni F, Caronni E, et al. Le Fort III advancement osteotomy in the growing child affected by Crouzon's and Apert's syndromes: presurgical and postsurgical growth. J Craniofac Surg 2005;16:369-377.
81. Nixon GM, Brouillette RT. Sleep. 8: paediatric obstructive sleep apnoea. Thorax 2005;60:511-516.
82. Franco RA, Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg 2000;123:9-16.
83. Raat H, Bonsel GJ, Essink-Bot ML, et al. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. Journal of clinical epidemiology 2002;55:67-76.
84. Raat H, Landgraf JM, Bonsel GJ, et al. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002;11:575-581.

85. Raat H, Landgraf JM, Oostenbrink R, et al. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res 2007;16:445-460.
86. Waters EB, Wake MA, Hesketh KD, et al. Health-related quality of life of children with acute lymphoblastic leukaemia: comparisons and correlations between parent and clinician reports. International journal of cancer 2003;103:514-518.
87. Buysse CM, Raat H, Hazelzet JA, et al. Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents. Qual Life Res 2007;16:1567-1576.
88. Damiano PC, Tyler MC, Romitti PA, et al. Health-related quality of life among preadolescent children with oral clefts: the mother's perspective. Pediatrics 2007;120:e283-290.
89. Warschausky S, Kay JB, Buchman S, et al. Health-related quality of life in children with craniofacial anomalies. Plastic and reconstructive surgery 2002;110:409-414; discussion 415-406.
90. Rescorla LA. Assessment of young children using the Achenbach System of Empirically Based Assessment (ASEBA). Mental retardation and developmental disabilities research reviews 2005;11:226-237.
91. Ivanova MY, Dobrean A, Dopfner M, et al. Testing the 8-syndrome structure of the child behavior checklist in 30 societies. J Clin Child Adolesc Psychol 2007;36:405-417.
92. Boltshauser E, Ludwig S, Dietrich F, et al. Sagittal craniosynostosis: cognitive development, behavior, and quality of life in unoperated children. Neuropediatrics 2003;34:293-300.

Part II

Screening tools, diagnostic methods and treatment of obstructive sleep apnea







Chapter 2

Can parents predict obstructive sleep apnea in children with syndromic or complex craniosynostosis?

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ABSTRACT

Objective

Obstructive sleep apnea (OSA) is a clinical syndrome characterized by snoring, apneas and difficulty in breathing. These symptoms can be rated and a risk score (Brouillette score) can be calculated to estimate the likelihood of OSA. This study aimed at establishing the predictive value of the Brouillette score and observation by parents at home in children with syndromic or complex craniosynostosis, compared with ambulatory polysomnography.

Methods

This prospective study included 78 patients (37 boys, mean age 7.3 years). Sensitivity and negative predictive values were calculated.

Results

Polysomnography showed clinically significant OSA in 11 children. The Brouillette score had a negative predictive value of 90% and a sensitivity of 55% in comparison with polysomnography. More than three quarters of all patients snored. The single question 'Is there difficulty with breathing during sleep?' showed a sensitivity of 64% and a high negative predictive value of 91%.

Conclusion

Thus, asking parents whether the child has difficulty in breathing during sleep can exclude the presence of clinical significant OSA and avoid polysomnography in children with syndromic and complex craniosynostosis.

INTRODUCTION

Obstructive sleep apnea (OSA) is a clinical syndrome characterized by difficulty in breathing, snoring and apneas during sleep resulting in sleep fragmentation, hypoxia and hypercapnia. Other features of OSA are restless sleep, mouth breathing and sweating. The 'gold standard' for diagnosing the presence and severity of OSA is polysomnography (PSG), but a feasible alternative is a questionnaire about the presence of symptoms. After discriminant analysis Brouillette et al. developed an OSA score, known as Brouillette score, to predict the presence of OSA with a high sensitivity[1]. This score is calculated from a respondent's rating on three items (figure 1). Some studies showed that the Brouillette score could not reliably distinguish between the presence of OSA and simple snoring[2-5] and that its sensitivity and specificity were not sufficient for affirming OSA[6].

Children with syndromic or complex craniosynostosis have a 40% risk of developing OSA due to midface hypoplasia and collapse of the pharynx. They must be screened for OSA from birth on. This is usually done by PSG, as the value of the Brouillette score

Questionnaire/ observation

D. Difficulty in breathing during sleep?

0 = never; 1 = occasionally; 2 = frequently; and 3 = always

A. Stops breathing during sleep?

0 = no; 1 = yes

S. Snoring?

0 = never; 1 = occasionally; 2 = frequently; and 3 = always

Brouillette score = 1.42 D + 1.41 A+ 0.71 S – 3.83

> 3.5:	diagnostic for OSA
between -1 and 3.5:	suggestive for OSA
< -1:	absence of OSA

Figure 1: Items of the questionnaire and observation for calculating the Brouillette score

as a screening tool in these children has not been established. An earlier study by the authors found a discrepancy between the high prevalence of OSA as established by the questionnaire and analysis of the medical records[7]. The present study aimed to determine the reliability of the Brouillette score and parents' observation at home compared with ambulatory PSG to predict clinically significant OSA in children with syndromic or complex craniosynostosis.

METHODS

Study design

A prospective cohort study was carried out at the authors' hospital. All patients between 0 and 18 years with syndromic or complex craniosynostosis registered at the Dutch Craniofacial Center were invited to participate in the study between January 2007 and March 2008. Syndromic craniosynostosis included Apert, Crouzon, Muenke, Pfeiffer and Saethre-Chotzen syndromes. Complex craniosynostosis was defined as fusion of two cranial sutures or more without known fibroblast growth factor receptor (FGFR) or TWIST gene mutation. 98 of the eligible 111 patients (88%) were included after informed consent.

This study at home had three components. The parents rated the three items of the Brouillette score (breathing difficulty, apnea and snoring) with regard to the sleep breathing pattern of their child over the previous 3 months. The parents observed their child at home during sleep for one period of 30 minutes and rated the items of the Brouillette score every 5 minutes and recorded any mouth breathing. The children underwent a cardiorespiratory polysomnography at home for one night.

The data were incomplete for 20 patients. Questionnaires on two patients and observation forms on 15 were not completed for various logistic reasons. During PSG the total sleep time was below 360 minutes for three patients, which was too short for analysis. The data from 78 patients were analyzed: 37 boys and 41 girls with a mean age of 7.3 ± 5.4 years (SD) at the time of PSG.

From the questionnaire and the observation form a Brouillette score (Br score 1) and observation score (Br score 2) were calculated using the equation 1.42 D + 1.41 A+ 0.71 S – 3.83 (figure 1)[1]. OSA is likely if the score is above –1 and is thought to be absent if the score is below –1. Mouth breathing was considered as continuous if parents observed mouth breathing during the whole observation.

Ambulatory PSG was carried out with Embletta Portable Diagnostic System and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland). Thoracic and abdominal movements, nasal flow, saturation, and pulse were monitored. A minimum of 360 minutes total sleep time was required. Obstructive apnea was defined as absence of airflow (measured by a nasal cannula) or as out-of-phase movement of thorax

and abdomen (scored as X flow). Hypopnea was defined as ≥ 50% reduction in nasal flow signal amplitude or X flow signal amplitude, both for more than two breaths[6, 8, 9]. The X flow signal was the sum of the amplitudes of the thoracic and abdominal movements[8, 9] and was used when nasal airflow was insufficient. Mixed apnea was defined as a type of obstructive apnea with a central component that mostly preceded the obstructive pattern, for more than two breaths. Central apneas were not included in this study. Desaturation was defined as ≥ 4% decrease with respect to the baseline value. The severity of OSA was expressed in an obstructive apnea hypopnea index (OAHI), which consisted of: the hourly number of obstructive and mixed apneas; and the hourly number of hypopneas followed by desaturation.

A score of ≤ 5 is considered to be of no clinical significance with no necessity to treat, between 6 and 25 as moderate OSA, and > 25 as severe OSA[10, 11].

For statistical analysis, contingency tables were made and the sensitivity (sens) and negative predictive value (NPV) with accessory 95% confidence intervals (CI) were calculated. The sensitivity of the questionnaire and observation (the number of Br scores ≥ -1 that correctly identified OSA) was tested in comparison with the results of the PSG. The negative predictive value (the number of Br scores < -1 that correctly diagnosed the absence of OSA) of the two scores was calculated.

RESULTS

For 52 of the 78 patients (67%) the Brouillette score (Br score 1) was < -1. For 57 of the 78 patients (73%) the observation score (Br score 2) was < -1. Continuous mouth breathing was observed in 23 patients. The X flow was used in 15 of them, for whom the nasal flow registration was insufficient. Eleven PSG's were clinically significant and scored as OSA, based on OAHI.

The predictive results for the presence of clinical significant OSA are shown in table 1. The questionnaire had a high negative predictive value of 90% and a sensitivity of 55% when related to PSG. Combining the questionnaire with the parents' observation gives a slight improvement of predicting OSA (sensitivity 64% and negative predictive value

Table 1: Questionnaire and observation as tools for predicting clinically significant OSA (OAHI >5)

	Questionnaire				Observation
	Br score 1 < -1	Difficulty in breathing +	Apnea +	Snoring +	Br score 2 < -1
Sens (%)	6/ 11 (55%)	7/ 11 (64%)	3/ 11 (27%)	10/ 11 (91%)	4/ 11 (36%)
95% CI	[0.23-0.83]	[0.31-0.89]	[0.06-0.61]	[0.59-1.00]	[0.11-0.69]
NPV (%)	47/ 52 (90%)	40/ 44 (91%)	54/ 62 (87%)	17/ 18 (94%)	50/ 57 (88%)
95% CI	[0.79-0.97]	[0.78-0.97]	[0.76-0.94]	[0.73-1.00]	[0.76-0.95]

91%). In 89% of the observations the findings of the parents for the observed 30 minutes corresponded with those for the matching PSG period.

For the questionnaire the sensitivity and negative predictive value for prediction of OSA were calculated per item of the Brouillette score (table 1). Only asking about difficulty in breathing during sleep (with the answer 'yes' or 'no') resulted in a sensitivity of 64% and a high negative predictive value of 91%. Snoring is very sensitive (91%), but not specific due to its high prevalence (77% 60/ 78).

DISCUSSION

Children with syndromic or complex craniosynostosis can be screened for the presence or absence of clinically significant OSA using a questionnaire administered at the outpatient clinic. The sensitivity of this questionnaire is relatively low, whereas its negative predictive value is high. This means that in the absence of positive answers on questions related to the child's breathing pattern, clinically significant OSA is highly unlikely. If the single question 'Has the child difficulty in breathing during sleep?' was answered negatively, the presence of OSA could also be excluded. Similar observation by parents at home for 30 minutes did not give a higher predictive value for OSA compared with the questionnaire.

The sensitivity of the questionnaire according to the Brouillette score for OSA was relatively low at 55%. In two earlier studies on normal healthy children sensitivities of 89% and 80% were reported[11, 12]. The Brouillette score was developed as a screening tool for normal, healthy children with OSA, related to adenotonsillar hypertrophy and not to craniofacial abnormalities[1]. A specific finding in children with syndromic and complex craniosynostosis is that nearly all snore (in this study 77%) due to a narrow nose and mid-face hypoplasia. In this specific population the question about snoring did not have any additional value. On the contrary, if there was no difficulty in breathing during sleep as reported by the parents, OSA can almost be excluded and additional PSG is not necessary.

In this study, the parents' observation during 30 minutes at home proved not to be a more sensitive test for OSA than the questionnaire. In a similar study, in children up to the age of 14 years and referred to a pediatric chest clinic, parents' observations at home did not reliably predict the severity of OSA[8]. PSG was needed for this assessment, although higher incidences of cyanosis, obstructive apnea and extremely loud snoring were reported for these children with severe OSA[8].

The present study is the first study to compare the results of ambulatory PSG with parental observation at home and a questionnaire. Ambulatory PSG was successful in this group of children in contrast to a previous study in healthy children scheduled for adenotonsillectomy[11]. As a possible explanation, children with syndromic or complex

craniosynostosis may be more familiar with examinations due to frequent check-ups and their parents may be more motivated.

A limitation of ambulatory PSG is the lack of various signals, such as nasal flow, which are gathered during a clinical registration. In 15 patients the nasal flow signal was insufficient and obstructive apneas needed to be analyzed using the X flow. A possible reason is the continuous mouth breathing commonly observed in these children.

In conclusion, the answer 'no' to the question 'Has the child difficulty in breathing during sleep?' is helpful to exclude OSA in children with syndromic and complex craniosynostosis.

REFERENCES

1. Brouillette R, Hanson D, David R, et al. A diagnostic approach to suspected obstructive sleep apnea in children. J Pediatr 1984;105:10-14.
2. Carroll JL, McColley SA, Marcus CL, et al. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 1995;108:610-618.
3. Goldstein NA, Sculerati N, Walsleben JA, et al. Clinical diagnosis of pediatric obstructive sleep apnea validated by polysomnography. Otolaryngol Head Neck Surg 1994;111:611-617.
4. Suen JS, Arnold JE, Brooks LJ. Adenotonsillectomy for treatment of obstructive sleep apnea in children. Arch Otolaryngol Head Neck Surg 1995;121:525-530.
5. Wang RC, Elkins TP, Keech D, et al. Accuracy of clinical evaluation in pediatric obstructive sleep apnea. Otolaryngol Head Neck Surg 1998;118:69-73.
6. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Arch Pediatr Adolesc Med 2005;159:775-785.
7. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 2004;15:670-674.
8. Preutthipan A, Chantarojanasiri T, Suwanjutha S, et al. Can parents predict the severity of childhood obstructive sleep apnoea? Acta Paediatr 2000;89:708-712.
9. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
10. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
11. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
12. Brouillette RT, Morielli A, Leimanis A, et al. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000;105:405-412.





Chapter 3

Use of ambulatory polysomnography in children with syndromic craniosynostosis

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ABSTRACT

Objective

Children with syndromic or complex craniosynostosis are at risk to develop obstructive sleep apnea due to midface hypoplasia and collapse of the pharynx. The golden standard to diagnose OSA is polysomnography. The aim of this study is to analyze the feasibility of a home cardiorespiratory monitor in children with syndromic or complex craniosynostosis and to analyze whether oximetry alone or the sum of the amplitudes of the thoracic and abdominal movements (X flow) are valuable alternative assessments to diagnose obstructive sleep apnea at home, when complete recording was not achieved.

Methods

We performed a prospective study in 129 children and analyzed 200 different ambulatory polysomnographies.

Results

In 41% of the measurements a complete analysis of the obstructive apnea hypopnea index was possible based on adequate recording of all sensors. Oximetry in comparison with polysomnography had a positive predictive value of 82% and negative predictive value of 79% for diagnosing obstructive sleep apnea. Moderate obstructive sleep apnea could be excluded with a negative oximetry. Comparing the X flow and the nasal flow signals the hypopneas were adequately recorded in 86% and the obstructive apneas in 55%, resulting in an underestimation of the severity of OSA in 10%.

Conclusion

In children with syndromic or complex craniosynostosis the home cardiorespiratory monitoring is feasible to diagnose obstructive sleep apnea. Oximetry alone can be used as a rough estimate screening and with a negative test moderate OSA can be excluded. X flow can be helpful to diagnose OSA in absence of nasal flow.

INTRODUCTION

Children with syndromic or complex craniosynostosis are at risk to develop obstructive sleep apnea (OSA) due to midface hypoplasia and collapse of the pharynx[1]. Regular screening of these patients for the presence of OSA is indicated. The golden standard to diagnose OSA is polysomnography (PSG) in a hospital setting. In 2003, Poels et al.[2] evaluated the feasibility of the home cardiorespiratory recording device during a single-night to assess OSA in children who snore, between the ages of two to seven. Only 29% of the recordings that were performed in 24 children were classified as successful. Possible explanations for this low percentage of successful studies were the limited tolerance of the patients for the sensors and the fact that caregivers had to apply the device themselves with the help of a written instruction.

In contrast to the healthy children studied by Poels et al.[2] children with syndromic or complex craniosynostosis undergo medical examinations regularly and might therefore tolerate application of the device better. With a successful use of home cardiorespiratory monitoring the number of the visits and admissions to the hospital for routine polysomnography can be reduced, which is of particular interest for these children and their families.

Home cardiorespiratory monitoring can be analyzed in the same way as polysomnography in a hospital setting, but the use of definitions for apnea and hypopnea in children is not uniform[2-5]. The aim of our study is to analyze the feasibility of a home cardiorespiratory monitor in children with craniosynostosis and to analyze whether oximetry alone or the sum of the amplitudes of the thoracic and abdominal movements (X flow) are valuable alternative assessments to diagnose OSA at home, when complete recording of all the sensor signals was not achieved.

METHODS

Patients and study design

In a prospective longitudinal study children with a craniosynostosis syndrome or complex craniosynostosis were included. Syndromic craniosynostosis included children with Apert, Crouzon, Muenke, Pfeiffer and Saethre-Chotzen syndrome. Complex craniosynostosis is defined as fusion of two cranial sutures or more without a known mutation in fibroblast growth factor receptor (FGFR) 1, 2, 3 or TWIST gene.

After informed consent the child underwent a polysomnography at home. This procedure was repeated annually. When treatment for OSA was needed the PSG was repeated three months after starting the treatment.

The institutional medical ethics committee of the Erasmus Medical Center Rotterdam approved the study protocol (MEC-2005-273).

Equipment

Polysomnography was done ambulatory with Embletta Portable Diagnostic System (Medcare Flaga, Reykjavik, Iceland). Thoracic and abdominal movements were registered by elastic trace belts. Nasal flow was measured by a nasal cannula (pressure transducer), oxygen saturation and heart rate (pulse) were recorded by a pulse oximeter. The signals from the sensors were displayed and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland).

Procedure of ambulatory polysomnography

The recording devices were transported to the children by a courier. Caregivers were instructed to apply the sensors and start the recording by connecting the adapter to the device at the usual bedtime. A manual was supplied. The next morning the recording was ended and the courier brought the device back to the hospital.

Criteria for analysis

1. Feasibility was assessed in terms of the number of adequate performed recordings (i.e. recordings during a minimal total sleep time) and the number of successful recordings (i.e., recordings with sufficient artefact-free signals of the various determinants to allow scoring of the PSG).

2. Definitions of the various determinants.

a. Nasal flow as tool for the registration of respiration was used to differentiate between an obstructive or central character of the apnea or hypopnea.

b. The minimum duration of total sleep time for overnight recordings on sleep apnea evaluation in adults and children is 360 minutes[6-8]. In this study in children with craniosynostosis a measurement was also considered adequately performed and successful if a minimal total sleep time of 360 minutes with artefact-free signals of the various determinants was available.

c. Obstructive apnea was defined as absence of airflow (measured by a nasal cannula) and hypopnea as reduction by ≥ 50% in nasal flow signal amplitude, both for more than two breaths[8-10]. Mixed apnea was defined as a type of obstructive apnea with a central component that mostly preceded the obstructive pattern, for more than two breaths. A central apnea was defined as the absence of airflow without effort of thorax and abdomen for more than two breaths and was considered pathologic if it was followed by a desaturation. A desaturation was defined as ≥ 4% decrease in saturation with respect to the baseline.

Criteria for diagnosis

The degree of OSA was expressed in an obstructive apnea hypopnea index (OAHI), the number of obstructive and mixed apneas with or without desaturation in combination with hypopneas followed by desaturation per hour. An OAHI score < 1 is considered to

be normal, between 1 and 5 is defined as mild OSA, between 6 and 25 as moderate OSA, and > 25 as severe OSA[2, 8, 9, 11]. A central apnea index (CAI) was calculated as the number of central apneas followed by desaturation per hour. An abnormal central apnea index was defined as ≥ 1. A combined obstructive apnea hypopnea index and central apnea index (OAHCAI) was calculated. The similar scores for gradation of the index were used.

Alternative assessments

1. Oximetry.

An oxygenation desaturation index (ODI) was determined, based on the number of desaturations per hour. A negative oximetry was defined as an ODI < 1.

2. X flow.

The X flow is the sum of the amplitudes of the thoracic and abdominal movements and in case of obstruction out-of-phase movement of the thoracic and abdominal movements is present. Within the group of successful recordings a comparison was made between the obstructive apneas and hypopneas determined with the nasal flow and the X flow. The correlations between nasal flow and X flow were determined with intraclass correlation with the accessory 95% confidence interval (CI)[12]. In the recordings in which nasal flow was absent the X flow was used to determine obstructive apneas and hypopneas.

Statistical analysis

For statistical analysis contingency tables were made to calculate the positive (PPV) and negative predictive value (NPV) for oximetry in comparison with polysomnography. A p-value of < 0.05 was considered to be statistically significant. All numbers are expressed as median and range.

RESULTS

Of 150 eligible children 129 (86%) participated in the study, of whom 50% were boys. Their median age at the moment of PSG was 6.2 years (range 2.5 mnths-20.3 yrs). In this group 200 different polysomnographies were performed. Overall, 81 (40.5%) recordings in 65 children were suitable for calculating an OAHI (figure 1) with all signals being present. Of the remaining 119 recordings an oxygen saturation profile was available in 83 (41.5%), the oxygen saturation recording was too short in 3 (1.5%), and the recording was not adequately performed in 33 (16.5%) because the total sleep time was too short (n = 28, 14%) or the child did not co-operate (n = 5, 2.5%).

The analysis of the 81 successful recordings demonstrated 26 recordings (32%) in 21 children with mild OSA and 8 (10%) recordings in 7 children with moderate OSA, based on OAHI (table 1).

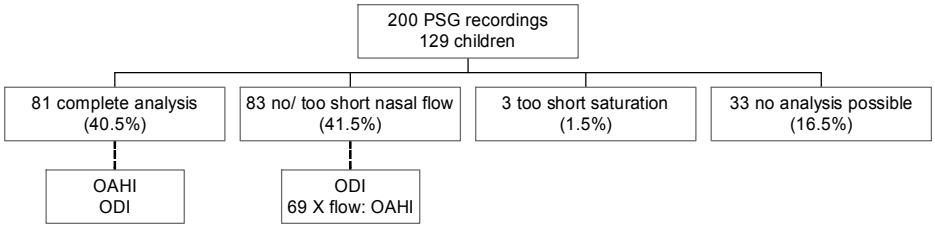

Figure 1: Analysis of 200 polysomnography recordings in 129 children

Central apneas

An abnormal central apnea index was seen in 14 recordings in 12 children. The number of pathologic central apneas varied from one to six per hour (median of two per hour). There was a significant difference (p= 0.000) in age between children diagnosed with or without an abnormal central apnea index (1.5 versus 9.0 years). A combined obstructive apnea hypopnea and central apnea index (OAHCAI) resulted in 42 (52%) recordings in 33 children in a mild index (between 1 and 5) and in 11 (14%) recordings in 9 children in a moderate index (between 6 and 25).

Oximetry

Analysis of the oxygenation desaturation index in the 81 successful recordings in 65 children showed a negative ODI in 53 recordings in 49 children (table 1). In these 53 recordings a positive OAHI despite of the negative oximetry was found in 11 measurements (negative predictive value of 79%). A negative oximetry never resulted in missing of moderate OSA;

Table 1: Overview of the results of 81 successful polysomnographies

	Polysomnographies n = 81 (65 children)
TST (min)	557 (360-900)
Mean saturation	97.5 (sd 1.1)
Nadir saturation	89.8 (sd 5.1)
Mean respiratory rate	17.2 (sd 4.3)
Mean heart rate	80.2 (sd 20.1)
OAHI < 1	47 (37 children)
OAHI 1-5	26 (21 children)
OAHI 6-25	8 (7 children)
CAI ≥ 1	14 (12 children)
OAHCAI < 1	28 (23 children)
OAHCAI 1-5	42 (33 children)
OAHCAI 6-25	11 (9 children)
ODI < 1	53 (49 children)
ODI 1-5	20 (16 children)
ODI 6-25	8 (6 children)

sd standard deviation

so the negative predictive value for moderate OSA was 100%. Of the 28 recordings with a positive ODI also a positive OAHI was found in 23 (positive predictive value 82%).

Of the 83 recordings in 65 children with only an available oximetry signal 40 recordings (48%) in 34 children showed OSA based on ODI; 30 mild OSA in 26 children, 9 moderate OSA in 7 children and 1 severe OSA.

X flow

Comparison of nasal flow with the X flow in successful recordings showed overall that 86% of the hypopneas recorded with nasal flow were also scored with the X flow, whereas 55% of the obstructive apneas recorded with nasal flow were also scored with the X flow. However, after comparison the degree of OSA in no, mild or moderate measured by nasal and X flow in these patients, in 10% the severity of OSA was underestimated.

In the 81 recordings with all signals the intraclass correlation of 0.77 between nasal flow and X flow was good (95% confidence interval [0.65-0.86]). Of the 83 recordings with only an available oximetry signal in absence of nasal flow the X flow was analyzed in 69 (34.5%) recordings in 56 children. These showed OSA in 33 recordings in 29 children; 23 mild in 20 children and 10 moderate in 9 children.

Analysis of the oxygenation desaturation index in these 69 recordings showed a negative ODI in 36 recordings in 35 children. In these 36 recordings a positive OAHI despite of the negative oximetry was found in 10 measurements (negative predictive value of 72%). A negative oximetry resulted in missing of one moderate OSA; so the negative predictive value for moderate OSA was 97%. Of the 33 recordings with a positive ODI also a positive OAHI was found in 23 (positive predictive value 70%). Using X flow as screening method raised the overall success rate from 40.5 to 75% (table 2).

Table 2: Diagnosis of obstructive sleep apnea based on OAHI measured by nasal flow or X flow and based on ODI

OSA	OAHI nasal flow n = 81 (65 children)	OAHI X flow n = 69 (56 children)	ODI n = 83 (65 children)
Mild	32% (21 children)	33% (20 children)	36% (26 children)
Moderate/ severe	10% (7 children)	14% (9 children)	12% (8 children)

DISCUSSION

In children with syndromic or complex craniosynostosis the use of home cardiorespiratory monitoring resulted in 40.5% successful recordings. This result is better than the previously mentioned study in 'healthy' children scheduled for adenotonsillectomy by Poels et al.[2] with a successful recording rate of only 29%. The higher number of successful recordings might be explained by the fact that parents of children with a serious medical condition were more motivated and maybe these children were more cooperative due to their frequent medical investigations. The first explanation seems to be confirmed by the high participation rate of 86% in this study, compared to 45% in the study of Poels et al.[2] Of the recordings 59.5% were not successful due to absence of nasal flow, technical failure or too short registration of the signals. Only 2.5% of the children did not accept the device.

The most logical reason for the absence or decreased presence of nasal flow was the shift of the nasal cannula during sleep, or the fact that children did not tolerate the nasal cannula. We expected that children below the age of one and older children who understand the aim of the recording would accept the nasal cannula better, but this was not seen in this study. In these children with syndromic or complex craniosynostosis we speculate that the main reason for the failing signal of the nasal cannula is the absence of nasal passage due to the severe anatomical malformations of the nasal cavity, leading to almost complete obstruction of the upper airway and as a consequence preferred mouth breathing[13]. This problem might be solved using a mouth thermistor to record oral flow but this application is not (yet) used at home.

In our definition of the OAHI we did not account for pathologic central apneas whereas in some previous studies this was done[2]. A combined OAHCAI showed a 20% increase of the children with an index between 1 and 5 and a 4% increase of the children with an index between 6 and 25. The high number of pathologic central apneas found in the very young children was especially related to central irregularity of breathing[14, 15]. It is however important to notice that in patients with severe OSA, which was not the case in this study, an increase of central apneas can be found due to ventilatory control instability[16, 17]. Therefore when central apneas are taking into account in the analysis of OSA the AHI can be considerably higher. Based on this study in children with syndromic or complex craniosynostosis we recommend excluding the pathologic central apneas in the AHI for defining OSA.

Concerning the definitions for the apnea hypopnea index we used the criteria stated in 2005 by the American Academy of Sleep Medicine[17]. Brouillette et al.[3] advocated using oximetry alone to show OSA in healthy children. A high positive predictive value of 97% was found if desaturations were recorded, but a negative oximetry could not rule out OSA. Children with a negative oximetry had a 47% probability of having OSA on full polysomnography in the hospital. In our study we compared within the successful recordings

oximetry with the other signals and found compared with the study of Brouillette et al.[3] a lower positive predictive value for oximetry (82%) and a higher negative predictive value (79%). However, if only moderate OSA is considered to be clinical significant a negative oximetry never resulted in missing a case of moderate OSA. Overall, we concluded that oximetry can be used as a rough estimate screening tool but with limited accuracy. In the 83 recordings in 65 children in which only an oximetry signal was present we found a negative test in 43 recordings in 31 children.

The use of X flow might be an alternative method in absence of the nasal flow. Previously Ciftci et al.[18] showed in a clinical setting in 90 symptomatic adult patients with an apnea hypopnea index > 5 that hypopneas monitored by only the effort amplitude of thoracoabdominal movements without regard for airflow amplitude had a sensitivity of 97% and a specificity of 84% to distinguish between OSA and non-OSA. They concluded that thoracoabdominal movements can be useful in situations when the nasal flow is difficult to interpret[18]. We are the first to report the use of X flow in ambulatory polysomnography in children in absence of a nasal flow measurement. Comparing the X flow and the nasal flow signals we found using the X flow that in 86% the hypopneas were recorded and in 55% the obstructive apneas. It was remarkable that hypopneas were detected better with X flow than obstructive apneas because obstructive apneas will result in a more extensive out-of-phase movement of thorax and abdomen. A possible explanation for the fact that this out-of phase movement was less well recorded could be the positioning of the trace belts during the recordings. Due to shifting of the trace belts, the same registration of movements of either the abdominal or thoracic movements could occur. On the contrary, the measurement of hypopnea is less dependent on the correct position of the trace belts and the definition itself is more flexible than the definition of an obstructive apnea. However, the underestimation of the degree of OSA is limited with 10%. In 69 recordings in 56 children using the X flow in absence of nasal flow OSA was showed in 33 recordings (48%) in 29 children. The negative (72%) and positive (70%) predictive value for oximetry were lower in comparison with nasal flow, but a negative oximetry resulted in missing of only one case of moderate OSA. If X flow was used as additional screening method the overall success rate for ambulatory polysomnography recordings would rise from 40.5 to 75%.

Overall, comparing the presence of OSA using the complete recording of all the sensor signals, oximetry or X flow, an almost similar percentage of 34% was found for mild OSA and 12% for moderate OSA in this patient group.

Several limitations are to be noticed in this study due to the use of ambulatory polysomnography in an uncontrolled environment. Parents were instructed by a written form to apply the sensors by themselves and due to inexperience not all sensors might be applied sufficiently. We tested the X flow measurements using these home recordings whereas we were not informed if the abdominal and thoracic belts were at the appropriate place. Furthermore only one of the researchers (Bannink N.) scored the signals whereas it should

be better to have two different scorers looking each at the same recording, one analyzing all signals with nasal flow and the other analyzing all signals minus nasal flow based on X flow. Even more ideal would be to apply the ambulatory polysomnography sensors in the hospital together with the sensors of regular full polysomnography to test the X flow for validity. However, despite these limitations we think that X flow can be helpful in the diagnosis of OSA in absence of nasal flow.

In conclusion, in children with syndromic or complex craniosynostosis the home cardio-respiratory monitoring is feasible to diagnose obstructive sleep apnea. Oximetry alone can be used as a rough estimate screening and with a negative test moderate OSA can be excluded. X flow can be helpful to diagnose OSA in absence of nasal flow.

REFERENCES

1. Bannink N, Nout E, Wolvius EB, et al. Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement. Int J Oral Maxillofac Surg 2010;39:115-121.
2. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
3. Brouillette RT, Morielli A, Leimanis A, et al. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000;105:405-412.
4. Guilleminault C, Li K, Khramtsov A, et al. Breathing patterns in prepubertal children with sleep-related breathing disorders. Archives of pediatrics & adolescent medicine 2004;158:153-161.
5. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146:1235-1239.
6. Ferber R, Millman R, Coppola M, et al. Portable recording in the assessment of obstructive sleep apnea. ASDA standards of practice. Sleep 1994;17:378-392.
7. Friedman M, Ibrahim H, Bass L. Clinical staging for sleep-disordered breathing. Otolaryngol Head Neck Surg 2002;127:13-21.
8. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
9. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Archives of pediatrics & adolescent medicine 2005;159:775-785.
10. Preutthipan A, Chantarojanasiri T, Suwanjutha S, et al. Can parents predict the severity of childhood obstructive sleep apnoea? Acta Paediatr 2000;89:708-712.
11. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
12. Tsai WH, Flemons WW, Whitelaw WA, et al. A comparison of apnea-hypopnea indices derived from different definitions of hypopnea. Am J Respir Crit Care Med 1999;159:43-48.
13. Lowe LH, Booth TN, Joglar JM, et al. Midface anomalies in children. Radiographics 2000;20:907-922; quiz 1106-1107, 1112.
14. Oliveira AJ, Nunes ML, Fojo-Olmos A, et al. Clinical correlates of periodic breathing in neonatal polysomnography. Clin Neurophysiol 2004;115:2247-2251.
15. Weintraub Z, Cates D, Kwiatkowski K, et al. The morphology of periodic breathing in infants and adults. Respiration physiology 2001;127:173-184.
16. White DP. Central sleep apnea. The Medical clinics of North America 1985;69:1205-1219.
17. White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med 2005;172:1363-1370.
18. Ciftci TU, Kokturk O, Ozkan S. Apnea-hypopnea indexes calculated using different hypopnea definitions and their relation to major symptoms. Sleep Breath 2004;8:141-146.





Chapter 4

Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement

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ABSTRACT

Objective

Almost 50% of patients with Apert, Crouzon or Pfeiffer syndrome develop obstructive sleep apnea (OSA), mainly due to midface hypoplasia. Midface advancement is often the treatment of choice, but the few papers on long-term outcome reported mixed results. This paper aimed to assess the long-term respiratory outcome of midface advancement in syndromic craniosynostosis with OSA and to determine factors contributing to its efficacy.

Methods

A retrospective study was performed on 11 patients with moderate or severe OSA, requiring oxygen, continuous positive airway pressure (CPAP), or tracheostomy. Clinical symptoms, results of polysomnography, endoscopy and digital volume measurement of the upper airways on CT scan before and after midface advancement were reviewed.

Results

Midface advancement had a good respiratory outcome in the short term in 6 patients and was ineffective in 5. In all patients without respiratory effect or with relapse, endoscopy showed obstruction of the rhino- or hypopharynx. The volume measurements supported the clinical and endoscopic outcome.

Conclusion

Despite midface advancement, long-term dependence on, or indication for, CPAP or tracheostomy was maintained in 5 of 11 patients. Pharyngeal collapse appeared to play a role in OSA. Endoscopy before midface advancement is recommended to identify airway obstruction that may interfere with respiratory improvement after midface advancement.

INTRODUCTION

Craniosynostosis is a congenital disorder affecting in 1 in 2.500 births; it is characterized by the premature fusion of calvarial sutures. This fusion restricts normal growth of the skull, brain, and face, and necessitates surgical correction. In about 40% of the cases it is part of a syndrome such as the Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome[1].

Almost 50% of children with Apert, Crouzon or Pfeiffer syndrome develop obstructive sleep apnea (OSA), mainly during the first 6 years of life.[2-4] These patients are at risk for OSA due to midface hypoplasia, but other factors such as adenotonsillar hypertrophy, and mandibular hypoplasia may be involved as well.[4, 5] According to its severity and cause, OSA can be treated pharmacologically, surgically (e.g. with adenotonsillectomy, midface advancement or tracheostomy), or non-surgically (e.g. with nocturnal oxygen or continuous positive airway pressure (CPAP)).[5, 6] If OSA is not treated sufficiently, disturbed sleep patterns may result in major physical and functional impairment, for instance failure to thrive, recurrent infections, disturbed cognitive functions, delayed development, cor pulmonale or sudden death.[7] As midface hypoplasia is the main cause of OSA in syndromic craniosynostosis, midface advancement appears to be the treatment of choice.[8]

In the long-term, mixed respiratory results were reported following midface advancement in patients with syndromic craniosynostosis.[9] It is unclear how long and to which level the improvement in breathing lasts, and which factors are predictors of respiratory outcome. To assess the respiratory outcome of midface advancement for moderate to severe OSA and to determine predictive factors, the authors carried out a retrospective study in patients suffering from Apert, Crouzon or Pfeiffer syndrome.

METHODS

Study group

Over 100 patients with Apert, Crouzon and Pfeiffer syndrome have been treated at the Dutch Craniofacial Center since 1983. For this study, the authors were only interested in the 14 patients with moderate or severe OSA, requiring treatment with nocturnal oxygen, CPAP, nasopharyngeal tube (NPT), or tracheostomy, who presented between 1987 and 2006. Their records were analyzed for clinical symptoms of OSA, results of polysomnography (PSG) and endoscopy of the upper airways, and the different treatment modalities for OSA. CT-scans were used to measure the airway volume before and after midface advancement. For this case series, sufficient data and follow-up were available in 11 patients.

Obstructive sleep apnea

The clinical symptoms of OSA were snoring, difficulty in breathing, apnea during sleep, perspiration, and daytime sleepiness. PSG was carried out ambulatory or during admission to hospital and the following criteria for analysis were used. Apnea was defined as absence of airflow for more than two breaths and hypopnea as reduction by ≥ 50% in nasal flow signal amplitude for more than two breaths. The analysis was expressed in an apnea hypopnea index (AHI), the number of obstructive apneas in combination with hypopneas followed by desaturation per hour, and an oxygenation desaturation index (ODI), the number of desaturations (≥ 4% decrease with respect to the baseline) per hour. A score < 1 is considered to be normal, 1-5 is defined as mild OSA, 6-25 as moderate OSA, and > 25 as severe OSA.[10-13]

Respiratory outcome of midface advancement

The timing, type and outcome of the following interventions were evaluated: oxygen, NPT, CPAP, adenotomy and tonsillectomy, tracheostomy and midface advancement. The different interventions in each patient were added to evaluate the total number of procedures carried out to improve the breathing.

The efficacy of treating OSA was determined on the basis of clinical symptoms and PSG before and after midface advancement. Midface advancement was considered to be effective on respiration, in the short term, if oxygen, CPAP, NPT or tracheostomy were discontinued within 1 year after midface advancement. Relapse of OSA was defined as the need for respiratory support again. Long-term effectiveness was defined as independence of respiratory support at least 2 years after midface advancement.

Endoscopy of the upper airway

Endoscopies were carried out under general anesthesia in a supine position. In 2 patients an additional endoscopy was done at the outpatient clinic in a sitting position. The endoscopies were carried out to identify the possible level of obstruction including anatomical malformations in the rhino- and hypopharynx.

Volume measurements of the upper airway

A software program (MevisLab) was used to import and analyze the CT scans by means of a custom-designed tool. Preoperative and postoperative scans were analyzed on transversal slices. The maxillary, ethmoidal, frontal and sphenoidal sinuses, concha bullosa and the oral cavity were manually excluded. The respiratory active air-holding cavities were segmented using semi-automatic region growing. The volumes of 2 separate anatomically defined areas were measured in mm^3, taking the scale into consideration: nasal cavity and rhinopharynx (defined to range from the most caudal point of the frontal sinus to the cranial point where the soft palate transformed into the uvula); and the oro- and hypo-

pharynx (ranged from the most cranial point where the soft palate transformed into the uvula, to the most caudal point of the hyoid bone). The total volume is being calculated by adding the volumes of the 2 areas. All patients were scanned according to a protocol, using the same CT scan, and the thickness of the transversal slices was similar.

Statistical analysis

The results were analyzed using SPSS 14.0 for Windows 2000. All numbers are expressed as median and range.

RESULTS

Eleven patients with Apert (n = 3), Crouzon (n = 6) or Pfeiffer (n = 2) syndrome who had moderate or severe OSA, requiring treatment with nocturnal oxygen, CPAP, NPT, or tracheostomy, were included. Four of the 11 patients were boys (36%), aged 14.9 years (range 4.1-23.1 years). All patients had midface hypoplasia. Six of the 11 patients underwent PSG before the start of treatment for OSA; this showed moderate OSA in 3 patients and severe OSA in 3 (median ODI 25, range 10-66). In the other patients, no PSG was performed due to the severity of the respiratory distress at presentation, which necessitated instant airway management, namely intubation or insertion of a tracheostomy. Airway treatment after diagnosis of OSA involved tracheostomy in 4 patients, oxygen in 3, CPAP or NPT in 3, and monobloc with NPT in 1. All patients underwent a midface advancement with distraction followed by a control PSG; in 3 a monobloc was performed; and in 8 a le Fort III.

In 10 of the 11 patients an endoscopy of the upper airway was performed to identify the level of obstruction; this was done preoperatively in 5, postoperatively in 1, and both in 4. In 4 patients, a CT scan, carried out before and after midface advancement, was available. After advancing the midface for at least 20 mm the occlusion was corrected from class III in class II with overcorrection in all patients (figure 1). Clinically, a sufficient advancement of the midface was achieved in all patients. Final adjustment of the level of occlusion is performed in patients aged 18 or older. So far, an additional le Fort I has been performed in 2, no patient underwent mandibular correction. The follow-up time after midface advancement was 3.5 years (range 2.4-11.4 years, mean 5.7 years).

Respiratory outcome of midface advancement

The follow-up of the 11 OSA patients at different ages is shown in figure 2. The respiratory outcome of each treatment option was considered. Adenotomy and tonsillectomy had a temporary beneficial effect on respiration in 1 of 5 patients, and no effect in 4.

In 6 of the 7 patients, oxygen and CPAP or NPT were effective in bridging time to the midface advancement. In the other patient, tracheostomy was required despite monobloc

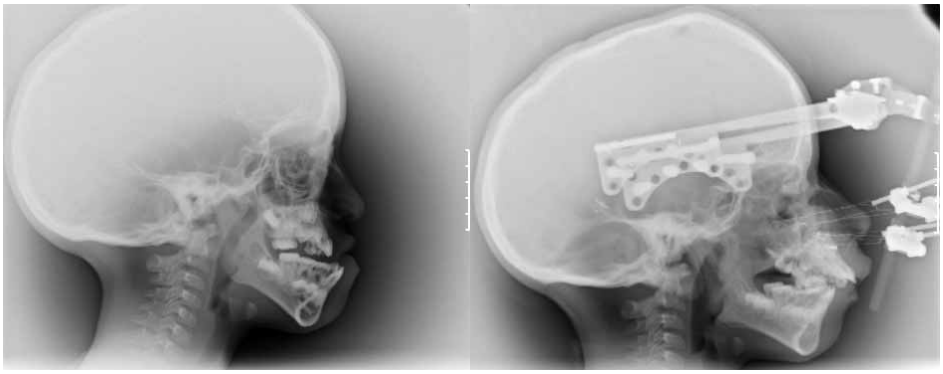


Figure 1: Sufficient correction was achieved in all patients; after advancing the midface for 20 mm the occlusion changed from class III to class II including the overcorrection

and NPT. Midface advancements were carried out in three different modes: monobloc with and without distraction, and le Fort III with distraction.

The patients with moderate or severe OSA underwent a median number of 5 (2-8) invasive or non-invasive treatment procedures to improve their breathing. Midface advancement in the short term had a good or improved respiratory outcome in 6 patients (patients 1, 2, 8, 10, 11 and patient 9, respectively), and was unsatisfactory in 5 (patients 3, 4, 5, 6, and 7) (table 1). In 2 patients (patients 1 and 11) OSA relapsed. In the long term, 4 of the 11 patients (patients 3, 4, 6 and 7) were still dependent on CPAP (2.5, 8.1 and 8.2 years after advancement) or tracheostomy (10.6 years) in spite of a surgically successful midface advancement and 1 (patient 11) had severe OSA without treatment following a parental decision.

Endoscopy and volume measurements of the upper airway

Anatomical malformations of the rhino- and hypopharynx were a common feature in nearly all patients, causing a functional obstruction at this level. Only 1 patient did not have this feature and had a good respiratory outcome after midface advancement. All patients had a narrow nasal cavity.

The volumes of the upper airway on CT scan before and after midface advancement were calculated in patients 1, 4, 6 and 8 (table 2). In figure 3 the changes in these volumes are shown. In patient 1 the CT scan 4 months post-surgery showed an increase in airway volume (1.4 times), mostly in the region nasal cavity and rhinopharynx (1.6 times). One year after midface advancement the CT scan illustrated the narrow hypopharynx seen with endoscopy, with a volume decrease in the region oro- and hypopharynx (0.7 times). The CT scans of patient 4, made 7 months before and 1 year after midface advancement, showed no increase in the total volume of the upper airway. The volume of the oro- and hypopharynx increased 1.2 times. Patient 6 showed no change in total volume of the

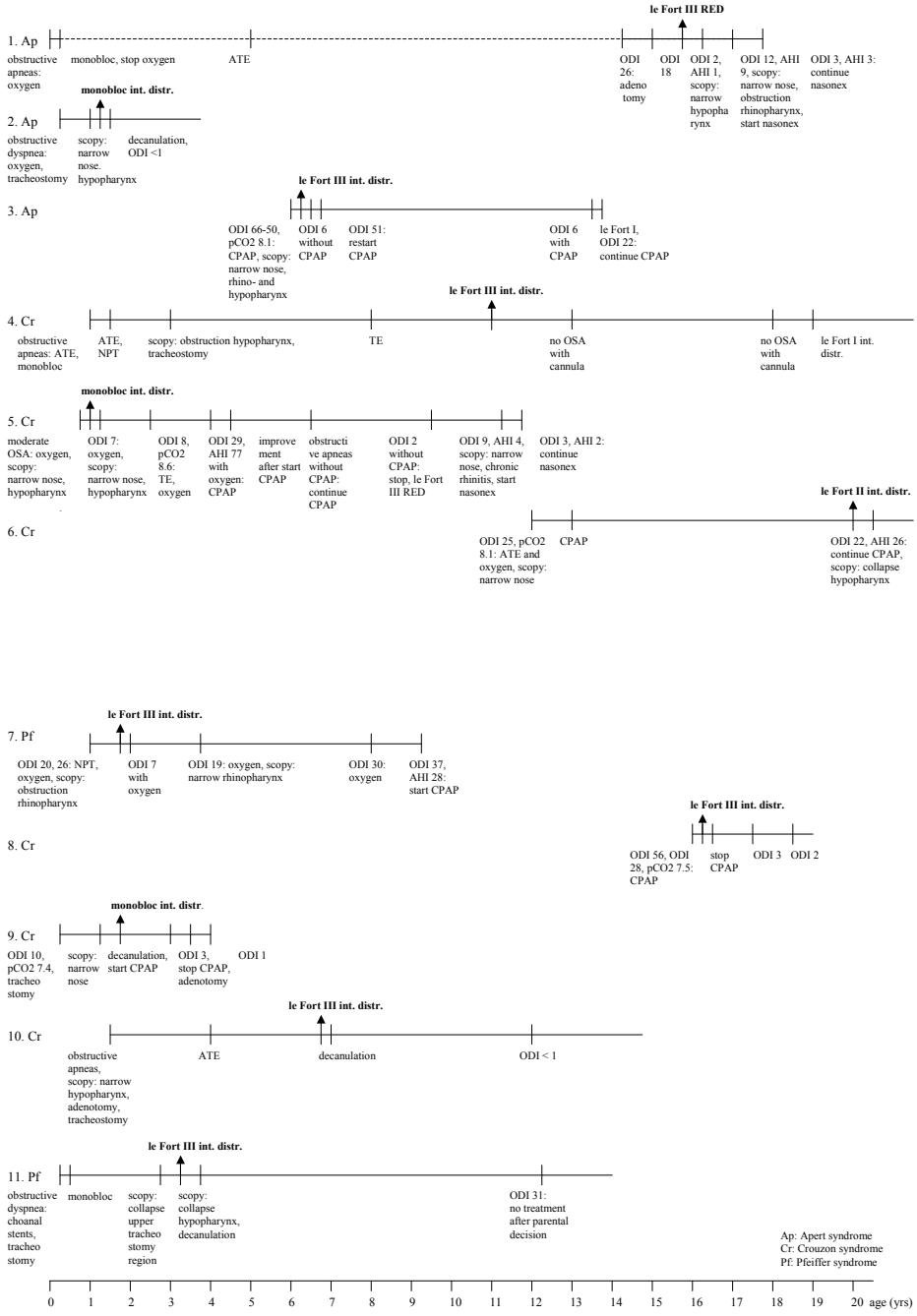


Figure 2: Follow-up of OSA in 11 patients at different ages

Table 1: Respiratory outcome of midface advancement in the short term

Treatment	Number of treatments	Effect	Insufficient effect
Monobloc without distraction	3	1	2
Monobloc with distraction	3	2	1
Le Fort III with distraction	8	4	4
Total view (N patients)	14 (11)	7 (6)	7 (5)

Table 2: Measurements of airway volume on CT scan before and 4 months and/or 1 year after midface advancement in mm^3

Patient	Nasal cavity and rhinopharynx			Oro- and hypopharynx			Total airway volume		
	Before	After 1	After 2	Before	After 1	After 2	Before	After 1	After 2
1	20.109	32.850	33.544	13.287	14.772	9.620	33.396	47.622	43.164
4	35.909	33.166		6.408	7.913		42.317	41.078	
6	19.639	20.327		9.166	6.252		28.804	26.578	
8	20.147	32.671		3.683	6.081		23.830	38.751	

upper airway 4 months after midface advancement in comparison with 1 year before, which matches the clinical presentation. After midface advancement the nasal cavity and rhinopharynx volume increased, but the oro- and hypopharynx region was 0.7 of the volume before. In patient 8, with a clinical good result, the volume of the upper airway increased by a factor of 1.6, 13 months after midface advancement in comparison with 3 months before. The volume of the nasal cavity and rhinopharynx increased 1.6 times and the volume of the oro- and hypopharynx was 1.7 times larger.

DISCUSSION

In the general population, adenotonsillectomy is the treatment of choice, as adenotonsillar hypertrophy is an important cause of OSA.[13, 14] In this study, in patients suffering from Apert, Crouzon or Pfeiffer syndrome with moderate or severe OSA, neither tonsillectomy nor adenotomy had a significant effect on respiration.

In patients with syndromic craniosynostosis, midface hypoplasia is generally considered to be the major cause of upper airway obstruction.[4] All children in this study also had midface hypoplasia. Although, midface advancement seemed to be a good treatment modality for compromised airways at the level of the midface[4, 15], in this study 6 of 11 patients (55%) had a favourable effect in the short term after monobloc or le Fort III with distraction. Witherow et al.[16] found an improvement in all patients suffering from Apert, Crouzon or

Figure 3: Volume measurements of the upper airway before and after midface advancement

Pfeiffer syndrome with abnormal PSG after monobloc with external distraction. Of the 14 patients with severe OSA, treated with tracheostomy or CPAP, OSA was resolved after surgery in 6 (43%). The other 8 patients remained dependent on tracheostomy or CPAP. The mean follow-up was 24 months.[16] Arnaud et al.[17] showed a respiratory improvement measured by oxygen level in 14 of 16 patients with Apert, Crouzon or Pfeiffer syndromes after monobloc with internal distraction. In the severe cases, removal of tracheostomy was possible in 4 of 6 (67%). In 1 patient a tracheostomy was needed 6 months after removal of distractors because of relapse of OSA. The mean follow-up after surgery was 2.5 years.[17] Nelson et al.[9] studied 18 patients with syndromic bilateral coronal synostosis and OSA, in 15 of them a tracheostomy or CPAP was required before midface advancement. After midface advancement, 5 patients were decanulated and in 6 CPAP was discontinued (73%). The mean time of follow-up was 3.2 years. In these 3 studies, midface advancement did not result in good respiratory outcome in all (similar to the present study). These studies and the present one showed that respiratory outcome after midface advancement in syndromic craniosynostosis patients who need it the most is not as successful as is generally thought. Inclusion of patients with mild OSA in other studies has given the impression that midface advancement with distraction gives a guaranteed improvement of OSA.

Endoscopy of the upper airway can show the level of obstruction and the dynamic influence of breathing. In the 4 patients with persistent OSA after advancement and in the patient with a relapse of OSA an obstruction of the rhino- or hypopharynx was seen. In Apert, Crouzon and Pfeiffer syndrome, the anatomy of the upper airway is different and there seems to be a dynamic function problem regarding the airway, possibly related to the mutation of the fibroblast growth factor receptor.[1] The nasal cavity is narrow in all patients; this is common in these syndromes. Collapse of the pharynx is a dynamic problem that may or may not improve with midface advancement. In the non-responders, the pharyngeal walls collapsed with each breath, and resulted in an airway obstruction. So the advancement did not result in a larger airway volume and could not overcome the tendency of the pharyngeal walls to collapse. The changes in airway volume on CT scan after midface advancement were similar to the results of endoscopy, and thus seem to illustrate the dynamic situation of the airway, including the level of obstruction. An improvement of airway volume on CT correlated with a good respiratory outcome. The authors consider that the degree of functional obstruction of the rhino- or hypopharynx correlates with respiratory outcome after midface advancement: a mild tendency for collapse can be overcome with the midface advancement. This hypothesis could not be substantiated in this retrospective analysis.

Measurement of airway volume on CT scan has some limitations, in particular the difficulty of manually defining the borders of the nasal cavity because of anatomical anomalies. A cold can affect the thickness of the mucosa and the size of the tonsils, and the position

and respiration state of the patient in the CT scan can influence the volume of the airway at the moment of scanning. The influence of growth in volume changes is not likely in patients with syndromic craniosynostosis since they have growth retardation of the maxilla[18] and restriction of normal transverse growth of the mandible, possibly secondary to cranial base abnormalities.[19]

Previous studies on airway changes after advancement were based on tracing of cephalograms.[20, 21] Ishii et al.[20] studying 16 patients with Apert or Crouzon syndrome found an improvement on cephalogram in the nasopharyngeal airway after le Fort III osteotomy, but no change in hypopharyngeal airway was found. In 12 'normal' adults who underwent maxillary and mandibular advancement for OSA Li et al.[21] found an increase in the airway dimension after surgery measured by cephalometric imaging. Fiberoptic nasopharyngoscopy with Müller maneuver (take a breath while the mouth is closed and the nostrils are plugged) showed a decrease in collapsibility of the upper airway, mostly the lateral pharyngeal wall. They suggested a reduction of the thickness of the muscular wall. Mandibular advancement seemed to be needed to enlarge the pharyngeal airway. In the present study group no mandibular advancement was carried out. Mandibular advancement is generally not considered in children with syndromic craniosynostosis to treat their OSA, although this may be an option in patients with disappointing results following midface advancement and remaining obstruction at the hypopharynx.

This study showed that moderate or severe OSA in children with syndromic craniosynostosis is a major problem and difficult to treat. It is not only directly correlated with midface hypoplasia. Endoscopy showed anomalies at different levels throughout the upper airway. Dynamic pharyngeal collapse can affect the respiratory outcome of midface advancement; endoscopy of the upper airway before midface advancement may predict respiratory improvement. It may be possible to treat obstructions at another level with other procedures, such as widening of the palate to enlarge the nose and mandibular advancement to create more space at the level of the hypopharynx. Long-term follow-up is important because OSA may relapse.

To implement these findings and to improve the prognostic information on respiratory outcome after midface advancement, the authors recommend performing an endoscopy of the upper airway before midface advancement to identify all levels of obstruction (also stated by Nelson et al.[9]). Treatment of OSA will then be better focussed on its cause. The volume measurements of the upper airway will be continued in further research as a tool to investigate the effect of midface advancement on airway volume and to specify the level of largest gain on respiration.

In conclusion, despite midface advancement, long-term dependence on, or indication for, CPAP or tracheostomy was maintained in 5 of 11 patients in whom Apert, Crouzon or Pfeiffer syndrome was combined with moderate or severe OSA. In the patients with

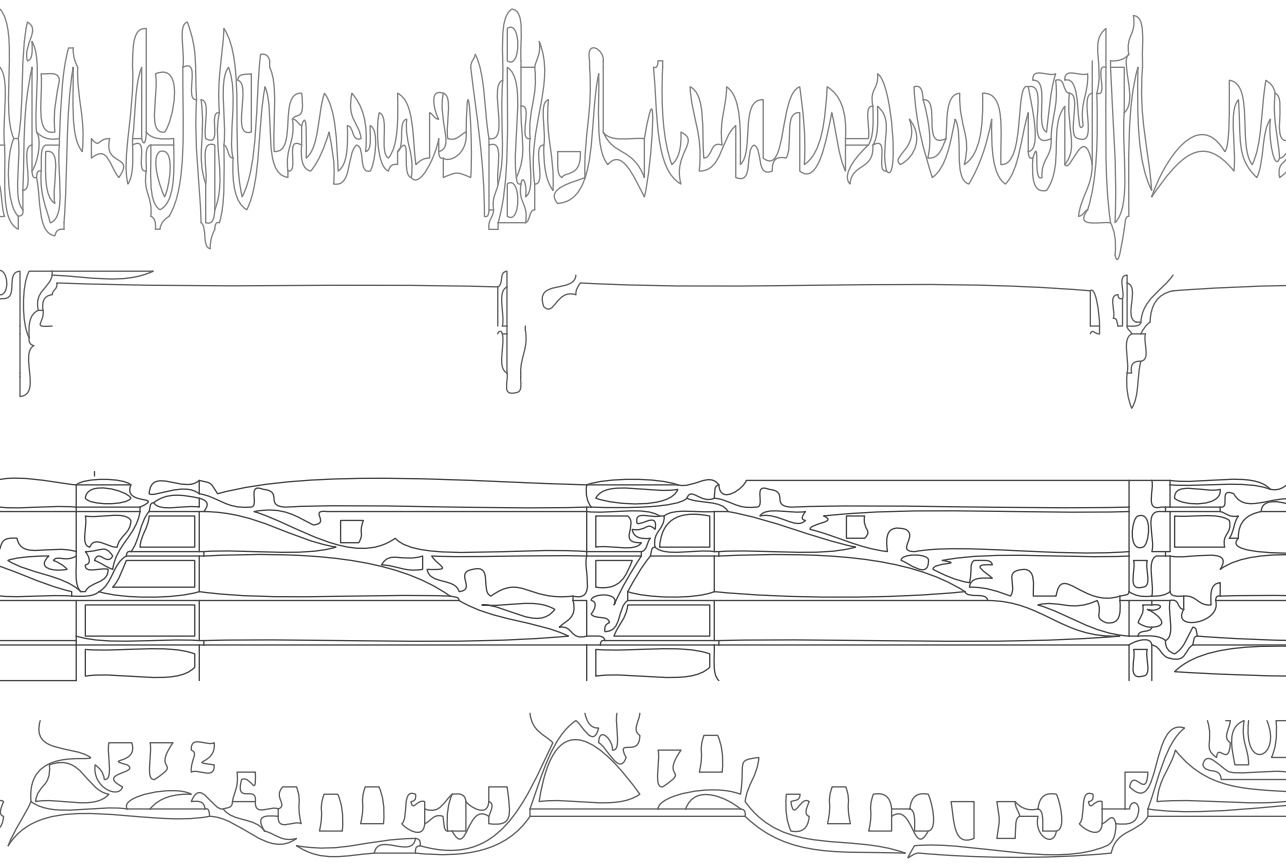
persistence of OSA despite optimal surgical treatment, pharyngeal collapse appeared to play a role in obstruction of the airway. Endoscopy makes it possible to identify a static or dynamic airway obstruction that may interfere with respiratory improvement, enabling a prediction of respiratory improvement and treatment to be adapted to the specific level of obstruction. Long-term follow-up is needed, because of the chance of relapse.

REFERENCES

1. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet 2006;14:289-298.
2. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 2004;15:670-674.
3. Hoeve LJ, Pijpers M, Joosten KF. OSAS in craniofacial syndromes: an unsolved problem. Int J Pediatr Otorhinolaryngol 2003;67 Suppl 1:S111-113.
4. Lo LJ, Chen YR. Airway obstruction in severe syndromic craniosynostosis. Ann Plast Surg 1999;43:258-264.
5. Hoeve HL, Joosten KF, van den Berg S. Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol 1999;49 Suppl 1:S59-61.
6. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;109:704-712.
7. Nixon GM, Brouillette RT. Sleep 8: paediatric obstructive sleep apnoea. Thorax 2005;60:511-516.
8. Nout E, Cesteleyn LL, van der Wal KG, et al. Advancement of the midface, from conventional Le Fort III osteotomy to Le Fort III distraction: review of the literature. Int J Oral Maxillofac Surg 2008
9. Nelson TE, Mulliken JB, Padwa BL. Effect of midfacial distraction on the obstructed airway in patients with syndromic bilateral coronal synostosis. J Oral Maxillofac Surg 2008;66:2318-2321.
10. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
11. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Archives of pediatrics & adolescent medicine 2005;159:775-785.
12. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
13. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
14. Goldberg S, Shatz A, Picard E, et al. Endoscopic findings in children with obstructive sleep apnea: effects of age and hypotonia. Pediatr Pulmonol 2005;40:205-210.
15. Mathijssen I, Arnaud E, Marchac D, et al. Respiratory outcome of mid-face advancement with distraction: a comparison between Le Fort III and frontofacial monobloc. J Craniofac Surg 2006;17:880-882.
16. Witherow H, Dunaway D, Evans R, et al. Functional outcomes in monobloc advancement by distraction using the rigid external distractor device. Plast Reconstr Surg 2008;121:1311-1322.
17. Arnaud E, Marchac D, Renier D. Reduction of morbidity of the frontofacial monobloc advancement in children by the use of internal distraction. Plast Reconstr Surg 2007;120:1009-1026.
18. Firmin F, Coccaro PJ, Converse JM. Cephalometric analysis in diagnosis and treatment planning of craniofacial dysostoses. Plast Reconstr Surg 1974;54:300-311.
19. Boutros S, Shetye PR, Ghali S, et al. Morphology and growth of the mandible in Crouzon, Apert, and Pfeiffer syndromes. J Craniofac Surg 2007;18:146-150.
20. Ishii K, Kaloust S, Ousterhout DK, et al. Airway changes after Le Fort III osteotomy in craniosynostosis syndromes. J Craniofac Surg 1996;7:363-370; discussion P-371.
21. Li KK, Guilleminault C, Riley RW, et al. Obstructive sleep apnea and maxillomandibular advancement: an assessment of airway changes using radiographic and nasopharyngoscopic examinations. J Oral Maxillofac Surg 2002;60:526-530; discussion 531.

Part III

Functional problems in syndromic craniosynostosis







Chapter 5

Papilledema in patients with Apert, Crouzon and Pfeiffer syndrome; prevalence, efficacy of treatment and risk factors

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ABSTRACT

Objective

Patients with syndromic craniosynostosis are at risk for elevated intracranial pressure because of various physiologic and anatomic abnormalities. The aims of this study were to determine the prevalence of papilledema in syndromic craniosynostosis, to evaluate the results of the treatment, and to examine the risk factors.

Methods

This is a retrospective study on 84 patients with Apert, Crouzon, or Pfeiffer syndrome. Papilledema was defined as blurring of the margins of the optic disk. The association between clinical symptoms, beaten-copper pattern on skull radiograph, ventricular dilatation on computed tomography scan, and papilledema was assessed.

Results

Papilledema was present in 51% of the patients. No relation between specific clinical symptoms and papilledema was found. The significant associations were complex craniosynostosis, exorbitism, and ventricular dilatation.

Conclusion

The prevalence of papilledema in patients with Apert, Crouzon, or Pfeiffer syndrome is high, not only before cranial decompression but also after vault expansion. Annual fundoscopy is recommended to screen for papilledema. We consider that early decompressive surgery (within the first year of age) prevents the development of papilledema and, most likely, elevated intracranial pressure.

INTRODUCTION

Craniosynostosis is a congenital disorder, arising in 1 in 2500 births, characterized by the premature fusion of calvarial sutures. This fusion restricts the normal growth of the skull, brain, and face and needs surgical correction. In about 40% of cases (1:6250), craniosynostosis is part of a syndrome, such as Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome[1].

Due to fusion of calvarial sutures the intracranial pressure (ICP) may be elevated. In isolated, single-suture craniosynostosis, the frequency of elevated ICP before vault expansion differs according to the site of the affected suture (e.g., 8% in trigonocephaly, 13% in scaphocephaly and 16% in frontal plagiocephaly)[2-4]. The reported frequency of elevated ICP is 31% in brachycephaly (bilateral coronal synostosis) and 47% in complex craniosynostosis (combination of 2 sutures, e.g., coronal and sagittal suture synostosis)[4]. In patients with either Apert or Crouzon syndrome, elevated ICP before vault expansion is seen in approximately 45% and 63%, respectively[5,6]. Untreated, elevated ICP may lead to irreversible visual loss caused by optic nerve dysfunction and mental impairment[4,7]. Therefore, surgical decompression is recommended within the first year of life[4]. Unfortunately, elevated ICP may still persist after early cranial expansion[8]. Information on the frequency of this problem, however, is limited[9].

Clinically, it is difficult to recognize significantly elevated ICP in these children because symptoms can be vague. The classic symptoms of elevated ICP -vomiting and disturbed consciousness- are typically absent. A skull radiograph and a computed tomography (CT) scan of the brain might be helpful in diagnosing signs of elevated ICP[10,11]. A reliable symptom, although rather late, is papilledema[12]. The criterion standard for measuring ICP is an invasive measurement. A drawback is the risk of complications such as haemorrhage, cerebrospinal fluid leak, and infection[9].

We have undertaken a retrospective study in patients with Apert, Crouzon, or Pfeiffer syndrome to determine the prevalence of papilledema before and after vault expansion. We have also assessed the risk factors for papilledema, and the results of surgery on papilledema.

METHODS

Study group

The records of all patients with Apert, Crouzon, and Pfeiffer syndrome (n = 90) who were treated at the Dutch Craniofacial Center between 1983 and 2006 were reviewed. Patients with Saethre-Chotzen syndrome or Muenke syndrome (P250R mutation in FGFR3 gene) were not included. On the basis of genetic analysis, Crouzon and Pfeiffer syndrome

often cannot be distinguished from each other[1]. Therefore, in this study, these clinical syndromes are considered to be a homogeneous group. The records were analyzed for clinical symptoms of elevated ICP, beaten-copper pattern on skull radiograph, results of fundoscopy, and CT scan.

Papilledema

All fundoscopies were performed by an ophthalmologist by indirect ophthalmoscopy after mydriasis of the pupil with phenylephrine 2.5% and tropicamide 0.5%. Papilledema was defined as blurring of the margins of the optic disk (figure 1). If this was seen, objective refraction (skiascopy) was performed to exclude hyperopia, which can resemble papilledema without being a sign of elevated ICP, so-called pseudopapilledema[13]. Papilledema was defined as persistent when it was still present 1 year after surgical intervention. Relapse of papilledema was defined as a recurrence of papilledema after at least 1 normal fundoscopy examination. The presence of papilledema on at least 1 occasion is included for analysis. Invasive ICP measurements were not reported because of the small amount.

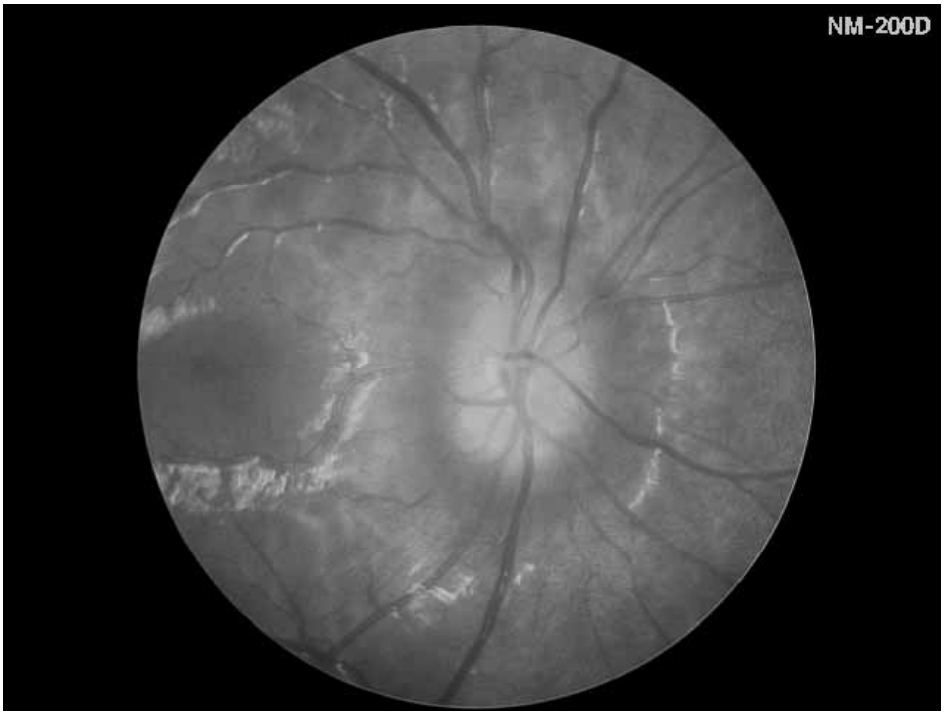

Figure 1: Fundus photograph showing papilledema in the right eye of a girl with Crouzon syndrome

Signs of elevated ICP

1. Clinical symptoms of elevated ICP.

Clinical symptoms suggestive of elevated ICP were taken as headache, vomiting, and changes in vision, and/or behavior.

2. Beaten-copper pattern on skull radiographs.

Beaten-copper pattern on skull radiographs were assessed until the age of 7 years. Only digital radiographs were evaluated, and these were available for 28 patients. The area of beaten-copper pattern was graded as mild (<33%), moderate (33-66%), and severe (66-100%)[11] using Image J software (Wayne Rasband, National Institute of Mental Health, Bethesda, MD). The ratio of the area with beaten-copper pattern to the total area of the skull, defined the gradation (J.J.N.M. van der Meulen, et al., unpublished data, 2007).

3. Ventricular dilatation on CT scan.

Ventricular dilatation was defined by an enlargement of the ventricles on CT scan, according to the radiology report[10].

Efficacy of treatment to resolve papilledema

The efficacy of cranial surgery for resolving papilledema was determined by fundoscopy during follow-up. The surgical intervention was considered to be effective if papilledema disappeared or if no papilledema developed within the first year after surgery.

Risk factors for elevated ICP

Potential risk factors for elevated ICP were the age at vault expansion, the number of fused sutures (with complex craniosynostosis defined as fusion of ≥ 2 sutures), midface hypoplasia, exorbitism, severe obstructive sleep apnea (OSA) -requiring supplemental oxygen, continuous positive airway pressure, nasopharyngeal tube or tracheal cannula[14-16] - and ventricular dilatation on CT scan.

Statistical analysis

The results were analyzed using SPSS 14.0 for Windows 2000. All numbers are expressed as median and range. Comparisons of categorical variables between patients with and without elevated ICP were performed using Fisher exact test. Logistic regression analysis with backward elimination was used to determine variables independently predictive of elevated ICP. Variables with a p-value < 0.20 after univariate analysis were used in a logistic regression model. Significance was defined as a p-value < 0.05.

RESULTS

Six of the 90 patients were excluded because there was no information on the level of papilledema (i.e., no fundoscopy was performed). Therefore, 84 patients with Apert (n = 33), Crouzon (n = 43), or Pfeiffer (n = 8) syndrome underwent full analysis. There were 44 boys (52%) and the patients were aged 11.4 years (range 5 months to 23.5 years) at the time of review.

Papilledema

Preoperatively, 66 patients were examined and 25 had papilledema (38%; 95% confidence interval 26-51%). The age at presentation with papilledema was 12 months (range 2-64 months) in the Crouzon/ Pfeiffer group (n = 23), and in 2 children with Apert syndrome, it was 8 and 12 months (figure 2).

Postoperatively, 70 patients underwent fundoscopy, and 30 patients had papilledema (43%; 95% confidence interval 31-55%), 7 with persistent papilledema after skull surgery, 5 with a relapse, and 10 with a first presentation after surgical decompression. In the remaining 8 patients, there was no preoperative fundoscopy. Two patients with Apert syndrome had pseudopapilledema due to hyperopia and were thus considered to have no papilledema. Another 7 patients with Apert syndrome and 2 with Crouzon syndrome had hyperopia and also true papilledema.

In total, 43 (51%) of the 84 patients had papilledema on at least 1 occasion.

Signs of elevated ICP (table 1)

1. Clinical symptoms of elevated ICP.

Headache, vomiting, changes in vision and/or changes in behavior were recorded in 10 (24%) of 42 patients with papilledema, which was not significantly different with the 9 (27%) of 33 patients with normal fundoscopy (table 1).

Table 1: Predictive variables of papilledema after univariate analysis

	Papilledema (n = 43)	Normal fundoscopy (n = 41)	p-value
Diagnosis Crouzon/Pfeiffer	31/ 43	20/ 41	0.044*
Complex craniosynostosis	31/ 42	20/ 40	0.040*
Midface hypoplasia	39/ 42	33/ 41	0.116
Exorbitism	42/ 43	34/ 39	0.097
Hyperopia	11/ 41	12/ 29	0.302
Headache, vomiting, changed vision and/or changed behavior	10/ 42	9/ 33	0.793
Impressiones	15/ 17	6/ 11	0.076
Severe OSA	8/ 41	3/ 31	0.331
Ventricular dilatation	26/ 40	8/ 36	0.000*

* $p < 0.05$

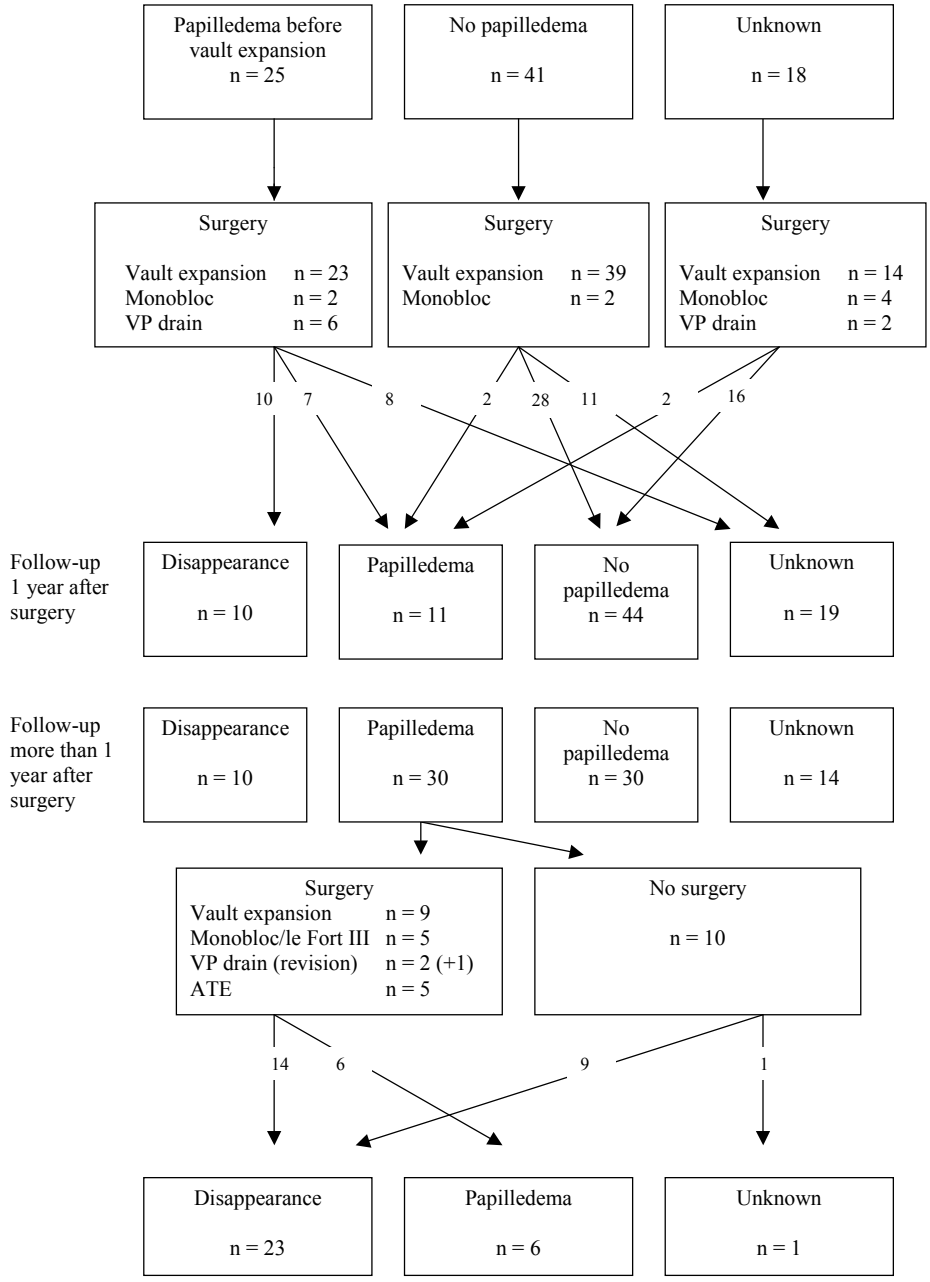

Figure 2: Papilledema before and after vault expansion
VP ventriculoperitoneal
ATE adenotonsillectomy

2. Beaten-copper pattern on the skull radiograph.
There were 28 children younger than 7 years with available digital skull radiographs. Fifteen (88%) of 17 with papilledema and 6 (55%) of 11 with normal fundoscopy had beaten-copper pattern. There was no significant difference between these 2 groups. The gradation in the first group was 27% mild, 20% moderate, and 53% severe, and in the second group, 67% mild and 33% severe.
3. Ventricular dilatation on CT scan.
Ventricular dilatation on CT scan was seen in 26 (65%) of 40 patients with papilledema, whereas it was present in only 8 (22%) of 36 patients with normal fundoscopy ($p \leq 0.001$).

Efficacy of treatment to resolve papilledema (figure 2)

Vault expansion

All 25 children with papilledema before surgery were treated with decompressive surgery within 2 months of the problem being diagnosed. In 8 patients, skull expansion was combined with midface surgery because of severe airway obstruction in 4 patients (one received supplemental oxygen and one had a tracheostomy), severe exorbitism in 1 patient, and severe midface hypoplasia in 3 patients. After decompressive surgery, papilledema disappeared in 10 (59%) of 17 patients for at least 1 year after surgery, it persisted in the other 7 patients (41%). The results were unknown 1 year after surgery in 8 patients. Thirty of the 41 patients without papilledema before decompressive surgery were screened postoperatively, and 2 (7%) of 30 developed papilledema within 1 year after surgery. Of the 18 patients with unknown preoperative state, papilledema was seen within 1 year of surgery in 2 (11%) of 18 patients (figure 2).

Fifty-four (83%) of the 65 patients did not have papilledema 1 year after surgery. No papilledema was seen preoperatively and postoperatively in 28 (93%) of 30 patients. After surgical treatment papilledema was eliminated in 10 (59%) of 17 patients.

More than 1 year after vault expansion 70 patients were screened, and papilledema was seen in 30 patients (43%); papilledema persisted in 7 patients; it relapsed after 2.5 years (range, 14 months to 4.5 years) in 5 patients, and it developed postoperatively in 18 patients (including 8 patients within 1 year). In 20 (67%) of the 30 patients with postoperative papilledema, secondary surgery (vault expansion, monobloc, or le Fort III, ventriculoperitoneal shunting, revision of shunting and adenotonsillectomy) was performed, and it was effective in treating papilledema in 14 patients (70%). In 6 patients, papilledema persisted, and the known risk factors for elevated ICP were evaluated. In 4 of them, complementary treatment (vault surgery and non-invasive OSA treatment) was necessary; in the other 2, the known risk factors were excluded. All patients were followed up on regular basis. The remaining 10 untreated children had papilledema, which occurred incidentally at 1 or 2 follow-up examinations. In them, no symptoms of elevated ICP were present;

hydrocephalus and OSA could be ruled out. In these patients no surgical treatment was performed, and they were followed up intensively, and in at least 9 cases papilledema disappeared.

Ventriculoperitoneal shunt

In the study group of 84 patients, 10 (12%) had a ventriculoperitoneal shunt; 6 because of hydrocephalus and 4 because of hydrocephalus and papilledema. Papilledema persisted in 1 patient and relapsed in 2 patients.

Risk factors for elevated ICP

Premature fusion of calvarial sutures was seen in all patients; in 7% of the patients 1 suture was fused; in 54%, 2 sutures; and in 39%, more than 2 sutures. The age at vault expansion in the children with preoperative papilledema was 20 months (range, 2 months to 5.5 years). In the group without papilledema, the age of vault expansion was 7 months (range, 2 months to 9 years). This difference is statistically significant (p = 0.007). In 11 patients, severe OSA was present. Papilledema was present before OSA treatment in 4 patients, absent in 4, and unknown in 3. After OSA treatment, papilledema disappeared in 1 patient, persisted in 1, relapsed in 2, and developed in 3; no control examination was done in 4 patients.

Univariate analysis revealed that the diagnosis of Crouzon/ Pfeiffer, complex craniosynostosis, and ventricular dilatation are statistically significant predictive variables for the presence of papilledema (table 1). Multivariate analysis showed that complex craniosynostosis, exorbitism, and ventricular dilatation were predictive of papilledema (table 2).

DISCUSSION

There are 2 principal findings in this study of papilledema in syndromic craniosynostosis. First, based on fundoscopy, papilledema occurred in more than half of the patients with Apert, Crouzon, or Pfeiffer syndrome, not only before but also after vault expansion. Second, we did not find any clinical symptoms that specifically indicated the presence of papilledema.

Table 2: Predictive model of papilledema after multivariate analysis

	Odds ratio	95% CI lower	95% CI upper	p-value
Complex craniosynostosis	6.119	1.549	24.179	0.010*
Exorbitism	18.800	1.376	256.916	0.028*
Ventricular dilatation	12.659	3.179	50.408	0.000*

* $p < 0.05$

CI confidence interval

In this study, we have used the presence of papilledema as a surrogate marker of elevated ICP. A major limitation of this approach, however, is that we may have underestimated the extent of elevated ICP in our population because the absence of papilledema does not definitely exclude elevated ICP[12]. Despite this limitation, the high prevalence of papilledema in our study is similar to that observed in previous studies[4,5], and we found that before vault expansion, it was particularly common in patients with Crouzon and Pfeiffer syndrome (~ 50%). Cases of Apert syndrome had a lower incidence of this finding (~ 10%). This observation differs from the study reported by Renier et al. in which 45% of patients with Apert syndrome had preoperative elevation in ICP[4,5]. A possible explanation for the lower percentage in our Apert group was the younger age at which fundoscopy was performed (3 versus 6 months)[5].

Because the absence of papilledema does not exclude elevated ICP[12], we also examined whether clinical symptoms commonly associated with elevated ICP might reliably indicate the presence of papilledema. In this study, they did not. It is possible that elevated ICP might still have been present in those with symptoms had we measured it invasively. However, our finding is consistent with the study reported by Tuite el al.[12], where only 8 of 41 patients with elevated ICP had clinical symptoms. Beaten-copper pattern on skull radiograph was seen more often in children with papilledema.

Treatment to resolve papilledema

Overall, within 1 year of primary surgery no papilledema was present in 83% of the patients. On follow-up of children with no preoperative papilledema, 93% remained papilledema-free after surgery. In respect to the timing of primary vault expansion, the children with no preoperative papilledema were 6 months younger at surgery compared with those who had preoperative papilledema. This significant difference suggests that decompressive surgery at a younger age prevents the development of papilledema in craniosynostosis. After surgical treatment, papilledema disappeared in 59% of the patients, but in a few specific instances, it persisted, or developed within 1 year, after decompression. Possible reasons for this finding were insufficient decompression, presence of ventricular dilatation, or residual papilledema after correction of ICP. More than 1 year after vault expansion, papilledema was seen in 43% of the patients. In 67% of these patients, secondary surgery was performed, and it was effective in treating papilledema in 14 of the 20 patients. The remaining patients were treated conservatively despite the incidental finding of papilledema on intensive follow-up with repeated fundoscopy.

Ventricular dilatation is a common finding in patients with craniosynostosis. Its contribution to elevated ICP may be difficult to establish. In our study, ventricular size was significantly increased in patients with papilledema, compared with those without (65% versus 22%). In one third of the patients with ventricular dilatation, a shunt was needed in addition to vault expansion.

These figures are comparable with a previous study reported by Collmann et al.[10], where it was found that papilledema could persist, relapse, or develop more than 1 year after vault expansion and placement of a ventriculoperitoneal shunt. Thus, annual fundoscopy is highly recommended until adulthood.

Risk factors for papilledema

We found that complex craniosynostosis, exorbitism, and ventricular dilatation were factors associated with papilledema. The first 2 of these variables were also reported in the study by Gupta et al[17]. Significant correlations were found between optic nerve damage from papilledema and multiple suture craniosynostosis and exorbitism[17]. Tuite et al.[11] showed that hydrocephalus had low sensitivity (40%), but high specificity (80%), for elevated ICP.

Other factors, which result in elevated ICP, are OSA and venous hypertension[18,19]. In a study of 13 patients with syndromic craniosynostosis, a significant correlation was found between the severity of upper airway obstruction and elevated ICP in active sleep[15]. In our study 11 patients had severe OSA. However, they all had this problem treated, and thus, association (or causation) with elevated ICP could not be shown. In addition, the retrospective design of our study meant that we could not obtain information about venous hypertension and stenosis of the jugular foramen as causes of elevated ICP[20].

In conclusion, in syndromic craniosynostosis, the prevalence of papilledema is high, not only before cranial decompression but also after vault expansion. Given the high prevalence of papilledema, annual review is highly recommended until adulthood. In our hospital, fundoscopy is the first choice, given its feasibility and low risk. We consider that early decompressive surgery (within the first year of age) prevents the development of papilledema and, most likely, elevated ICP. The origin of papilledema may be complex and difficult to establish. It is therefore important to check all known risk factors to identify the specific cause(s) and plan optimal treatment. Hence, management of these patients should be multidisciplinary and focussed in specialized centers.

REFERENCES

1. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet 2006;14:289-298.
2. Arnaud E, Renier D, Marchac D. Prognosis for mental function in scaphocephaly. J Neurosurg 1995;83:476-479.
3. Mathijssen I, Arnaud E, Lajeunie E, et al. Postoperative cognitive outcome for synostotic frontal plagiocephaly. J Neurosurg 2006;105:16-20.
4. Renier D, Lajeunie E, Arnaud E, et al. Management of craniosynostoses. Childs Nerv Syst 2000;16:645-658.
5. Renier D, Arnaud E, Cinalli G, et al. Prognosis for mental function in Apert's syndrome. J Neurosurg 1996;85:66-72.
6. Renier D, Sainte-Rose C, Marchac D, et al. Intracranial pressure in craniostenosis. J Neurosurg 1982; 57:370-377.
7. Bartels MC, Vaandrager JM, de Jong THR, et al. Visual loss in syndromic craniosynostosis with papilledema but without other symptoms of intracranial pressure. J Craniofac Surg 2004;15:1019-1022.
8. Taylor WJ, Hayward RD, Lasjaunias P, et al. Enigma of raised intracranial pressure in patients with complex craniosynostosis: the role of abnormal intracranial venous drainage. J Neurosurg 2001;94:377-385.
9. Tamburrini G, Caldarelli M, Massimi L, et al. Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Childs Nerv Syst 2005;21:913-921.
10. Collmann H, Sörensen N, Krauß J. Hydrocephalus in craniosynostosis: a review. Childs Nerv Syst 2005;21:902-912.
11. Tuite GF, Evanson J, Chong WK, et al. The beaten copper cranium: a correlation between intracranial pressure, cranial radiographs, and computed tomographic scans in children with craniosynostosis. Neurosurgery 1996;39:691-699.
12. Tuite GF, Chong WK, Evanson J, et al. The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. Neurosurgery 1996;38:272-278.
13. Fried M, Meyer-Schwickerath G, Koch A. Excessive hypermetropia: review and case report documented by echography. Ann Ophthalmol 1982;14:15-19.
14. Davidson Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
15. Gonsalez S, Hayward R, Jones B, et al. Upper airway obstruction and raised intracranial pressure in children with craniosynostosis. Eur Respir J 1997;10: 367-375.
16. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Arch Pediatr Adolesc Med 2005;159:775-785.
17. Gupta S, Ghose S, Rohatgi M, et al. The optic nerve in children with craniosynostosis. A pre and post surgical evaluation. Doc Ophthalmol 1993;83:271-278.
18. Hayward R, Gonsalez S. How low can you go? Intracranial pressure, cerebral perfusion pressure, and respiratory obstruction in children with complex craniosynostosis. J Neurosurg 2005;102:16-22.
19. Hayward R: Venous hypertension and craniosynostosis. Childs Nerv Syst 2005;21:880-888.
20. Rich PM, Cox TCS, Hayward RD: The jugular foramen in complex and syndromic craniosynostosis and its relationship to raised intracranial pressure. Am J Neuroradiol 2003;24:45-51.





Chapter 6

Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile

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ABSTRACT

Objective

Little is known about the long-term prevalence of elevated intracranial pressure (ICP), obstructive sleep apnea (OSA), level of education, language and motor skills, impaired sight and hearing in craniosynostosis syndromes. The objective of this study was to define the prevalence per syndrome of elevated ICP, OSA, impaired sight and impaired hearing.

Methods

A retrospective study was undertaken on 167 consecutive patients diagnosed with Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome, aged 1-25 years and treated between 1983 and 2008. The mean age at time of referral and review was 1 years and 2 months and 10 years and 3 months, respectively.

Results

Patients with Apert and Crouzon/ Pfeiffer syndrome had the highest prevalence of elevated ICP (33% and 53%, respectively) and OSA (31% and 27%, respectively), while Saethre-Chotzen syndrome was also associated with a fair risk for elevated ICP. The prevalence of impaired sight (61%) and hearing (56%) was high in all syndromes.

Conclusion

Based on these data a syndrome specific risk profile with suggestions for screening and treatment is presented.

INTRODUCTION

Syndromic craniosynostosis is a complex disease with a broad spectrum of problems. Elevated intracranial pressure (ICP) has a high prevalence in patients with Apert and Crouzon/ Pfeiffer syndrome[1, 2], but its prevalence in Muenke or Saethre-Chotzen syndrome is unclear. One of the factors that is related to elevated ICP is obstructive sleep apnea (OSA)[3, 4]. OSA is a known problem in children with craniosynostosis but little is known about the prevalence among the different syndromes[5]. Other problems that are often seen are ocular and hearing deficits, with the most frequent ocular problems being strabismus and refractive errors[6-8]. Hearing deficits are conductive in most cases caused by recurrent otitis media that occurs during their entire life[9, 10]. A retrospective study was undertaken to determine the prevalence of these problems per syndrome. Based on these data, guidelines for follow-up of patients per syndrome are suggested.

METHODS

Study group

A retrospective study on all consecutive patients with Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome treated at the Dutch Craniofacial Center between 1983 and 2008 was performed. Crouzon and Pfeiffer syndrome often cannot be distinguished from each other genetically, and were therefore considered to be a homogeneous group in this study. The only exclusion criterium was an age of less than 12 months at the time of review, leaving a total of 167 patients were included.

Protocol for intake, treatment and follow-up

Patients who were referred to our center were assessed by a multidisciplinary team, which consisted of a plastic surgeon, neurosurgeon, maxillofacial surgeon, clinical geneticist, orthodontist, ophthalmologist, otolaryngologist, paediatrician, radiologist, psychologist, and a nurse practitioner. All patients were offered a genetic analysis. Depending on their phenotype, exons of FGFR 1, 2 and 3 and TWIST were tested. Routine diagnostic tests, besides a complete physical examination, were skull X-rays, cephalograms, photographs, fundoscopy, and a three-dimensional computed tomography (3D-CT) scan of the skull. In case of anamnestic respiratory problems, a polysomnography was done either at home or at the clinic. The day before surgery fundoscopy was repeated.

Vault remodelling is scheduled at the age of 6-9 months or as soon as possible if patients were already older at time of referral. During the period under review, a fronto-orbital advancement was performed routinely as primary vault remodelling. A monobloc was only done in the very young in case of severe OSA or severe exorbitism. Le Fort III or

monobloc was preferably postponed until adult age, unless functional problems necessitated an earlier intervention. Psychosocial functioning and the wish for correction of patient and parents were also taking into account in timing the midface advancement. If for these reasons the midface advancement was performed between the ages of 9 and 12, the necessity for le Fort I osteotomy at 18 is the resulting consequence.

Follow-up visits of these patients are scheduled once every 3-6 months during their first 2.5 years. Thereafter, check-ups are scheduled once a year, up to the age of 9, after which the frequency drops to once every 3 years until the age of 18 for those patients who have no functional problems requiring extra attention. During follow-up visits, patients and their parents were specifically asked about complaints suggestive for elevated ICP, respiratory problems, ocular problems, and hearing difficulty. Skull circumference was measured and facial features were assessed. Skull X-rays were checked for impressiones, progressive sutural synostosis, sutural widening, vascular impressions, and deepening of the sella.

Ophthalmologic and audiologic tests were regularly repeated. CT scans were taken on indication only, such as anamnestic complaints suggestive of elevated ICP, decline in growth curve of skull circumference, presence of papilledema or indication for surgery (e.g. vault remodelling, le Fort III or monobloc).

Functional assessment

Intracranial pressure

Papilledema was used as an indicator of elevated ICP. A paediatric ophthalmologist performed all fundoscopies after pharmacological pupillary dilation with a combination of phenylephrine 2.5% and tropicamide 0.5%. Papilledema was diagnosed when blurring of the optic disc margins was present. Pseudopapilledema, which can resemble papilledema without being a sign of elevated ICP, was excluded. To differentiate papilledema from pseudopapilledema, objective refraction was performed to rule out high hyperopia. If papilledema was still present 1 year after surgery it was defined as persistent, and a relapse was defined as reappearing papilledema following at least one normal fundoscopy. All patients with papilledema were considered to have elevated ICP[11].

ICP measurements were performed with an intraventricular catheter or with an intraparenchymal device (Camino or Codman). Invasive ICP measurements were recorded for at least 24 hours. Elevated ICP was defined as an average of 15 mmHg or higher and/or more than three plateau waves of 35 mmHg lasting more than 5 minutes[12]. For the analysis the term elevated ICP refers to the presence of papilledema and/or elevated ICP on invasive measurement. Invasive ICP measurement was not done routinely, but only in specific cases such as severe OSA, headache or persisting papilledema after surgery.

Obstructive sleep apnea

OSA was diagnosed based on a nocturnal pulse oximetry, which measures the oxygen saturation[13]. This was usually done ambulatory, with an Embletta Portable Diagnostic System using a Nonin Oximeter and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland). From this oxygen saturation profile the oxygenation desaturation index (ODI) was calculated. The ODI was defined as the average number of oxygen desaturations of 4% or more, below the baseline level, per hour. Patients were classified as having mild OSA with an ODI of 1-5, moderate OSA with an ODI of 6-25 and severe OSA with an ODI higher than 25[14, 15].

Sight and hearing

Sight was assessed based on the test results done by an orthoptist or ophthalmologist. It was scored as normal, myopic, hyperopic, astigmatic, anisometropic or blind.

Hearing was assessed based on the results of hearing tests performed by an otolaryngologist or audiologist. Hearing was scored as normal or loss due to conductive, sensorineural or mixed cause.

Statistical methods

Statistical analyses were performed using SPSS 14.0 for Windows 2000 (SPSS, Inc., Chicago, IL, USA). All numbers are expressed as mean and range. The Pearson's chi-square was used or when a table contained numbers smaller than 5 the Fisher's exact test was used to compare proportions. A two-sided p-value of 0.05 or less was considered significant.

RESULTS

Baseline

Of the 167 patients who were included, 36 had Apert, 55 had Crouzon/ Pfeiffer, 38 had Muenke and 38 had Saethre-Chotzen syndrome. The mean age at time of referral and review was 1 year and 2 months and 10 years and 3 months, respectively. Of the 167 patients, 81 (48%) were boys and 123 (74%) diagnoses were confirmed genetically (table 1). Of the 43 in whom no mutation was found, 12 were not tested, because parents did not give consent or they were tested in another hospital but no information was available. In the Apert patients 24 were tested, 16 had the S252W mutation and eight the P253R mutation. In nine of the tested patients with Crouzon/ Pfeiffer syndrome, no mutation was found. No TWIST mutation or deletion was found in 11 patients with Saethre-Chotzen syndrome, in whom a FGFR 2 or 3 mutation was excluded. In these patients, we adhered to the clinical diagnoses made by the geneticist. All patients with the Muenke syndrome had the FGFR 3 P250R mutation.

Table 1: Overview of genetic diagnosis

	Apert n = 36	Crouzon/ Pfeiffer n = 55	Muenke n = 38	Saethre-Chotzen n = 38
FGFR 2				
S 252 W	16			
P 253 R	8			
C 342 Y		4		
C 342 W		1		
C 342 T		1		
C 278 F		4		
Y 105 C		1		
Y 340 H		3		
F 276 V		2		
G 271 V		1		
G 338 R		1		
Q 289 P		3		
S 351 C		2		
S 354 C		1		
S 267 P		3		
W 290 R		3		
A 362 T		3		
C 342 R		2		
C 342 W		1		
K 641 R		1		
1084+3a>g		1		
FGFR 3				
A 391 E		1		
P 250 R			38	
TWIST				
Y103X				2
D157A				1
N114S				1
R116G				1
P136S				1
P136H				1
R749C				1
T137M				1
7p21				1
165ins10				2
417dup21				1
CA-repeat				1
Unilateral deletion				
TWIST region chr. 7				3
Deletion region 7p21				3
No mutation found		10		11
Not tested	12	8		7

Table 2: Overview of surgery per syndrome

Syndrome	Primary vault expansion	Secondary vault expansion	Midface advancement
Apert	35 (97%)	5 (14%)	16 (44%)
Crouzon/ Pfeiffer	46 (84%)	10 (18%)	21 (38%)
Muenke	38 (100%)	2 (5%)	0
Saethre-Chotzen	34 (89%)	5 (15%)	0
Total	153 (92%)	22 (13%)	37 (22%)

Table 3: Type and timing of first midface advancement

	Mean age first midface advancement (years)	Apert (n = 12)	Crouzon/ Pfeiffer (n = 17)
Monobloc	2.3	5	6
Le fort III	10.3	6	9
Le fort II	10.3	1	2

The type of primary surgery is described in table 2. No surgery was performed in 14 patients because they were relatively old at time of referral and did not have signs of elevated ICP or because their parents did not give their consent. The mean age at primary vault expansion was 14 months (range: 2 months to 9 years). A total of 92 (55%) patients underwent surgery before the age of 1 year. The main reason for performing primary skull remodelling after the age of 1 year was a delay in referral. In 22 of the 167 (13%) a second vault expansion was needed, and in 1 a third vault expansion was needed. The indication for this secondary surgery was elevated ICP in eight, scheduled fronto-orbital surgery after initial occipital expansion without any sign of elevated ICP in one, and in five patients because of unsatisfactory aesthetic effect of the first vault expansion. Of the 22 patients with a second vault expansion result, three patients were referred for a second opinion following initial vault surgery that was performed by a surgeon who was inexperienced with the treatment of syndromic craniosynostosis. In 29 patients (12 Apert and 17 Crouzon/ Pfeiffer syndrome) 37 midface advancements were conducted. Complications caused by midface advancement were previous described by Nout et al.[16]. The type and timing of the midface advancements are described in table 3. A ventriculoperitoneal shunt was placed in 13 patients (three Apert, nine Crouzon/ Pfeiffer, and one Muenke syndrome) because progressive ventricular dilatation was present and intracranial volume was more than appropriate.

ICP

A complete fundoscopic assessment was performed in 164 patients; of these 55 (33%) were diagnosed with elevated ICP on at least one occasion. The mean age at the first diagnosis of elevated ICP was 3.5 years (range: 5 months to 18.3 years). Forty-two were diagnosed based on the presence of papilledema and 13 based on the presence of papilledema and a positive invasive ICP measurement. Invasive measurements were made when papilledema

Table 4: Prevalence of papilledema before and after the first vault expansion

	Preoperative[1]	Postoperative[2]	Total
Apert	2/ 22 (9%)	11/ 31 (35%)	12/ 36 (33%)
Crouzon/ Pfeiffer	24/ 45 (53%)	8/ 40 (20%)	29/ 55 (53%)
Muenke	1/ 28 (4%)	1/ 24 (4%)	2/ 38 (5%)
Saethre-Chotzen	5/ 26 (19%)	4/ 24 (17%)	8/ 38 (21%)

[1] Number of patients with papilledema divided by the number of patients tested for papilledema

[2] Includes new onset and recurrent cases of papilledema

was present without any clinical or radiological evidence for elevated ICP. The prevalence of papilledema varied strongly before and after first vault expansion and among different syndromes (table 4). The 1-year cumulative incidence (CI) of first occurrence of papilledema varied strongly between different syndromes and in time (figure 1).

OSA

Because of a high suspicion for respiratory problems (e.g., snoring, difficulty in breathing during sleep or apneas during sleep) in 66 patients, a screening for OSA with nocturnal pulse oximetry was done. In 30 (18%) of the 167 patients, OSA was diagnosed. Patients with Apert and Crouzon/ Pfeiffer syndrome had a much higher prevalence of OSA than patients with Muenke and Saethre-Chotzen syndrome, and if OSA was present in patients with Muenke and Saethre-Chotzen syndrome it was only mild (table 5).

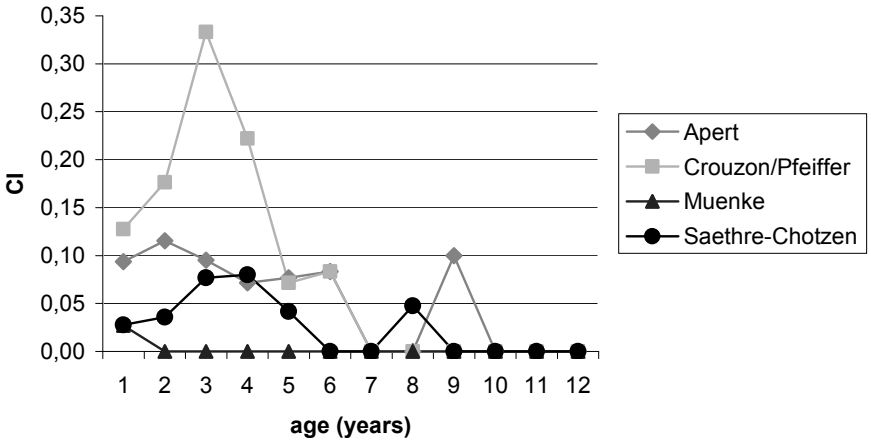


Figure 1: 1-year cumulative incidence (CI) of first occurrence of papilledema per syndrome*

* includes only patients checked for papilledema at least once every 3 years, Apert syndrome n = 32, Crouzon/ Pfeiffer syndrome n = 47, Muenke syndrome n = 36, Saethre-Chotzen syndrome n = 36

Table 5: Number of patients with OSA per syndrome

	Mild	Moderate	Severe	Total
Apert	4 (11%)	3 (8%)	4 (11%)	11/ 36 (31%)
Crouzon/ Pfeiffer	8 (15%)	4 (7%)	3 (5%)	15/ 55 (27%)
Muenke	2 (5%)	0	0	2/ 38 (5%)
Saethre-Chotzen	2 (5%)	0	0	2/ 38 (5%)

Table 6: Prevalence of refractive errors, strabismus and impaired hearing

	Refractive error	Strabismus	Impaired hearing
Apert	22/ 29 (76%)	27/ 29 (93%)*	21/ 29 (72%)
Crouzon/ Pfeiffer	16/ 41 (39%)	27/ 43 (63%)	20/ 40 (50%)
Muenke	17/ 35 (49%)	14/ 36 (39%)	24/ 36 (67%)
Saethre-Chotzen	14/ 27 (52%)	13/ 35 (37%)	13/ 35 (37%)

* statistical significant compared to all other syndromes

Sight

In 132 patients information of sight was available. Refractive errors were reported in 69 (52%) patients, 18 were myopic and 51 hyperopic (table 6). In 48 (70%) patients it was corrected with glasses. Astigmatism was reported in five (4%), anisometropia in five (4%), and severe visual loss in four (3%). The four patients with severe visual loss were previously reported by Bartels et al.[17]. Strabismus was diagnosed in 81 patients. Patients with Apert syndrome had significantly ($p < 0.001$) more strabismus than all patients with other syndromes (table 6).

Hearing

Hearing loss was reported in 78 of 140 (56%) patients. Conductive hearing loss was reported in 62 (44%), sensorineural hearing loss (SNHL) in six (4%) and mixed hearing loss was reported in 10 (7%) of the patients. The prevalence was the highest in Apert and Muenke syndrome (table 6). Of the 16 patients with SNHL, four had Apert syndrome, five had Crouzon/ Pfeiffer syndrome and seven had Muenke syndrome. Conductive hearing loss was present in 20 patients with Apert syndrome, in 19 patients with Crouzon/ Pfeiffer syndrome, in 20 patients with Muenke and in 13 patients with Saethre-Chotzen syndrome. Eighteen of the 140 (13%) patients needed a hearing aid: four patients with Apert syndrome, nine with Crouzon/ Pfeiffer syndrome, three with Muenke syndrome and two with Saethre-Chotzen syndrome

DISCUSSION

This study highlights the high prevalence of elevated ICP in patients with Apert, Crouzon/ Pfeiffer and Saethre-Chotzen syndrome. OSA is prevalent in Apert and Crouzon/ Pfeiffer syndrome and hearing and visual problems are frequent in all of the syndromes. This retrospective description of our population guides us to a diagnosis-specific screening and treatment protocol (table 7).

Table 7: Overview of diagnosis-specific screening and treatment protocol

Clinical diagnosis	Apert	Crouzon/ Pfeiffer	Muenke	Saethre-Chotzen	Comment
Genetic research	FGFR 2	FGFR 2	1st P250R FGFR 3 2nd TWIST	1st TWIST 2nd P250R FGFR 3	No FGFR 1 analysis included
Fundoscopy	Yearly up till 6 years	Yearly up till 6 years. In patients without craniosynostosis every 3 months during the first 2 years	At age of 2 years	Yearly up till 6 years	At first visit and pre-surgery in all patients. Papilledema without clinical or radiological symptoms: invasive ICP measurement
Polysomnography and/or pulse-oximetry	Yearly till 6 years. For older patient only if anamnestic breathing difficulties are present. Yearly after surgical treatment of moderate or severe OSA		If anamnestic breathing difficulties are present	If anamnestic breathing difficulties are present	If OSA is diagnosed: inspection of tonsils and endoscopy of upper airway
Hearing	Otoscopy and tympanometry at all ages. Otoacoustic Emission (OAE) till 4 years. Pure tone audiometry in patients of 4 years and older. If a hearing deficit is found on OAE or pure tone audiometry, Brainstem Response Audiometry is indicated.				
Sight	At first visit: screening for strabismus, if present; further ophthalmic work up is needed. When possible given child's development, information about visual acuity is required.				
(3D-)CT scan	Prior to any craniofacial surgery in all patients				
MRI	At age 0 and 4 If papilledema is present				
First cranial vault remodelling	Occipital expansion between 6 and 9 months (if synostosis is present). If severe OSA or severe exorbitism is present: monobloc + distraction		Fronto-orbital advancement between 9 and 12 months	Fronto-orbital advancement between 6 and 9 months	
Elevated ICP in follow-up	Occipital expansion with distraction or biparietal widening based on shape of skull		Occipital remodelling		
Midface advancement (monobloc or le Fort III with distraction)	Relative indication: between age 9 and 12 (and le Fort I at 18) or at 18		Not indicated		
Psychological testing	At the age of 1.5; 3.5; 6; 8; 12; 15 and 18 years				

All patients need genetic analysis to establish the diagnosis, for selective screening on related abnormalities, genetic counseling and research. Given the fact that we never encountered a mutation in the FGFR 1 gene, we have now stopped routine analysis of this gene (table 1).

In general, all patients undergo vault expansion within their first year of life[18, 19], but surgery is scheduled earlier whenever papilledema is detected. According to our current protocol, initial vault expansion in patients with Apert or Crouzon/ Pfeiffer syndrome is occipital remodelling. This way we leave the fronto-orbital area untouched, which facilitates a monobloc at a later stage. In Muenke and Saethre-Chotzen syndrome, we choose to perform a fronto-orbital advancement, to expand the cranial volume and restore the appearance of their upper face. Given the very low risk on elevated ICP in Muenke syndrome and reports on the disappointing aesthetic results requiring additional surgery [20-22], we suggest to postponement of surgery for these patients (table 7).

A monobloc with distraction is chosen as primary surgery whenever patients suffer from severe OSA and/or severe exophthalmus.

Some patients with Crouzon/ Pfeiffer syndrome may not develop craniosynostosis at all or postnatal. These patients should be seen at an interval of 3 months within the first 2 years and vault surgery is indicated whenever elevated ICP is detected.

Despite early vault expansion, the prevalence of postoperative new onset elevated ICP remained high in our and other studies especially for patients with the Apert, Crouzon/ Pfeiffer and Saethre-Chotzen syndrome[18,23]. The craniofacial group from London has presented similar findings in patients with the Apert syndrome[2], in whom vault expansion was only performed once signs of elevated ICP were detected. Despite surgery at a later age, these patients experienced a similar risk on re-occurrence of elevated ICP at about 5 years of age. Apparently, expansion of the skull does prevent and treat elevated ICP for a few years. The second episode with elevated ICP about the age of 4-5 years is not related to a craniocerebral disproportion because most of the brain growth has already taken place. Other possible factors that can cause the second rise in ICP are OSA[4], hydrocephalus and venous hypertension.

To diagnose elevated ICP, we recommend yearly fundoscopy in Apert, Crouzon/ Pfeiffer and Saethre-Chotzen syndrome up to the age of 6 and for Muenke up to the age of 2. If papilledema is present, a computed tomography (CT) or magnetic resonance imaging (MRI) is indicated to exclude progressive ventricular dilatation.

In this study, we probably have an underestimation of the prevalence of OSA due to measuring only a selected group of patients with anamnestic breathing difficulties and due to the use of pulse-oximetry instead of polysomnography. Pulse-oximetry is a diagnostic test for straightforward OSA, but a negative pulse-oximetry cannot rule out OSA[13]. Taking into account these limitations, we found OSA in more than 25% of the suspected children with the Apert and Crouzon/ Pfeiffer syndrome and 5% in the children with

Saethre-Chotzen or Muenke syndrome. Because the high prevalence of OSA in Apert and Crouzon/ Pfeiffer syndrome, we advocate yearly screening for OSA with polysomnography. Children with Saethre-Chotzen or Muenke syndrome should be tested when difficulties in breathing during sleep are reported. Once the presence of OSA is confirmed, additional work-up is indicated including inspection of the size of the tonsils and endoscopy of the upper airways to determine the level(s) of obstruction. In a previous study we have demonstrated that OSA in syndromic craniosynostosis can be caused by airway obstruction at various levels and is therefore not always cured by a midface advancement (Bannink 2009, submitted). Treatment of OSA should be individualized for each specific patient, depending on severity of OSA, level of obstruction, contributing factors to OSA, age of the patient and additional functional or psychosocial problems. Treatment may consist of adjusting the sleeping position, nasal spray with steroids, respiratory support (for instance with nocturnal oxygen, continuous positive airway pressure (CPAP) or tracheal cannula), (adeno)tonsillectomy, maxillary or even mandibulary advancement or a monobloc procedure.

This retrospective study showed that impaired sight and hearing had a high prevalence in all syndromes and should therefore be an integral part of follow-up. Regular screening is therefore indicated.

Genetic analysis is necessary for counseling and screening on syndrome-specific anomalies and functional deficits. Follow-up by a multidisciplinary team is needed till the age of 18 years to guarantee the best possible outcome.

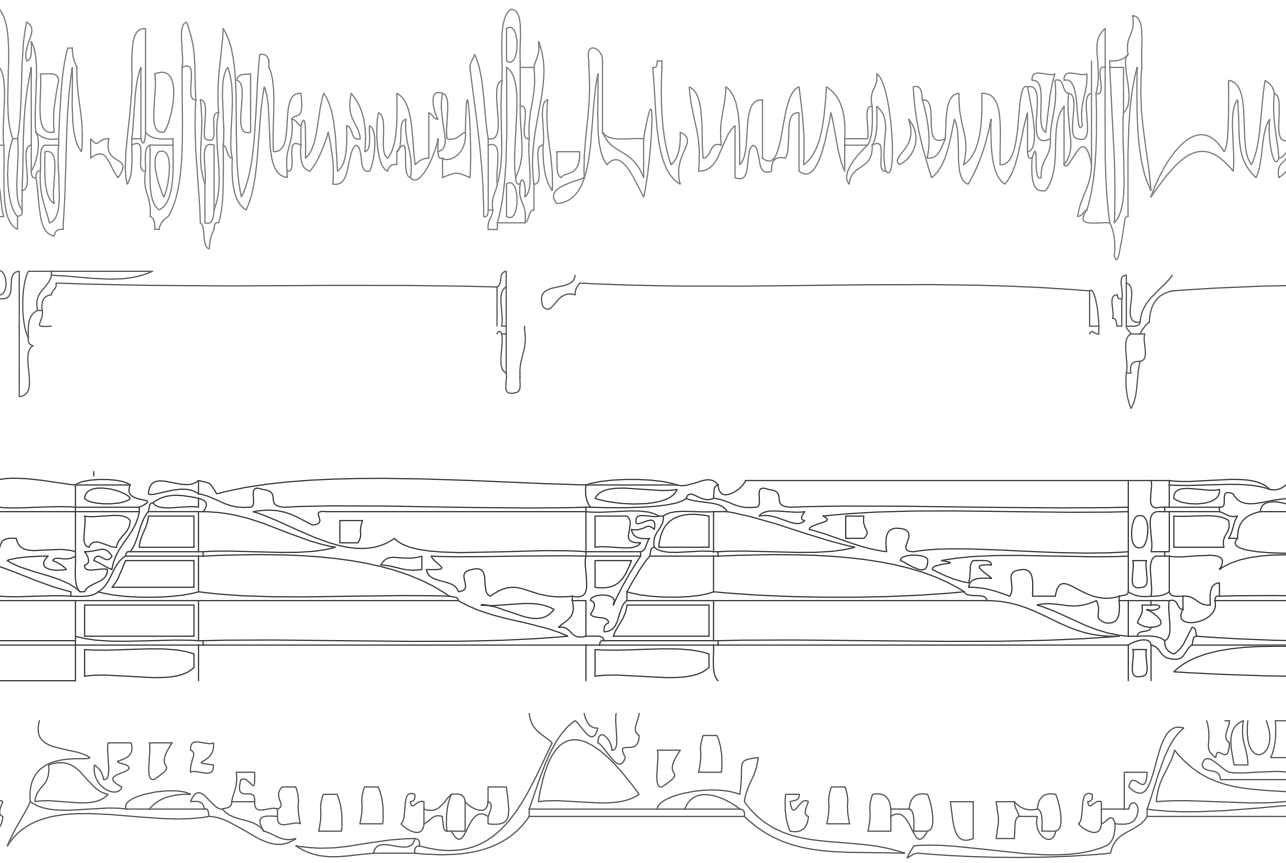
REFERENCES

1. Bannink N, Joosten KF, van Veelen ML, et al. Papilledema in patients with Apert, Crouzon, and Pfeiffer syndrome: prevalence, efficacy of treatment, and risk factors. J Craniofac Surg 2008: 19: 121-7.
2. Marucci DD, Dunaway DJ, Jones BM, Hayward RD. Raised intracranial pressure in Apert syndrome. Plast Reconstr Surg 2008: 122: 1162-8; discussion 69-70.
3. Gonsalez S, Hayward R, Jones B, Lane R. Upper airway obstruction and raised intracranial pressure in children with craniosynostosis. Eur Respir J 1997: 10: 367-75.
4. Hayward R, Gonsalez S. How low can you go? Intracranial pressure, cerebral perfusion pressure, and respiratory obstruction in children with complex craniosynostosis. J Neurosurg 2005: 102: 16-22.
5. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 2004: 15: 670-4.
6. Hertle RW, Quinn GE, Minguini N, Katowitz JA. Visual loss in patients with craniofacial synostosis. J Pediatr Ophthalmol Strabismus 1991: 28: 344-9.
7. Tay T, Martin F, Rowe N, et al. Prevalence and causes of visual impairment in craniosynostotic syndromes. Clin Experiment Ophthalmol 2006: 34: 434-40.
8. Jadico SK, Huebner A, McDonald-McGinn DM, et al. Ocular phenotype correlations in patients with TWIST versus FGFR3 genetic mutations. J Aapos 2006: 10: 435-44.
9. Church MW, Parent-Jenkins L, Rozzelle AA, et al. Auditory brainstem response abnormalities and hearing loss in children with craniosynostosis. Pediatrics 2007: 119: e1351-60.
10. Rajenderkumar D, Bamiou DE, Sirimanna T. Audiological profile in Apert syndrome. Arch Dis Child 2005: 90: 592-3.
11. Tuite GF, Chong WK, Evanson J, et al. The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. Neurosurgery 1996: 38: 272-8.
12. Wiegand C, Richards P. Measurement of intracranial pressure in children: a critical review of current methods. Dev Med Child Neurol 2007: 49: 935-41.
13. Brouillette RT, Morielli A, Leimanis A, et al. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000: 105: 405-12.
14. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995: 127: 905-12.
15. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992: 146: 1235-9.
16. Nout E, Wolvius EB, van Adrichem LN, et al. Complications in maxillary distraction using the RED II device: a retrospective analysis of 21 patients. Int J Oral Maxillofac Surg 2006: 35: 897-902.
17. Bartels MC, Vaandrager JM, de Jong TH, Simonsz HJ. Visual loss in syndromic craniosynostosis with papilledema but without other symptoms of intracranial hypertension. J Craniofac Surg 2004: 15: 1019-22; discussion 23-4.
18. Renier D, Lajeunie E, Arnaud E, Marchac D. Management of craniosynostoses. Childs Nerv Syst 2000: 16: 645-58.
19. Mathijssen IM, Arnaud E. Benchmarking for craniosynostosis. J Craniofac Surg 2007: 18: 436-42.
20. Becker DB, Fundakowski CE, Govier DP, et al. Long-term osseous morphologic outcome of surgically treated unilateral coronal craniosynostosis. Plast Reconstr Surg 2006: 117: 929-35.
21. Honnebier MB, Cabiling DS, Hetlinger M, et al. The natural history of patients treated for FGFR3-associated (Muenke-type) craniosynostosis. Plast Reconstr Surg 2008: 121: 919-31.

22. McCarthy JG, Glasberg SB, Cutting CB, et al. Twenty-year experience with early surgery for craniosynostosis: I. Isolated craniofacial synostosis--results and unsolved problems. Plast Reconstr Surg 1995: 96: 272-83.
23. Kress W, Schropp C, Lieb G, et al. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet 2006: 14: 39-48.

Part IV

Quality of life and behavior






Chapter 7

Health-related quality of life in children and adolescents with syndromic craniosynostosis

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ABSTRACT

Objective

Syndromic craniosynostosis is a congenital disorder characterized by premature fusion of calvarial sutures combined with other anomalies. The facial appearance is different and patients may show physical impairment, mental or developmental disabilities, elevated intracranial pressure and obstructive sleep apnea. The impact of this condition on daily functioning has not been studied before. The aim of this study is to assess the health-related quality of life in children and adolescents with syndromic or complex craniosynostosis and to determine the impact of these syndromes on parents.

Methods

A prospective study was performed in 111 children. Health-related quality of life was measured by international standardised quality of life questionnaires, the Infant Toddler Quality of Life Questionnaire (ITQoL), Child Health Questionnaire Parental Form 50 (CHQ-PF50), Child Health Questionnaire Child Form 87 (CHQ-CF87) and the Short Form Health Survey (SF-36). For comparison, we used Dutch population norms of health-related quality-of-life-scores.

Results

Parents' scores for patients with syndromic or complex craniosynostosis were significant lower than those for the norm population. Apert syndrome had the largest impact on the different domains. Scores on the CHQ-PF50 scales for 'physical functioning', 'parental impact emotional' and 'family activities' for these patients were significantly lower than scores for patients with other syndromes, possibly due to the complexity of the syndrome, which includes complex syndactyly, cognitive impairment and behavior problems. Parents reported a reduced health-related quality of life for themselves, mostly psychosocial with clearly significantly lower general health perceptions.

Conclusion

Syndromic craniosynostosis has a large impact on the health-related quality of life of these children and their parents, both physical and psychosocial.

INTRODUCTION

Craniosynostosis, characterized by premature fusion of calvarial sutures, is a congenital anomaly that occurs in 1 in 2500 births. In about 40% of cases, craniosynostosis is part of a syndrome, such as Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome[1]. Fusion of two cranial sutures or more without a known fibroblast growth factor receptor (FGFR) 1, 2, and 3, TWIST, or ephrin-B1 (EFNB1) mutation[1-3] is defined as complex craniosynostosis.

Patients are at risk of elevated intracranial pressure (ICP), obstructive sleep apnea, hearing and visual disorders, and delayed motor and language development[4]. All these could affect the daily life of these patients and of their parents; however the impact has not been studied so far.

The facial appearance of children with syndromic or complex craniosynostosis is clearly different and they may show physical, mental or developmental disabilities. This study aimed at assessing the health-related quality of life in children with syndromic or complex craniosynostosis and additionally at determining the impact of these syndromes on the daily functioning of their parents.

METHODS

Study population

A prospective study was performed at the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. All patients between 2 and 18 years with syndromic or complex craniosynostosis registered at the Dutch Craniofacial Center were invited between January 2007 and September 2008 to participate, along with their parents.

Health-related quality of life questionnaires

Health-related quality of life of the past 4 weeks was measured with international standardized quality of life questionnaires. For children between the ages of 2 and 4 years, the parents completed the Infant Toddler Quality of Life (ITQoL)[5], and for children between 4 and 18 years the Child Health Questionnaire Parental Form 50 (CHQ-PF50)[6] was used. Children aged between 12 and 18 years completed the Child Health Questionnaire Child Form 87 (CHQ-CF87)[7] themselves. Parents also completed a questionnaire on their own health, the Short-Form Health Survey (SF-36)[8] (see appendices 1-3).

Item scores per scale were summed up and transformed into a 0-100 score; the lower the score, the poorer the subjective health status. For the CHQ-PF50, a 'physical summary score' and 'psychosocial summary score' were calculated; for the SF-36, a 'physical component summary score' and 'mental component summary score' were calculated by

the sum of all scales except 'change in health', 'family activity' and 'family cohesion' based on an exploratory factor-analytic model[9]. The 'change in health' scale differs from the other scales in that it measures change over the past year. A score of 50 indicates no change and a score of 100 maximal improvement. All questions were short and closed with responses on Likert-scales. They were phrased to avoid difficult words where possible. The confidentiality of the answers was guaranteed.

Data of the research group were compared with Dutch healthy population norms of health-related quality-of-life-scores[5, 7, 8]. Scores for patients with the different syndromes were also compared with the norms and between the syndromes.

Potential predictive factors on health-related quality of life

We compared scores for parents with and without the same craniosynostosis syndrome as their child to evaluate how suffering from syndromic craniosynostosis themselves would effect reporting on their children.

Furthermore, we determined the effect of obstructive sleep apnea (OSA) on health-related quality of life. OSA was detected through a nocturnal ambulatory sleep study and was defined as an obstructive apnea hypopnea index ≥ 1 (N. Bannink et al., unpublished data, 2009).

Elevated intracranial pressure may have impact on health-related quality of life. It is detected through fundoscopy, which reveals papilledema in those cases.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 for Windows (SPSS, Chicago, IL, USA) and with GraphPad Prism 4.0 (GraphPad Prism Inc., CA, USA). The mean values of the different domains with standard deviation were calculated. The independent t-test was used to compare the children's and parents' quality of life with a sample of the Dutch population[5, 7]. The groups were large enough to use this test. Because of the small numbers of patients in the syndromic subgroups, Z-scores were calculated and compared in an analysis of variance (ANOVA) procedure.

Significant differences were defined as a p-value ≤ 0.05. All quality-of-life domains were expressed as mean and standard deviation. Pooled effect size of the difference between study population and norm population was calculated for each domain, which is measured by the difference between norm scores and patient scores divided by the pooled standard deviation[10].

To analyze the effects of OSA and ICP on each domain, multivariate analysis was performed with age, sex, diagnosis, OSA and papilledema as independent variables.

RESULTS

Study population

A total of 136 patients with syndromic or complex craniosynostosis were approached, and 117 (86%) children and their parents gave informed consent. Of those, 111 (95%) returned the questionnaires; that is, 23 patients returned the ITQoL and 88 patients the CHQ-PF50. Twenty-nine of the 32 patients between 12 and 18 years completed the CHQ-CF87. The three other patients were unable to complete due to low mental capacity. One parent returned the CHQ-PF50 without answering all questions; the analysis therefore included 87 instead of 88 questionnaires.

All 110 parents (74% mothers) completed the SF-36. Their median age was 39 (23-61) years. As many as 85% of the mothers and 84% of the fathers were born in the Netherlands. The educational level of 6% was elementary school, of 72% secondary education and of 22% higher education or university.

The study group consisted of 53 boys (48%) and 57 girls. Eighteen patients had Apert syndrome, 26 Crouzon, 17 Muenke, 20 Saethre-Chotzen syndrome, and 29 had complex craniosynostosis. Their median age was 7 (2-18) years. A total of 95% was born in the Netherlands.

Health-related consequences in children with syndromic or complex craniosynostosis below 4 years of age

The mean ITQol scores of the study population in comparison with the norm population scores are shown in table 1. Children under the age of 4 years were assigned significantly lower scores on the domains such as 'physical functioning', 'growth and development', 'general health perceptions' and 'parental impact: emotional and time'.

Health-related consequences in children with syndromic or complex craniosynostosis above 4 years of age

The mean CHQ-PF50 scores of the study population in comparison with the norm population are also shown in table 1. Children above 4 years of age were assigned lower scores on all domains except 'family cohesion' and 'change in health'.

Subgroup analysis of age groups 4-12 years (n = 55) and 12-18 years (n = 32) revealed no statistical differences in the scores in any domain. Families with a lower socioeconomic status reported a lower health-related quality of life of their children, but only on psychosocial domains.

Syndrome-specific health-related consequences in children with syndromic or complex craniosynostosis

Table 2 and figure 1 show the scores per syndrome in comparison with the norm population.

Table 1: The mean health-related quality-of-life scores with standard deviation of the ITQol and the CHQ-PF50 of our study population in comparison with the norm population

	Children with craniosynostosis	Norm population	p-value[1]	Effect size[2] d
ITQoL (2-4 years)	n = 23	n = 314		
Physical functioning (PF)	86.1 (23.8)	97.2 (9.8)	<0.0001**	0.61
Growth and development (GD)	79.9 (19.7)	86.5 (10.6)	0.0063**	0.42
Bodily pain (BP)	84.4 (18.0)	83.8 (16.8)	0.86	-0.04
Temperament and moods (TM)	78.7 (12.6)	77.2 (10.5)	0.51	-0.13
General behavior (GB)	75.3 (15.0)	72.8 (12.7)	0.36	-0.18
Getting along (GA)	72.2 (10.0)	71.4 (8.8)	0.69	-0.08
General health perceptions (GH)	67.8 (22.0)	79.0 (14.5)	0.0007**	0.60
Parental impact: Emotional (PE)	83.1 (19.7)	92.1 (10.5)	0.0002**	0.57
Parental impact: Time (PT)	84.9 (24.2)	93.0 (11.0)	0.0018**	0.43
Family activity (FA)	82.8 (22.5)	86.2 (13.5)	0.26	0.18
Family cohesion (FC)	82.8 (23.0)	75.3 (18.8)	0.06	-0.36
Change in health (CH)	61.4 (21.4)	56.1 (18.4)	0.20	-0.26
CHQ-PF50 (4-18 years)	n = 87	n = 353		
Physical functioning (PF)	90.6 (16.4)	99.1 (4.3)	<0.0001**	0.72
Role functioning: Emotional/behavior (REB)	87.2 (23.4)	97.9 (7.2)	<0.0001**	0.61
Role functioning: Physical (RP)	87.9 (27.2)	95.8 (15.6)	0.0004**	0.36
Bodily pain (BP)	78.8 (25.4)	85.7 (17.2)	0.0044**	0.31
General behavior (GB)	73.6 (15.5)	78.5 (13.1)	0.0046**	0.33
Mental health (MH)	74.9 (15.8)	81.4 (12.1)	<0.0001**	0.45
Self-esteem (SE)	73.6 (15.1)	79.2 (11.0)	0.0001**	0.42
General health perceptions (GH)	65.8 (23.9)	82.9 (13.4)	<0.0001**	0.87
Parental impact: Emotional (PE)	72.3 (23.7)	86.3 (15.2)	<0.0001**	0.69
Parental impact: Time (PT)	82.6 (26.7)	94.0 (13.0)	<0.0001**	0.54
Family activity (FA)	80.3 (21.9)	91.5 (11.9)	<0.0001**	0.61
Family cohesion (FC)	71.1 (19.7)	72.2 (19.4)	0.81	0.03
Change in health (CH)	56.9 (19.7)	56.1 (18.4)	0.58	-0.06
Physical summary (PHS)	50.9 (10.4)	56.4 (5.7)	<0.0001**	0.81
Psychosocial summary (PSS)	52.0 (9.6)	53.2 (6.4)	<0.0001**	0.43

** p-value ≤ 0.01

[1] 2-sided one-sample t-test of the scale scores between study population and norm population

[2] pooled effect size d measured the difference in mean scores divided by the standard deviations of the parental group, 0.2 ≤ d < 0.5 indicated a small effect, 0.5 ≤ d < 0.8 a moderate effect, d ≥ 0.8 a large effect, a negative effect size meant a higher score with regard to the norm group[10]

Apert syndrome

The three 2- to 4-year-olds with Apert syndrome scored significantly lower than the norm at 'physical functioning', 'growth and development', 'general health perceptions', 'parental impact: time', and 'family activity'. They showed a significant 'change in health'. The 15 children above 4 years of age were assigned significantly lower scores in each domain except 'family cohesion' and 'change in health'. Compared with children with other syndromes,

Table 2: The mean health-related quality-of-life scores with standard deviation of the ITQol and the CHQ-PF50 per syndrome

	Norm population	Apert	Crouzon/ Pfeiffer	Muenke	Saethre-Chotzen	Complex
ITQoL (2-4 years)	n = 314	n = 3	n = 8	n = 4	n = 2	n = 6
Physical functioning (PF)	97.2 (9.8)	68.9 (25.5)**	93.0 (16.2)**	98.3 (3.3)	100.0 (0.0)	76.7 (35.3)**
Growth and development (GD)	86.5 (10.6)	74.2 (26.3)**	85.5 (16.2)	96.3 (7.5)	87.5 (10.6)	73.3 (25.3)**
Bodily pain (BP)	83.8 (16.8)	83.3 (8.3)	89.4 (9.2)	91.7 (9.6)	95.8 (5.9)	83.3 (13.9)
Temperament and moods (TM)	77.2 (10.5)	78.7 (14.8)	83.1 (12.1)	89.2 (10.4)*	79.2 (3.9)	76.4 (2.9)
General behavior (GB)	72.8 (12.7)	75.7 (21.7)	81.0 (12.7)	84.7 (5.6)	73.8 (5.4)	71.6 (9.6)
Getting along (GA)	71.4 (8.8)	73.9 (20.4)	74.3 (6.9)	78.9 (5.4)	76.7 (2.4)	69.6 (7.3)
General health perceptions (GH)	79.0 (14.5)	59.0 (31.8)*	71.0 (19.5)	91.3 (1.5)	78.9 (16.2)	67.2 (25.8)
Parental impact: Emotional (PE)	92.1 (10.5)	80.9 (16.9)	83.8 (18.9)*	99.1 (1.8)	92.9 (10.1)	88.1 (16.4)
Parental impact: Time (PT)	93.0 (11.0)	74.6 (22.5)**	92.2 (10.7)	98.8 (2.4)	100.0 (0.0)	79.4 (37.3)**
Family activity (FA)	86.2 (13.5)	68.1 (24.4)*	89.0 (16.6)	100.0 (0.0)*	89.6 (8.8)	87.5 (17.1)
Family cohesion (FC)	75.3 (18.8)	86.7 (23.1)	87.3 (15.2)	96.3 (7.5)*	72.5 (17.7)	90.0 (7.7)
Change in health (CH)	56.1 (18.4)	91.7 (14.4)**	57.5 (12.1)	50.0 (0.0)	62.5 (17.7)	58.3 (25.8)
CHQ-PF50 (4-18 years)	n = 353	n = 15	n = 18	n = 13	n = 18	n = 23
Physical functioning (PF)	99.1 (4.3)	83.1 (14.3)**##	95.9 (10.4)**	92.3 (12.7)**	97.2 (5.5)	85.0 (24.4)**
Role functioning:						
Emotional/behavior (REB)	97.9 (7.2)	82.2 (22.9)**	86.4 (27.4)**	85.5 (21.5)**	95.7 (10.2)	85.5 (28.5)**
Role functioning: Physical (RP)	95.8 (15.6)	78.8 (35.9)**	89.8 (27.5)	88.5 (22.9)	94.4 (17.1)	86.9 (29.7)*
Bodily pain (BP)	85.7 (17.2)	75.3 (29.9)*	83.9 (23.8)	74.6 (31.3)*	73.3 (21.7)**	83.9 (22.9)
General behavior (GB)	78.5 (13.1)	64.9 (15.7)**	77.6 (15.7)	69.2 (5.5)*	74.4 (12.1)	77.3 (16.1)
Mental health (MH)	81.4 (12.1)	69.0 (13.4)**	77.5 (16.9)	74.5 (20.3)*	74.7 (14.5)*	76.9 (15.1)
Self-esteem (SE)	79.2 (11.0)	68.0 (12.9)**	71.9 (15.4)**	70.5 (18.4)**	74.1 (14.5)	79.9 (13.9)
General health perceptions (GH)	82.9 (13.4)	50.6 (29.0)**	74.7 (20.5)*	65.6 (26.6)**	68.0 (15.7)**	67.5 (23.8)**
Parental impact: Emotional (PE)	86.3 (15.2)	56.7 (22.3)**##	80.6 (16.4)	61.4 (29.2)**	80.1 (15.9)	75.0 (26.5)**
Parental impact: Time (PT)	94.0 (13.0)	72.6 (23.7)**	84.6 (27.0)**	84.3 (26.1)*	88.9 (22.9)	81.6 (31.4)**
Family activity (FA)	91.5 (11.9)	63.1 (23.2)**##	87.9 (19.2)	67.1 (18.5)**	70.3 (21.5)**	79.3 (24.0)**
Family cohesion (FC)	72.2 (19.4)	71.5 (20.1)	70.8 (16.1)	80.8 (20.5)	87.9 (14.0)**	73.9 (22.3)
Change in health (CH)	56.1 (18.4)	63.3 (22.9)	63.9 (21.4)	48.1 (18.9)	52.8 (8.1)	55.4 (21.3)
Physical summary (PHS)	56.4 (5.7)	46.6 (11.9)**	54.3 (9.3)	49.1(10.3)**	53.5 (4.7)*	49.6 (12.6)**
Psychosocial summary (PSS)	53.2 (6.4)	47.3 (9.2)**	52.7(9.7)	50.0 (12.9)	53.9 (7.1)	54.0 (9.4)

2-sided one-sample t-test of the scale scores between each syndrome and the norm population
* p-value ≤ 0.05
** p-value ≤ 0.01
2-sided one-sample t-test of the scale scores between each syndrome and the other syndromes
p-value ≤ 0.05
p-value ≤ 0.01

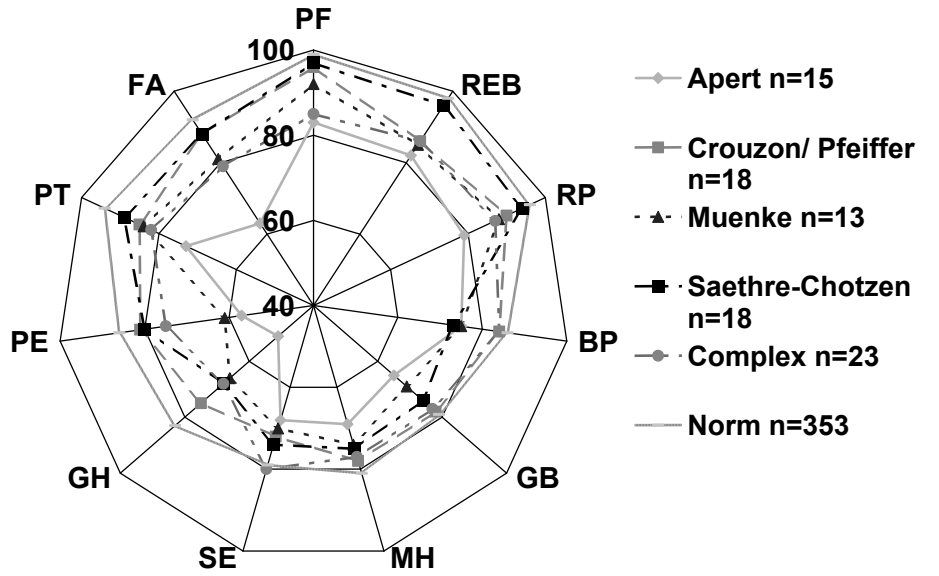

Figure 1: The mean health-related quality-of-life scores of the CHQ-PF50 per syndrome

those with Apert syndrome had significantly lower scores at 'physical functioning', 'parental impact: emotional' and 'family activity'. No correlation with age was found.

The nine children with a S252W mutation scored lower at each domain on the CHQ than the four children with a P253R mutation, and significantly lower at 'role functioning: emotional/ behavior' (mean 74.1 vs. 100.0, p = 0.01), 'mental health' (mean 62.8 vs. 85.0, p = 0.03) and 'self-esteem' (mean 61.9 vs. 80.2, p = 0.02).

Crouzon and Pfeiffer syndrome

The 2- to 4-year-olds with Crouzon or Pfeiffer syndrome scored significantly lower at 'physical functioning' and 'parental impact: emotional'. Their scores did not differ very much from the norm. Those above 4 years scored significantly lower at 'physical functioning', 'role functioning: emotional/ behavior', 'self-esteem', 'general health perceptions', and 'parental impact: time'.

Muenke syndrome

The under 4-year-olds with Muenke syndrome scored significantly higher at 'temperament and moods' and 'family activity and cohesion'. Scores for those above 4 years were almost the same as for children with Apert syndrome, apart from better scores on 'role functioning: physical' and 'parental impact: time'.

Saethre-Chotzen syndrome

The under 4-year-olds with Saethre-Chotzen syndrome scored according to the norm on all domains. The older children scored significantly lower on 'bodily pain', 'mental health', 'general health perceptions', and 'family activity' and significantly higher on 'family cohesion'.

Complex craniosynostosis

The under 4-year-olds with complex craniosynostosis scored significantly lower at 'physical functioning', 'growth and development' and 'parental impact: time'. Those above 4 years scored significantly lower at 'physical functioning', 'role functioning: emotional/behavior and physical', 'general health perceptions', 'parental impact: emotional and time' and 'family activity'.

Potential predictive factors on health-related quality of life

Hereditary craniosynostosis

Scores of the five parents of 2- to 4-year-olds who suffered from the same syndrome as their child were more in agreement with the norm on all quality-of-life domains of their children, except 'change in health', than parents without the syndrome (n=18). Significant differences were seen in the following domains: 'physical functioning' (mean 98.7 vs. 82.6, p = 0.02), 'growth and development' (mean 93.5 vs. 76.1, p = 0.02), 'bodily pain' (mean 96.7 vs. 81.0, p = 0.01), 'parental impact: emotional (mean 97.1 vs. 79.2, p = 0.004) and time' (mean 99.0 vs. 81.0, p = 0.01) and 'family activity' (mean 96.7 vs. 78.9, p = 0.01).

Parents of children above 4 years of age, 24 with the same syndrome and 63 without, showed no differences in this respect.

Obstructive sleep apnea

Thirty-seven of all children had OSA, of whom six suffered from Apert syndrome (16%), 12 from Crouzon syndrome (32%) and nine from complex craniosynostosis (24%). After multivariate analysis OSA was an independent predictor for the domain 'change in health' on the CHQ only.

Elevated ICP

Nineteen children had elevated ICP, of whom 13 suffered from Crouzon syndrome, one from Apert syndrome, three from Saethre-Chotzen syndrome and two from complex craniosynostosis. ICP was an independent predictor for the domains 'parental impact: emotional, 'family activity' and 'change in health' on the ITQol and 'physical functioning', 'general behavior', 'general health perceptions', 'parental impact: time' and 'family activity' on the CHQ.

Health-related consequences reported by patients themselves

The 29 children between 12 and 18 years of age who completed the CHQ-CF87 scored almost similar to the norm. They scored significantly lower at 'general health perceptions' (mean 68.3 vs. 75.0, p = 0.03) and 'family cohesion' (mean 66.4 vs. 76.0, p = 0.03). In comparison with their parents two domains were significantly different. Parents reported more limitations due to physical health ('role functioning: physical') and more behavioral problems ('general behavior') than their children.

Health-related consequences in parents

The results of the SF-36, completed by parents, are shown in table 3. They reported more limitations in work or other daily activities. The 'mental component summary' score was lower in comparison with the norm population. Parents of the under 4-year-olds reported significantly lower scores on 'physical functioning' (mean 55.0 vs. 95.8, p = 0.03) and 'role limitations due to physical functioning' (mean 45.0 vs. 78.5, p = 0.03) when they had the same syndrome as their child. Parents of children above the age of 4 years who suffered from the same syndrome scored similar to those without any syndrome.

DISCUSSION

In this large, selected group of children with only syndromic or complex craniosynostosis, health-related quality of life was significantly lower than in the norm population. For all syndromes, scores at 'general health perceptions' were significantly lower. Apert syndrome had the largest impact on the different domains. Two earlier studies reported quality of life of a small group of children with craniosynostosis. Warschausky et al.[11] compared 27 children with primary cleft lip and/ or palate and 28 children with other craniofacial diagnoses. There were only five children with Apert syndrome, Crouzon syndrome or complex craniosynostosis. The children with other craniofacial diagnoses perceived significantly more general health concerns; but no specific physical or mental health concerns were reported. Boltshauser et al.[12] evaluated behavior and quality of life in 30 children with isolated sagittal craniosynostosis. Parents reported behavior to be within the normal range and health-related quality of life was comparable with the norms, except for lower scores on positive emotional functioning.

For the two age groups, 2-4 years and 4-18 years, in which we used different questionnaires, we found comparably low scores in similar domains. There was no significant correlation between age and the results of questionnaires.

Subgroup analysis for the different syndromes showed that parents of 2- to 4-year-olds with Apert syndrome and complex craniosynostosis reported lower health-related quality of life for their children. The low scores on 'physical functioning' and 'growth and

Table 3: The mean health-related quality-of-life scores with standard deviation of the SF-36 of the parents

	Parents	Norm population	p-value[1]	Effect size[2] d
SF-36	n = 110	n = 314		
Physical functioning (PF)	86.5 (24.7)	87.0 (21.8)	0.21	0.13
Role functioning: Physical (RP)	74.2 (27.9)	81.6 (30.3)	0.03*	0.25
Social functioning (SF)	78.0 (24.4)	84.2 (22.5)	0.01**	0.27
Bodily pain (BP)	82.8 (26.3)	75.3 (22.9)	0.004**	-0.30
Mental health (MH)	74.0 (17.3)	76.2 (18.2)	0.28	0.12
Role functioning: Emotional (RE)	76.6 (22.9)	85.5 (39.9)	0.03*	0.27
General health perceptions (GH)	59.9 (21.8)	73.6 (29.6)	<0.0001**	0.53
Physical component summary (PCS)	50.3 (7.8)	50.3 (8.2)	0.26	0.03
Mental component summary (MCS)	48.0 (6.9)	51.3 (10.3)	0.01**	0.35

* p-value ≤ 0.05

** p-value ≤ 0.01

[1] 2-sided one-sample t-test of the scale scores between parents and the norm population

[2] pooled effect size d measured the difference in mean scores divided by the standard deviations of the parental group, 0.2 ≤ d < 0.5 indicated a small effect, 0.5 ≤ d < 0.8 a moderate effect, d ≥ 0.8 a large effect, a negative effect size meant a higher score with regard to the norm group[10]

development' might be explained by the higher complexity of these conditions than in the other syndromes. Whereas no scores on comparable domains differed between the two age groups and were all significantly lower than the norm, the score on the domain 'change in health' did not significantly differ from the norm in the older age group. A likely explanation is improved function of the hand after surgical correction of the complex syndactyly in the younger age group.

Scores for the older children with Apert syndrome or Muenke syndrome differed most significantly from the norms, with significantly higher scores in 11 out of the 13 domains and 10 out of the 13 domains, respectively. This might be because children with Apert syndrome are more prone to mental retardation and behavioral problems, such as autism. Muenke syndrome was always considered a mild type of syndromic craniosynostosis, given the low risk of elevated ICP or OSA; however, in the present study, children with this syndrome showed many problems on physical and emotional domains, possibly related to headache and behavior problems. Furthermore, we found a relatively low impact on health-related quality of life for patients with Crouzon or Pfeiffer syndrome, despite their distinct facial features. They showed better intelligence and motor development than children with the other syndromes and seemed to have fewer behavioral problems. On the other hand, they have the highest risk to develop craniosynostosis-related problems such as elevated ICP, OSA and tonsillar herniation[13, 14]. These findings support the assumption that behavioral disturbances and lowered mental capacities in Apert and Muenke syndrome are inborn and not a consequence of elevated ICP. In the group with complex

craniosynostosis, significant higher scores were found on the domains 'physical impairment' and 'high parental impact'. These children tend to have more associated problems such as developmental retardation. For all syndromes, scores on the domain 'general health perceptions' were significantly lower, probably due to the chronic character of the syndromes and the uncertainty about future developments.

Scores for children with Apert syndrome were also much lower than those for children with other syndromes. The children with a S252W mutation had a lower health-related quality of life. These children had more severe skull and facial abnormalities than children with a P253R mutation, who are characterized by more severe syndactyly. Possibly mental retardation and behavior problems were important factors for the lower scores.

Parents who suffered from the same syndrome as their child reported better scores than their children at all domains. Perhaps they recognize their own character in their child and consider this to be normal. However, denial of the problems seen in their own child might be an explanation as well.

In multivariate analysis, OSA was the only independent predictor for the domain 'change in health', possibly associated with its treatment. Furthermore, elevated ICP was an independent predictor for lower scores on several domains. This might be explained by the fact that this condition could result in behavioral changes that influence scores. Further, once it is detected, extra hospital visits are necessary, which may cause more parental concerns.

Interestingly, parents of children aged 12-18 years reported more problems in different domains than their children. Children seem to cope with the disabilities, minimizing concerns about functioning and health[15]. Parents may have been influenced by their own mental health and the concerns about the syndrome of their child. Therefore, it is important to collect information from both to get an impression about the health-related quality of life because they may have different views and consequences for support are different[15, 16].

Parents themselves also scored their quality of life lower at different domains, mainly psychosocial. Their child's condition seems to have a major impact. There was a difference on physical domains between parents suffering from syndromic craniosynostosis and those without, but only if their child was below 4 years. Treatment is most intense in the first years due to vault expansion and requires very regular visits to the outpatient clinic. This might influence the physical condition of the parents with syndrome.

A major strength of this study is the large study population of children with syndromic or complex craniosynostosis. The health-related quality-of-life questionnaires are standard measures used to assess the quality of life, but a limitation is the use of these questionnaires in children with syndromic or complex craniosynostosis without validation in this specific population. Another possible limitation could be that outcomes for the two age groups are not completely comparable because different questionnaires were used.

In conclusion, syndromic craniosynostosis has an important impact on health-related quality of life of these children and their families. The impact is not only most obvious for children with Apert syndrome, but also clear-cut for children with Muenke, Crouzon, Pfeiffer, or Saethre-Chotzen syndrome and complex craniosynostosis. The impact on daily functioning does not differ much at the different ages between 2 and 18 years. Parents themselves also experienced restrictions in quality of life.

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APPENDIX 1

ITQoL scales, items per scale and score interpretation[a]

The ITQoL consists of 103 items with 4, 5 or 6 response options. The items are arranged into 10 multi-item scales and 2 single-item scales: 'physical functioning', growth and development', 'bodily pain', 'temperaments and moods', 'general behavior', 'getting along', 'general health perceptions', 'parental impact: emotional', 'parental impact: time', 'family activity', 'family cohesion' and 'change in health'[5].

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	10	Child is limited a lot in performing physical activities such as eating, sleeping, grasping, and playing due to health problems	Child performs all types of physical activities such as eating, sleeping, grasping, and playing without limitations due to health problems
Growth and development (GD)	10	Parent is very dissatisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament	Parent is very satisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament
Bodily pain (BP)	3	Child has extremely severe, frequent and limiting bodily pain/discomfort	Child has no pain or limitations due to pain/discomfort
Temperament and moods (TM)	18	Child has very often certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness	Child never has certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness
General behavior (GB)	13	Parent believes child's behavior is poor and likely to get worse	Parent believes child's behavior is excellent and will continue to be so
Getting along (GA)	15	Child very often exhibits behavior problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behaviors, such as ability to cooperate, appear sorry, and adjustment to new situations are seldom shown	Child never exhibits behavior problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behaviors, such as ability to cooperate, appear sorry, and adjustment to new situations are frequently shown
General health perceptions (GH)	12	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact: Emotional (PE)	7	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development	Parent does not experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development
Parental impact: Time (PT)	7	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development	Parent does not experience limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development
Family activity (FA)	6	The child's health and/or growth and development very often limits and interrupts family activity or is a source of family tension	The child's health and/or growth and development never limits and interrupts family activities or is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated 'poor'	Family's ability to get along is rated 'excellent'
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

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APPENDIX 2

CHQ-PF50 scales, items per scale and score interpretation[a]

The CHQ-PF50 consists of 50 items with 4, 5 or 6 response options. The items are arranged into 11 multi-item scales and 2 single-item scales: 'physical functioning', 'role functioning: emotional/ behavior', 'role functioning: physical', 'bodily pain', 'general behavior', 'mental health', 'self-esteem', 'general health perceptions', 'parental impact: emotional', 'parental impact: time', 'family activity', 'family cohesion' and 'change in health'[6].

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	6	Child is limited a lot in performing all physical activities, including self-care due to health	Child performs all types of physical activities, including the most vigorous, without limitations due to health
Role functioning: Emotional/behavior (REB)	3	Child is limited a lot in schoolwork or activities with friends as a result of emotional or behavior problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavior problems
Role functioning: Physical (RF)	2	Child is limited a lot in schoolwork or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain (BP)	2	Child has extremely severe, frequent and limiting bodily pain	Child has no pain or limitations due to pain
General behavior (GB)	6	Child very often exhibits aggressive, immature, delinquent behavior	Child never exhibits aggressive, immature, delinquent behavior
Mental health (MH)	5	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self-esteem (SE)	6	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall
General health perceptions (GH)	6	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact: Emotional (PE)	3	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health	Parent does not experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health
Parental impact: Time (PT)	3	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health	Parent does not experience limitations in time available for personal needs due to child's physical and/or psychosocial health
Family activity (FA)	6	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits and interrupts family activities nor is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated 'poor'	Family's ability to get along is rated 'excellent'
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

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The CHQ-CF87 consists of 87 items with 4, 5 or 6 response options. The items are arranged into 10 multi-item scales and 2 single-item scales: 'physical functioning', 'role functioning: emotional', 'role functioning: behavior', 'role functioning: physical', 'bodily pain', 'general behavior', 'mental health', 'self esteem', 'general health perceptions', 'family activity', 'family cohesion' and 'change in health'[7].

APPENDIX 3

SF-36: scales, items per scale and score interpretation

The SF-36 consists of 36 items with 3, 4, 5 or 6 response options. The items are arranged into 7 multi-item scales: 'physical functioning', 'role limitations due to physical functioning', 'social functioning', 'bodily pain', 'mental health', 'role limitations emotional' and 'general health perceptions'[8, 17].

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	10	Very limited in performing all physical activities, including bathing or dressing due to health	Performs all types of physical activities, including the most vigorous, without limitations due to health
Role functioning: Physical (RF)	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Social functioning (SF)	2	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference with normal social activities due to physical or emotional problems
Bodily pain (BP)	2	Very severe and extremely limiting bodily pain	No pain or limitations due to pain
Mental health (MH)	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Role functioning: Emotional (RE)	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
General health perceptions (GH)	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent

REFERENCES

1. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet 2006;14:289-298.
2. Kress W, Schropp C, Lieb G, et al. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet 2006;14:39-48.
3. Twigg SR, Matsumoto K, Kidd AM, et al. The origin of EFNB1 mutations in craniofrontonasal syndrome: frequent somatic mosaicism and explanation of the paucity of carrier males. American journal of human genetics 2006;78:999-1010.
4. de Jong T, Bannink N, Bredero-Boelhouwer HH, et al. Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. J Plast Reconstr Aesthet Surg 2009
5. Raat H, Landgraf JM, Oostenbrink R, et al. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res 2007;16:445-460.
6. Landgraf JM, Maunsell E, Speechley KN, et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Qual Life Res 1998;7:433-445.
7. Raat H, Landgraf JM, Bonsel GJ, et al. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002;11:575-581.
8. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of clinical epidemiology 1998;51:1055-1068.
9. Anagnostopoulos F, Niakas D, Tountas Y. Comparison between exploratory factor-analytic and SEM-based approaches to constructing SF-36 summary scores. Qual Life Res 2009;18:53-63.
10. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care 2003;41:582-592.
11. Warschausky S, Kay JB, Buchman S, et al. Health-related quality of life in children with craniofacial anomalies. Plastic and reconstructive surgery 2002;110:409-414; discussion 415-406.
12. Boltshauser E, Ludwig S, Dietrich F, et al. Sagittal craniosynostosis: cognitive development, behavior, and quality of life in unoperated children. Neuropediatrics 2003;34:293-300.
13. Cinalli G, Spennato P, Sainte-Rose C, et al. Chiari malformation in craniosynostosis. Childs Nerv Syst 2005;21:889-901.
14. Gonsalez S, Hayward R, Jones B, et al. Upper airway obstruction and raised intracranial pressure in children with craniosynostosis. Eur Respir J 1997;10:367-375.
15. Stancin T, Drotar D, Taylor HG, et al. Health-related quality of life of children and adolescents after traumatic brain injury. Pediatrics 2002;109:E34.
16. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Archives of disease in childhood 2001;84:205-211.
17. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992;30:473-483.





Chapter 8

Reliability and validity of the obstructive sleep apnea (OSA)-18 survey in healthy children and children with syndromic or complex craniosynostosis

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ABSTRACT

Objective

Obstructive sleep apnea (OSA) affects the child's quality of life. Rosenfeld developed a quality of life questionnaire, the OSA-18, on obstructive sleep apnea for children with OSA not caused by specific craniofacial syndromes. With regard to the use of the OSA-18 in children with syndromic and complex craniosynostosis, we assessed the internal consistency, test-retest reliability and discriminative validity of the OSA-18 in these children; we also applied the OSA-18 in healthy children to obtain reference values.

Methods

The OSA-18 was translated into Dutch using the procedure of multiple forward and backward-translations. Test-retest reliability and internal consistency were examined. In a prospective study, the craniosynostosis patients underwent an ambulatory polysomnography to diagnose OSA. The ability of the OSA-18 to discriminate between subgroups of patients with or without OSA was evaluated. We compared OSA-18 scores of children with syndromic or complex craniosynostosis with scores in healthy children.

Results

The Crohnbach's alpha was ≥ 0.70 for the total OSA-18 score and for most of the domains in both the craniosynostosis and general population. In the craniosynostosis group the test-retest intraclass correlation coefficients were ≥ 0.70, except for the domain 'physical suffering' with 0.69. The discriminative validity of the domains 'sleep disturbance', 'physical suffering', 'caregiver concerns' and total OSA-18 score was significant between the general and craniosynostosis population.

Conclusion

This study supports the reliability and validity of the OSA-18 in children with syndromic or complex craniosynostosis.

INTRODUCTION

Obstructive sleep apnea (OSA) is a clinical syndrome characterized by difficulty in breathing, snoring and apneas during sleep due to a partial or complete obstruction of the upper airway. The gold standard for diagnosing OSA is polysomnography[1]. Leaving OSA untreated may result in major physical and functional impairment due to the disturbed sleep patterns, for instance failure to thrive, recurrent infections, feeding difficulties, disturbed cognitive functions (attention deficit, impaired concentration and memory), delay of development, cor pulmonale and sudden death[2].

Obstructive sleep apnea affects the child's quality of life, because of fatigue during the day, disturbed cognitive functions and the implications of treatment. Sleep problems, physical symptoms related to adenotonsillar hypertrophy, behavioral aspects and fatigue or impaired concentration are domains of quality of life that are of particular relevance. R.M. Rosenfeld has developed a disease-specific quality of life questionnaire for healthy children with OSA due to adenotonsillar hypertrophy, the OSA-18[3]. It consists of 18 age-independent items grouped into five domains: 'sleep disturbance', 'physical suffering', 'emotional distress', 'daytime problems' and 'caregiver concerns'. The OSA-18 has been shown to be reliable and valid to measure the impact of OSA in American children with a history of snoring and disrupted sleep for three months or longer, who were referred for polysomnography and who had enlarged tonsils or adenoids.

In previous studies of OSA and quality of life only children without specific syndromes were studied; children with OSA based on underlying syndromes, such as craniofacial abnormalities, were excluded. This study aims at evaluating the OSA-18 in children with syndromic and complex craniosynostosis. These patients have a 40% risk for OSA[4,5,6] mainly during the first six years of life due to midface hypoplasia and collapse of the pharynx, but other factors such as adenotonsillar hypertrophy and mandibular hypoplasia may be involved as well[7,6].

In this study we assessed the internal consistency and the test-retest reliability and the discriminative validity of the OSA-18 in children with syndromic or complex craniosynostosis. We compared OSA-18 scores of these children with scores in healthy children.

METHODS

Before the start of this study, authorisation was granted by the medical ethics committee (MEC-2005-273) of the Erasmus Medical Center.

Craniosynostosis population

A prospective study was carried out in the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital in Rotterdam. Patients with syndromic (genetically confirmed) or complex craniosynostosis registered at the Dutch Craniofacial Center were invited to participate in the study between January 2007 and March 2009. Syndromic craniosynostosis included Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome and is characterized by the premature fusion of calvarial sutures with additional congenital malformations[8]. Fusion of two cranial sutures or more without a known FGFR (fibroblast growth factor receptor) 1, 2, 3 or TWIST gene mutation[8, 9] was defined as complex craniosynostosis.

General population

A convenience sample of parents of healthy children was approached at day-care centers, primary and secondary schools and sport clubs in Rotterdam, Rijswijk and Leiden in the Netherlands.

OSA-18 survey

First, we translated the OSA-18 to the Dutch language with permission of R.M. Rosenfeld using a procedure with multiple forward and back-translations[10]. Three independent persons have translated the survey from English to Dutch and thereafter we asked two native speakers for back-translation to English as check.

All parents were asked to complete the survey, the parent form. They decided whether the father or the mother should do that. After several months the same survey was sent to a random sample of parents to be completed by the same person to assess the test-retest reliability.

The total OSA-18 score, subdivided in 5 domains, is the sum of scores for all 18 items with a score ranging from 18 to 126. The domains 'sleep disturbance', 'physical suffering', and 'caregiver concerns' consisted each of four items and the domains 'emotional distress' and 'daytime problems' of three. Each item can be answered with 1 (never) to 7 (always). Additionally it provided a 10-point visual analogous scale with specific semantic anchors (appendix 1).

Additionally children between 12 and 18 years completed a child form of the questionnaire themselves. Six items of the OSA-18 were excluded in the self-report child form, the OSA-12. In the domain 'sleep disturbance' children cannot report pauses in their breathing and gasping sounds during sleep by themselves and therefore the domain 'sleep disturbance' consisted two items. The domain 'caregiver concerns', which consists 4 items, cannot be used as well in the child form. The total OSA-12 score ranged from 12 to 84.

An additional questionnaire was given regarding items on socio-demographic variables as age, sex, school performance and the presence of sickness, allergy, behavior problems,

adenotonsillectomy, use of medication and the presence of cough and use of nose drops, nasal or inhalation corticosteroids in the preceding four weeks. These items were needed to exclude OSA in the general population.

Polysomnography

The craniosynostosis population underwent a polysomnography to diagnose obstructive sleep apnea. Polysomnography was done ambulatory with Embletta Portable Diagnostic System and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland). Thoracic and abdominal movements, nasal flow, saturation, and pulse were monitored. The minimal total sleep time was 360 minutes. Obstructive apnea was defined as absence of airflow (measured by a nasal cannula) or out-of-phase movement of thorax and abdomen (scored as X flow) and hypopnea as ≥ 50% reduction in nasal flow signal amplitude or X flow signal amplitude, both for more than two breaths[1, 11, 12]. The X flow signal was the sum of the amplitudes of the thoracic and abdominal movements[11, 12] and was used when nasal airflow was insufficient. Mixed apnea was defined as a type of obstructive apnea with a central component that mostly preceded the obstructive pattern, for more than two breaths. Central apneas were not included in this study. Desaturation was defined as ≥ 4% decrease with respect to the baseline value.

The severity of OSA was expressed in an obstructive apnea hypopnea index (OAHI), the hourly number of obstructive and mixed apneas in combination with the hourly number of hypopneas followed by desaturation. A score < 1 is considered to be normal, between 1-5 is defined as mild OSA, between 6 and 25 as moderate OSA, and > 25 as severe OSA[13, 14].

Analysis

Reliability

Reliability refers to the stability or reproducibility of survey results. Internal consistency was examined per domain and for the total OSA-18 score in the craniosynostosis and general population. The Crohnbach's alpha was used to calculate this internal consistency and a value ≥ 0.70 was considered as adequate both in children with syndromic or complex craniosynostosis, as in healthy children.

The test-retest reliability in the sample of the craniosynostosis population was evaluated by applying the paired t-test of the means at the group level and by intraclass correlation coefficients (ICC) at the individual level. ICCs ≥ 0.70 were considered as adequate.

Validity

Validity is the degree to which the survey measures what it purports to measure[3]. We tested the discriminative validity by comparing domains and the total OSA-18 scores in the general and in the craniosynostosis population. We hypothesized that the craniosynostosis

population reported higher mean scores, i.e. a lower quality on life due to OSA than the general population. In addition, in the population children with syndromic or complex craniosynostosis we evaluated the ability of the OSA-18 to discriminate between patients with and without OSA; we hypothesized that OSA patients have higher mean scores than the non OSA patients.

All analyses were performed with SPSS 16.0 for Windows (SPSS, Chicago, IL). The numbers were given in median and range. All domains were expressed as mean and standard deviation. The independent t-test was used to compare the craniosynostosis with the general population. The groups were large enough to use this test. Because of the small numbers of patients in the OSA subgroups Z-scores were calculated and compared in an ANOVA procedure.

Significant differences were defined as a p-value ≤ 0.05. Pooled effect size of the difference between craniosynostosis and general population was calculated for each domain. Pooled effect size is measured by the difference between norm scores and patient scores divided by the pooled standard deviation[15].

RESULTS

Craniosynostosis population

In total 163 patients with syndromic or complex craniosynostosis and their parents were approached, of whom 141 (87%) children and their parents gave informed consent for this research project. Of them 119 (73%) returned the questionnaires and underwent a polysomnography. Of these 119 parents 34 had children between 12 and 18 years of age and 29 of them completed the child form themselves and underwent a polysomnography. The others were unable to do so, due to low mental capacity.

The characteristics of the craniosynostosis population are shown in table 1. The median age of the parents, who completed the questionnaires, was 39 (23-61) years and 88% of them were born in the Netherlands. A sample consisting of 64 out of the 72 (89%) parents, who received the OSA-18 twice, completed the survey as retest after a mean time of 6.3 (sd 3.1) months (range 1-16 months). The median age of the children, who completed the child form, was 14 (12-18) years.

General population

After distribution of 1500 questionnaires, parents of 459 healthy children returned the questionnaire, the parent form. The median age of the respondent, who completed the questionnaire, was 41 (17-55) years and 91% were born in the Netherlands. Of these 459 returned questionnaires children themselves completed also the child form in 162 cases

Table 1: Characteristics of the craniosynostosis and general population

		Craniosynostosis population n = 119	General population n = 459	p-value
Completed by				
Mother		104 (87%)	402 (87%)	ns
Father		15 (13%)	50 (11%)	
Other			7 (2%)	
Age respondent (years)	range	23-61	17-55	ns
	median	39	41	
Education respondent				
Low		7 (6%)	7 (1.5%)	0.00**
Middle		78 (65.5%)	251 (55%)	
High		31 (26%)	198 (43%)	
Unknown		3 (2.5%)	3 (0.5%)	
Age child (years)	range	2-18	2-18	0.04*
	median	8	9	
Sex child	boy	56 (47%)	239 (52%)	ns
	girl	63 (53%)	220 (48%)	
Syndrome/ sex (boy/ girl)				
Apert		19 (16%) (9/ 10)		
Crouzon/ Pfeiffer		31 (26%) (14/ 17)		
Muenke		18 (15%) (8/ 10)		
Saethre-Chotzen		21 (18%) (8/ 13)		
Complex craniosynostosis		30 (25%) (17/ 13)		
Obstructive sleep apnea child				
Non		75 (63%)		
Mild		37 (31%)		
Moderate		7 (6%)		

ns not significantly different

* p-value ≤ 0.05

** p-value ≤ 0.01

(median age 14 (12-18) years). The craniosynostosis and general population were comparable, shown in table 1. However, the educational level of the parents was lower in the craniosynososis population with regard to the general population (p = 0.00).

Obstructive sleep apnea

Based on the calculated obstructive apnea hypopnea index (OAHI) 44 patients (37%) were diagnosed as having obstructive sleep apnea; 37 mild with a mean OAHI of 2.3 (sd 1.1) and 7 moderate with a mean OAHI of 9.0 (sd 5.1) with a maximum index of 20. Severe OSA was not diagnosed in this craniosynostosis population at the moment of the study.

Internal consistency

With regard to parent-completed questionnaires, in the study and general population the Crohnbach's alpha for almost all domains and for the total OSA-18 score was ≥ 0.70. The

exceptions were the domains 'daytime problems' in the non OSA craniosynostosis group (0.63) and 'sleep disturbance' in the general (0.56) and craniosynostosis (0.62) population, as shown in table 2.

With regard to child-completed questionnaires, the Crohnbach's alpha for three domains and for the total OSA-12 score was ≥ 0.70, except for the domain 'sleep disturbance'. In the OSA subgroup (n = 7) the Crohnbach's alpha was < 0.70 for 'physical suffering', 'emotional distress' and the total OSA-12 score.

Test-retest reliability in the craniosynostosis population

With regard to parent-completed questionnaires in the craniosynostosis population the test-retest reliability was shown in table 3. The domains showed no statistically different mean scores between the test and retest. The intraclass correlations were ≥ 0.70, except the domain 'physical suffering' with 0.69. OSA treatment in the interim was only performed in two patients.

Table 2: Internal consistency in the craniosynostosis versus general population of the parent and child form

Parent form	Items n	General population Crohnbach's α	Craniosynostosis population Crohnbach's α Total group/	Non OSA/	OSA
		n = 459	n = 119	n = 75	n = 44
Sleep disturbance	4	0.56	0.62	0.73	0.83
Physical suffering	4	0.83	0.83	0.76	0.89
Emotional distress	3	0.81	0.86	0.79	0.92
Daytime problems	3	0.70	0.70	0.63	0.79
Caregiver concerns	4	0.77	0.91	0.88	0.94
Total OSA-18 score	18	0.85	0.89	0.84	0.95
Child form	Items n	General population Crohnbach's α	Craniosynostosis population Crohnbach's α Total group/	Non OSA/	OSA
		n = 162	n = 29	n = 22	n = 7
Sleep disturbance	2	0.25	0.58	0.67	0.29
Physical suffering	4	0.78	0.79	0.83	0.65
Emotional distress	3	0.74	0.76	0.78	0.65
Daytime problems	3	0.71	0.85	0.79	0.97
Total OSA-12 score	12	0.81	0.84	0.87	0.60

OSA obstructive sleep apnea

Table 3: Test-retest reliability of the parent form in a sample of the craniosynostosis population

Parent form	Test mean (sd) n = 64	Retest mean (sd) n = 64	p-value[1]	ICC
Sleep disturbance	9.90 (5.81)	9.08 (4.96)	0.49	0.93
Physical suffering	11.88 (5.77)	12.12 (5.66)	0.86	0.69
Emotional distress	6.67 (3.64)	7.49 (4.02)	0.97	0.82
Daytime problems	7.02 (3.61)	7.73 (3.58)	0.73	0.77
Caregiver concerns	7.98 (5.41)	7.92 (4.88)	0.94	0.71
Total OSA-18 score	42.71 (19.15)	43.51 (16.96)	0.56	0.82

sd standard deviation

ICC intraclass correlation coefficient

[1] 2-sided paired t-test of the mean between the test and retest, time between test and retest: mean 6.3 (3.1) months, range 1-16 months

Table 4: Discriminative validity in the craniosynostosis versus general population of the parent and child form

Parent form	General population mean (sd) n = 459	Craniosynostosis population mean (sd) n = 119	Cranio vs General p-value[1]	Cranio vs General (pooled) effect size[2] (d)
Sleep disturbance	5.8 (2.4)	8.9 (4.8)	0.000**	0.81
Physical suffering	8.1 (4.3)	11.1 (5.8)	0.000**	0.60
Emotional distress	6.2 (3.1)	6.5 (3.4)	0.35	0.10
Daytime problems	6.2 (3.1)	6.8 (3.5)	0.12	0.17
Caregiver concerns	5.2 (2.4)	7.0 (4.2)	0.000**	0.52
Total OSA-18 score	31.2 (10.4)	39.9 (16.7)	0.000**	0.63
Child form	**General population mean (sd) n = 162**	**Craniosynostosis population mean (sd) n = 29**	**Cranio vs General p-value[1]**	**Cranio vs General (pooled) effect size[2] (d)**
Sleep disturbance	3.7 (1.8)	5.6 (3.3)	0.006**	0.71
Physical suffering	9.0 (4.4)	9.9 (5.3)	0.37	0.19
Emotional distress	5.9 (3.4)	5.4 (2.9)	0.43	0.15
Daytime problems	7.7 (4.0)	7.7 (4.3)	0.99	0.00
Total OSA-12 score	26.4 (9.9)	28.4 (11.6)	0.39	0.19

sd standard deviation

** p-value ≤ 0.01

[1] 2-sided paired t-test of the means between the study population and the norm

[2] pooled effect size d measured the difference in mean scores divided by the standard deviations of the study group, 0.2 ≤ d < 0.5 indicated a small effect, 0.5 ≤ d < 0.8 a moderate effect, d ≥ 0.8 a large effect, a negative effect size meant a higher score with regard to the norm group[15]

Table 5: Discriminative validity of obstructive sleep apnea in the craniosynostosis population of the parent and child form

Parent form	Non OSA mean (sd) n = 75	Mild OSA mean (sd) n = 37	Moderate OSA mean (sd) n = 7	Mild vs Non OSA p-value[1]	Moderate vs Non OSA p-value[1]	Mild vs Non OSA (pooled) effect size[2]	Moderate vs Non OSA (pooled) effect size[2]
Sleep disturbance	8.1 (4.2)	9.1 (5.0)	15.0 (6.3)	0.34	0.03*	0.21	1.29
Physical suffering	10.6 (5.1)	10.9 (6.2)	17.7 (6.2)	0.80	0.02*	0.05	1.26
Emotional distress	6.3 (3.1)	6.7 (3.8)	8.5 (4.4)	0.72	0.28	0.07	0.57
Daytime problems	6.6 (3.3)	6.7 (3.6)	8.7 (4.9)	0.89	0.31	0.03	0.50
Caregiver concerns	6.6 (3.8)	7.5 (4.9)	8.2 (4.0)	0.35	0.40	0.20	0.39
Total OSA-18 score	38.0 (13.0)	41.0 (20.8)	55.0 (20.4)	0.45	0.10	0.17	0.99
Child form	**Non OSA mean (sd) n = 22**	**Mild OSA mean (sd) n = 5**	**Moderate OSA mean (sd) n = 2**	**Mild vs Non OSA p-value[1]**	**Moderate vs Non OSA p-value[1]**	**Mild vs Non OSA (pooled) effect size[2]**	**Moderate vs Non OSA (pooled) effect size[2]**
Sleep disturbance	5.2 (3.2)	4.8 (2.5)	11.0 (1.4)	0.73	0.04*	0.18	2.30
Physical suffering	10.0 (5.3)	10.2 (4.9)	9.5 (7.8)	0.90	0.96	0.07	0.05
Emotional distress	5.6 (3.1)	5.2 (1.6)	6.0 (4.2)	0.84	0.88	0.08	0.16
Daytime problems	7.7 (4.1)	7.2 (4.8)	11.5 (7.8)	0.90	0.60	0.07	0.65
Total OSA-12 score	28.4 (12.1)	25.8 (7.1)	38.0 (9.9)	0.62	0.37	0.23	0.89

OSA obstructive sleep apnea
sd standard deviation
* p-value ≤ 0.05
[1] 2-sided paired t-test of the means between the degrees of severity of OSA
[2] pooled effect size d measured the difference in mean scores divided by the standard deviations of the study group, 0.2 ≤ d < 0.5 indicated a small effect, 0.5 ≤ d < 0.8 a moderate effect, d ≥ 0.8 a large effect, a negative effect size meant a higher score with regard to the norm group[15]

Discriminative validity

With regard to parent-completed questionnaires the mean scores between the general and the craniosynostosis population were significantly different in the domains 'sleep disturbance', 'physical suffering', 'caregiver concerns' and total OSA-18 score with higher scores, i.e. lower quality of life, in the craniosynostosis population (table 4). The ability of the OSA-18 to discriminate between the degrees of severity of OSA was significant in the first two domains (table 5). Patients with moderate OSA (OAHI ≥ 5) discriminated

significantly from the children without OSA on the two domains 'sleep disturbance' and 'physical suffering'. The total OSA-18 score had a positive trend (p = 0.10) (table 5).

With regard to child-completed questionnaires, the mean scores in the general and the study population were significantly different in the domain 'sleep disturbance' (table 4). Children with moderate OSA (OAHI ≥ 5) discriminated significantly from the children without OSA on the domain 'sleep disturbance' (table 5).

DISCUSSION

Until now, the OSA-18 was used for healthy children with OSA due to adenotonsillar hypertrophy without specific syndromes. In this study norm scores of the general population were provided for clinical studies. We showed that the OSA-18 completed by parents is also reliable to measure the quality of life of children with syndromic or complex craniosynostosis and to measure the impact of obstructive sleep apnea on the health-related quality of life in the craniosynostosis population; the results supported the internal consistency and test-retest reliability. The results on the test and retest were very consistent; the dynamic character of obstructive sleep apnea did not influence the scores.

The OSA-18 domains 'sleep disturbance', 'physical suffering', 'caregiver concerns' and the total score discriminated significantly between children with syndromic or complex craniosynostosis and the general population independent of the presence of OSA whereas the domains 'emotional distress' and 'daytime problems' did not. Children with syndromic or complex craniosynostosis had more sleep related problems and physical symptoms due to the severe anatomical malformations of the nasal cavity resulting in nasal obstruction and to a higher prevalence of OSA in comparison with the general population. Caregiver concerns were probably related to having a child with a syndrome with the additional problems. For the child form the domain 'sleep disturbance' discriminated between the craniosynostosis and the general population. This difference is mainly based on the frequency of a good bit, most or all of the time (answers 5, 6 or 7 on item 1 of the OSA-18) loud snoring during the past 4 weeks: 26% in the craniosynostosis population (n = 29) versus 1% in the general population (n = 162).

In general, parents of children with syndromic craniosynostosis reported a lower quality of life compared to parents of children in the general population. But, with the use of the OSA-18 survey it was possible to discriminate between the presence of moderate OSA and mild or no OSA on two domains, 'sleep disturbance' and 'physical suffering'. This means that if the child is suffering from moderate OSA the impact on quality of life is the largest (table 5).

In the child-completed questionnaires children scored higher than the general population on 'sleep disturbance', but not on other domains. A reason for these comparable scores on the other domains might be that children with syndromic or complex cranio-

synostosis tend to minimize their concerns about functioning and health[16-18], they reported their quality of life as better than their parents did. It might also be possible that children aged between 12 and 18 in the general population scored higher on different items, due to their puberty, more than the children in the craniosynostosis population. In that case the general scores were higher than expected resulting in a smaller difference in mean scores between the general and craniosynostosis population. Another point is the completion of the questionnaires; maybe children in the general population really completed the survey by themselves and children in the craniosynostosis population talked to their parents about some questions, for example about loud snoring, resulting in the different scores on the domain 'sleep disturbance'.

To unravel differences in the scores between parents and children a comparison was made using the paired-samples t-test between the scores of the parents about their child and the scores of children themselves in the general and the craniosynostosis population in the selections in whom the parent and the child form were available. In the craniosynostosis population (n = 29) the answers on all 12 items were comparable (not significantly different) between parent and child. In the general population (n = 162) the answers on 6 items (restless sleep, mouth breathing, frequent colds, nasal discharge, aggressive behavior and difficulty getting out of bed) were statistically significant different between parent and child, the other 6 were comparable. So, in the general population children and parents had different views about above-mentioned items in contrast with the craniosynostosis population. This difference may be due to more communication between parents and craniosynostosis patients regarding their sleep and health.

Overall, the OSA-18 completed by parents is more reliable and valid than the OSA-12 child form. We will recommend using the OSA-18 survey anyhow for all children.

A limitation is the small number of moderate OSA patients, and for this reason we used the Z-scores for the independent t-test. The educational level of the respondents was significantly lower in the craniosynostosis population than in the general population, which can influence the OSA-18 results. However this study showed that the OSA-18 survey is reliable, also in this population.

In conclusion, the OSA-18 can be used in future studies to evaluate the disease-specific impact of obstructive sleep apnea, also in children with syndromic or complex craniosynostosis.

ACKNOWLEDGEMENTS

We thank R.M. Rosenfeld for permission to translate the OSA-18 into the Dutch language and to use this questionnaire in The Netherlands.

APPENDIX 1

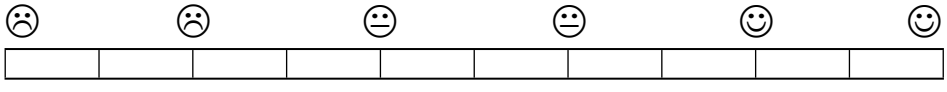
OSA-18 Quality of Life Survey

Instructions. For each question below, please circle the number that best describes how often each symptom or problem has occurred during the past 4 weeks. Please circle only one number per question. Thank you.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Sleep Disturbance							
During the past *4 weeks*, how often has your child had…							
…loud snoring?	1	2	3	4	5	6	7
…breath holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
…choking or gasping sounds while asleep?	1	2	3	4	5	6	7
…restless sleep or frequent awakenings from sleep?	1	2	3	4	5	6	7
Physical Symptoms							
During the past *4 weeks*, how often has your child had…							
…mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
…frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
…nasal discharge or runny nose?	1	2	3	4	5	6	7
…difficulty in swallowing foods?	1	2	3	4	5	6	7
Emotional Distress							
During the past *4 weeks*, how often has your child had…							
…mood swings or temper tantrums?	1	2	3	4	5	6	7
…aggressive or hyperactive behavior?	1	2	3	4	5	6	7
…discipline problems?	1	2	3	4	5	6	7
Daytime Problems							
During the past *4 weeks*, how often has your child had…							
…excessive daytime drowsiness or sleepiness?	1	2	3	4	5	6	7
…poor attention span or concentration?	1	2	3	4	5	6	7
…difficulty getting out of bed in the morning?	1	2	3	4	5	6	7
Caregiver Concerns							
During the past *4 weeks*, how often have the above problems…							
…caused you to worry about your child's general health?	1	2	3	4	5	6	7
…created concern that your child is not getting enough air?	1	2	3	4	5	6	7
…interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
…made you frustrated?	1	2	3	4	5	6	7

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF THE ABOVE PROBLEMS?

(Circle one number)



0 1 2 3 4 5 6 7 8 9 10

Worst Possible Quality-of-Life — Half-way Between Worst and Best — Best Possible Quality-of-Life

REFERENCES

1. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Arch Pediatr Adolesc Med. 2005;159:775-785.
2. Nixon GM, Brouillette RT. Sleep. 8: paediatric obstructive sleep apnoea. Thorax. 2005;60:511-516.
3. Franco RA, Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg. 2000;123:9-16.
4. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg.2004;15:670-674.
5. Hoeve LJ, Pijpers M, Joosten KF. OSAS in craniofacial syndromes: an unsolved problem. Int J Pediatr Otorhinolaryngol. 2003;67 Suppl 1:S111-113.
6. Lo LJ, Chen YR. Airway obstruction in severe syndromic craniosynostosis. Ann Plast Surg. 1999;43:258-264.
7. Hoeve HL, Joosten KF, van den Berg S. Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol.1999;49 Suppl 1:S59-61.
8. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet. 2006;14:289-298.
9. Kress W, Schropp C, Lieb G, et al. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet. 2006;14:39-48.
10. Silva VC, Leite AJ. Quality of life in children with sleep-disordered breathing: evaluation by OSA-18. Rev Bras Otorinolaringol (Engl Ed). 2006;72:747-756.
11. Preutthipan A, Chantarojanasiri T, Suwanjutha S, et al. Can parents predict the severity of childhood obstructive sleep apnoea? Acta Paediatr. 2000;89:708-712.
12. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol. 1996;13:198-207.
13. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr. 1995;127:905-912.
14. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg. 2003;129:1281-1284.
15. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care.2003;41:582-592.
16. Stancin T, Drotar D, Taylor HG, et al. Health-related quality of life of children and adolescents after traumatic brain injury. Pediatrics. 2002;109:E34.
17. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. Health technology assessment (Winchester, England). 2001;5:1-157.
18. Theunissen NC, Vogels TG, Koopman HM, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res. 1998;7:387-397.





Chapter 9

Obstructive sleep apnea-specific quality of life (OSA-18) and behavioral problems in children with syndromic or complex craniosynostosis

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ABSTRACT

Objective

This study aimed at evaluating the impact of syndromic craniosynostosis on quality of life, assessing the association between presence of craniosynostosis syndrome and prevalence of behavioral problems and assessing the impact of obstructive sleep apnea (OSA) in syndromic craniosynostosis compared to healthy controls and the association with behavior.

Methods

A prospective study was carried out using the OSA-18 survey and Child Behavior Checklist (CBCL) in 119 syndromic craniosynostosis patients and 459 controls. The craniosynostosis population underwent a ambulatory polysomnography to diagnose OSA.

Results

The domains 'sleep disturbance', 'physical suffering', 'caregiver concerns' and total OSA-18 score were significantly higher in the craniosynostosis group than in controls. After subgroup analysis 67% and 50% of boys with Apert and Muenke syndrome showed behavioral problems. The correlation between obstructive apnea hypopnea index and total OSA-18 and CBCL score was significant. Mean scores for the domains 'sleep disturbance' and 'physical suffering' were significantly higher in moderate OSA.

Conclusion

Children with syndromic craniosynostosis reported lower quality of life measured with OSA-18 than controls. Behavioral problems were common in boys with Apert and Muenke syndrome. Obstructive sleep apnea reduced the quality of life of craniosynostosis children. OSA-18 and CBCL scores are correlated with OSA severity.

INTRODUCTION

Apert, Crouzon, Pfeiffer, Muenke and Saethre-Chotzen syndrome are craniosynostosis syndromes caused by FGFR (fibroblast growth factor receptor) 1, 2, 3 mutations and TWIST gene mutations or deletions. These syndromes are characterized by the premature fusion of calvarial sutures, brain anomalies, characteristic facial features, hand and feet malformations and hearing deficits amongst others[1, 2]. Fusion of two cranial sutures or more without a known mutation[1, 2] is defined as complex craniosynostosis. Patients with a syndromic or complex craniosynostosis are at risk for obstructive sleep apnea due to midface hypoplasia and collapse of the pharynx, but other factors such as adenotonsillar hypertrophy may be involved as well[3, 4]. They can also have behavioral problems, such as attention deficit hyperactive disorder and autism[5, 6]. The prevalence and severity of the behavioral problems among patients with craniosynostosis syndromes are unknown, but the problems seem to occur more frequent in comparison with the general population.

Obstructive sleep apnea (OSA) is characterized by difficulties in breathing, snoring and apneas during sleep due to a partial or complete obstruction of the upper airway. OSA is associated with major physical and functional impairment due to disturbed sleep patterns, for instance failure to thrive, recurrent infections, feeding difficulties, disturbed cognitive functions (attention deficit, impaired concentration and memory), delay of development, cor pulmonale and sudden death[7]. OSA can be treated pharmacologically (e.g. with intranasal corticosteroids or antibiotics), surgically (e.g. with adenotonsillectomy (ATE) or midface advancement), or non-surgically (e.g. with nocturnal oxygen or continuous or bi-level positive airway pressure (CPAP or BiPAP))[3, 8, 9].

Obstructive sleep apnea may affect the child's quality of life because of these physical and functional consequences and the treatment. Previously a disease-specific quality of life survey was developed and validated, the OSA-18, for healthy children who got OSA due to adenotonsillar hypertrophy[10].

This study aimed (a) at evaluating the impact of syndromic craniosynostosis on quality of life, (b) at assessing the association between the presence of a craniosynostosis syndrome and the prevalence of behavioral problems and (c) at assessing the impact of obstructive sleep apnea on the quality of life in a population of patients with syndromic craniosynostosis compared to healthy controls and the association with the presence of behavioral problems.

METHODS

Authorisation was granted by the medical ethics committee (MEC-2005-273) of the Erasmus Medical Center.

Craniosynostosis population

A prospective study was carried out in the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital in Rotterdam. Patients with syndromic (genetically confirmed) or complex craniosynostosis between the age of 2 and 18 years treated at the Dutch Craniofacial Center between January 2007 and March 2009 were included (table 1). Parents were asked to complete the OSA-18 survey and the Child Behavior Checklist (CBCL).

General population

Parents of healthy children between the age of 2 and 18 years were approached at day-care centers, primary and secondary schools and sports clubs in Rotterdam, Rijswijk and Leiden (table 1). They were asked to complete the OSA-18 survey on their child and to return this to the hospital. A child with Down syndrome was excluded. No child had anamnestic complaints suggestive of OSA. Behavioral problems were not excluded.

Table 1: Characteristics of the craniosynostosis and general population

		Craniosynostosis population n = 119	General population n = 459	p-value
Completed by				
Mother		104 (87%)	402 (87%)	ns
Father		15 (13%)	50 (11%)	
Other			7 (2%)	
Age respondent (years)	range	23-61	17-55	ns
	median	39	41	
Education respondent				
Low		7 (6%)	7 (1.5%)	0.00**
Middle		78 (65.5%)	251 (55%)	
High		31 (26%)	198 (43%)	
Unknown		3 (2.5%)	3 (0.5%)	
Age child (years)	range	2-18	2-18	0.04*
	median	8	9	
Sex child	boy	56 (47%)	239 (52%)	ns
	girl	63 (53%)	220 (48%)	
Syndrome/ sex (boy/ girl)				
Apert		19 (16%) (9/ 10)		
Crouzon/ Pfeiffer		31 (26%) (14/ 17)		
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Saethre-Chotzen		21 (18%) (8/ 13)		
Complex		30 (25%) (17/ 13)		
Obstructive sleep apnea child				
Non		75 (63%)		
Mild		37 (31%)		
Moderate		7 (6%)		

ns not significantly different

* p-value ≤ 0.05

** p-value ≤ 0.01

OSA-18 survey

The questionnaire consisted of 18 age-independent items grouped into five domains: 'sleep disturbance', 'physical suffering', 'emotional distress', 'daytime problems' and 'caregiver concerns'. Each item had seven optional answers ranging from 1 (never) to 7 (always). The total OSA-18 score was the sum of the 18 items and ranged from 18 to 126. It also provided a 10-point visual analogous scale with specific semantic anchors[10] (appendix 1). Total scores less than 60 suggest a small impact on health-related quality of life, scores between 60 and 80 a moderate impact and scores above 80 a large impact[10].

Prior to this study the internal consistency, test-retest reliability and discriminative validity of the translated OSA-18 survey in healthy children and children with syndromic or complex craniosynostosis were demonstrated (Bannink et al., unpublished data, 2010).

Child Behavior Checklist

The standardized Child Behavior Checklist (CBCL) was used to measure the parent-reported child problem-behavior frequency. The CBCL is a widely used norm-referenced measure (Rescorla, Manual for the ASEBA Preschool Forms & Profiles[11] and Achenbach, Manual for the Child Behavior Checklist/4-18 & Profile[12]). The CBCL 1.5-5 years consisted of 100 items and the CBCL 6-18 years of 113 items. Each item is scored as 0, not true; 1, somewhat or sometimes true; and 2, very true or often true. The known Dutch norm scores were used as cut-off values. Scores < 95th percentile are scores in the normal range. Scores ≥ 95th percentile but < 98th percentile were defined as scores in the borderline and ≥ 98th percentile as scores in the clinical range, so these scores are considered as abnormal.

The CBCL provided age- (1.5-5, 6-11 and 12-18 years) and gender-specific scores for internalizing, externalizing and total problems. Internalizing scores were based on the three domains 'anxiety', 'withdrawal' and 'somatic complaints'. Externalizing scores were based on 'rule-breaking behavior' and 'aggressive behavior'. The total score is a combination of the two scores plus 'social', 'thought' and 'attention problems', and 'other problems' (e.g. overeating, overtired).

Behavioral problems were defined as the presence of scores in the (borderline) clinical range[11]. The results were analyzed in the craniosynostosis population and per syndrome.

Polysomnography

The children of the craniosynostosis population underwent a polysomnography, the gold standard to diagnose obstructive sleep apnea. Polysomnography was done ambulatory with Embletta Portable Diagnostic System and analyzed with Somnologica for Embletta software 3.3 ENU (Medcare Flaga, Reykjavik, Iceland). Thoracic and abdominal movements, nasal flow, saturation, and pulse were monitored. The required minimal total sleep time was 360 minutes. Obstructive apnea was defined as absence of airflow (measured by a nasal cannula) or out-of-phase movement of thorax and abdomen (scored as X flow) and

hypopnea as ≥ 50% reduction in nasal flow signal amplitude or X flow signal amplitude, both for more than two breaths[13-15]. The X flow signal was the sum of the amplitudes of the thoracic and abdominal movements[14, 15] and was used when nasal airflow was insufficient. Mixed apnea was defined as a type of obstructive apnea with a central component that mostly preceded the obstructive pattern, for more than two breaths. Central apneas were not included in this study. Desaturation was defined as ≥ 4% decrease with respect to the baseline value.

The degree of OSA was expressed in an obstructive apnea hypopnea index (OAHI), the hourly number of obstructive and mixed apneas in combination with the hourly number of hypopneas followed by desaturation. A score < 1 is considered to be normal, between 1 and 5 is defined as mild OSA, between 6 and 25 as moderate OSA, and > 25 as severe OSA[16, 17].

Statistical analysis

All analyses were performed with SPSS 16.0 for Windows (SPSS, Chicago, IL). The analyses were performed in several subgroups, in boys and girls and in each craniosynostosis syndrome separately. The independent t-test was used to compare the means of the different craniosynostosis syndromes with the general population. The correlations between OSA-18, CBCL and OAHI were assessed. Significant differences were defined as a p-value ≤ 0.05. The numbers were given in median and range.

RESULTS

Craniosynostosis population

A total of 163 patients with syndromic or complex craniosynostosis were approached, of whom 141 (87%) children and their parents gave informed consent for this research project. Of them 119 (73%) returned the OSA-18 survey and underwent a polysomnography. Out of these 119 the parents of two girls did not complete the CBCL, due to very low mental capacity of one child (several items could not be answered) and due to a logistic reason in the other.

Most of the questionnaires, namely 87% were completed by mothers compared to 13% completed by fathers and 88% of them were born in the Netherlands. The craniosynostosis group consisted of 56 boys (47%) and 63 girls (table 1).

General population

Parents of 459 healthy children returned the questionnaire. Also in this healthy population most of the questionnaires (87%) were completed by mothers and 91% of the respondents

were born in the Netherlands. The reference group consisted of 239 boys (52%) and 220 girls (table 1).

OSA-18 survey

The quality of life measured with the OSA-18 in patients with a syndromic or complex craniosynostosis was lower than that measured in the general population (table 2). The mean total OSA-18 score in the craniosynostosis population was 39.9 (sd 16.7). The maximum score was 100. A score above 60 was present in 12%, above 80 in 3%. The mean OSA-18 score in the general population was 31.2 (sd 10.4) with a score above 60 in 2% and above 80 in none of the healthy children.

The domains 'sleep disturbance', 'physical suffering', and 'caregiver concerns' and the total OSA-18 score were significantly higher in the craniosynostosis group than in the general population (p = 0.000). Specifically children with Apert, Crouzon/ Pfeiffer syndrome and complex craniosynostosis scored significantly higher than the general population on all these domains. Children with Muenke syndrome scored significantly higher on 'sleep disturbance' (table 2).

Table 2: Means of the OSA-18 scores in the craniosynostosis population and per syndrome in comparison with the general population

	General population	Craniosynostosis population	Apert	Crouzon/ Pfeiffer	Muenke	Saethre-Chotzen	Complex
	mean (sd) n = 459	mean (sd) n = 119	mean (sd) n = 19	mean (sd) n = 31	mean (sd) n = 18	mean (sd) n = 21	mean (sd) n = 30
Sleep disturbance	5.8 (2.4)	8.9 (4.8)**	12.7 (5.2)**+	9.3 (7.1)**	8.8 (5.3)*	7.8 (5.1)	7.2 (3.1)*
Physical suffering	8.1 (4.3)	11.1 (5.8)**	14.7 (6.3)**#	10.8 (6.1)**	8.7 (4.6)	9.7 (5.8)	11.1 (5.1)**
Emotional distress	6.2 (3.1)	6.5 (3.4)	6.7 (3.7)	5.9 (4.1)	6.5 (3.2)	6.1 (2.7)	7.1 (3.4)
Daytime problems	6.2 (3.1)	6.8 (3.5)	7.5 (3.4)	6.0 (3.7)	7.7 (4.6)	7.1 (3.1)	6.3 (3.1)
Caregiver concerns	5.2 (2.4)	7.0 (4.2)**	8.3 (3.9)**	6.9 (5.5)*	6.3 (4.1)	6.2 (2.9)	6.9 (4.1)*
Total OSA-18 score	31.2 (10.4)	39.9 (16.7)**	49.8 (16.8)**^	39.0 (19.0)*	38.2 (19.2)	37.4 (14.4)	37.9 (14.5)*

sd standard deviation

* p-value ≤ 0.05

** p-value ≤ 0.01

+ scores were significantly higher in Apert syndrome in comparison with Muenke, Saethre-Chotzen syndrome and complex craniosynostosis

scores were significantly higher in Apert syndrome in comparison with all other four syndromes

^ scores were significantly higher in Apert syndrome in comparison with Saethre-Chotzen syndrome and complex craniosynostosis

Within the group of children with syndromic or complex craniosynostosis Apert syndrome scored significantly higher than the other syndromes on different domains as demonstrated in table 2.

Child Behavior Checklist

The prevalence of behavioral problems is 32% in boys with syndromic or complex craniosynostosis and 16% in girls (table 3). The total CBCL score between 1.5 and 5 years was 31.8 (sd 17.9) in boys and 28.1 (sd 27.7) in girls and between 6 and 18 years 38.1 (sd 29.6) in boys and 28.4 (sd 14.6) in girls. The maximum score was 144.

Table 3 also showed the results of the CBCL scores per syndrome. Of the boys with Apert syndrome 67% scored in the (borderline) clinical range in contrast with none of the girls. This 67% prevalence of behavioral problems in boys is significantly higher than in Crouzon/ Pfeiffer syndrome and complex craniosynostosis. Boys with Muenke syndrome also scored high (50%) in the (borderline) clinical range.

Obstructive sleep apnea

Out of the 119 patients 44 (37%) were diagnosed with an obstructive sleep apnea; 37 mild with a mean OAHI of 2.3 (sd 1.1) and 7 moderate with a mean OAHI of 9.0 (sd 5.1) with a maximum index of 20.

Table 3: The numbers and percentages of the CBCL scores in the (borderline) clinical range in the craniosynostosis population and per syndrome in boys and girls

	Craniosynostosis population (borderline) clinical range n (%)	Apert (borderline) clinical range n (%)	Crouzon/ Pfeiffer (borderline) clinical range n (%)	Muenke (borderline) clinical range n (%)	Saethre-Chotzen (borderline) clinical range n (%)	Complex (borderline) clinical range n (%)
Boy	n = 56	n = 9	n = 14	n = 8	n = 8	n = 17
Internalizing score	14 (25)	4 (44)	3 (21)	3 (38)	1 (13)	3 (18)
Externalizing score	12 (21)	4 (44)-	1 (7)	3 (38)	1 (13)	3 (18)
Total score	18 (32)	6 (67)#	3 (21)	4 (50)	2 (25)	3 (18)
Girl	n = 61	n = 10	n = 16	n = 10	n = 12	n = 13
Internalizing score	12 (20)	0 (0)	2 (13)	4 (40)^	4 (33)+	2 (15)
Externalizing score	5 (8)	0 (0)	1 (6)	1 (10)	3 (25)	0 (0)
Total score	10 (16)	0 (0)	1 (6)	3 (30)	3 (25)	3 (23)

- scores were significantly higher in Apert syndrome in comparison with Crouzon/ Pfeiffer syndrome

scores were significantly higher in Apert syndrome in comparison with Crouzon/ Pfeiffer syndrome and complex craniosynostosis

^ scores were significantly higher in Muenke syndrome in comparison with Apert syndrome

+ scores were significantly higher in Saethre-Chotzen syndrome in comparison with Apert syndrome

Obstructive sleep apnea in the patients with syndromic or complex craniosynostosis had impact on the quality of life. There was a significant positive correlation between the total OSA-18 score and the OAHI (r = 0.34, p = 0.000), also after exclusion of the patients without OSA (r = 0.40, p = 0.009) (figure 1). Patients without OSA had a mean total OSA-18 score of 38.0, with mild OSA 41.0 and with moderate OSA 55.0 (figure 2). All patients with a total OSA-18 score above 80 had OSA, and 9 out of 14 (64%) with a total score above 60.

The domains 'sleep disturbance' and 'physical suffering' were significantly higher in the moderate OSA group than in the non OSA and than in the mild OSA group ($p \leq 0.05$), but not in the mild OSA group in comparison with the non OSA group.

The degree of obstructive sleep apnea also has impact on behavior. The correlation between the total CBCL score in children between 6 and 18 years and the OAHI was significant (r = 0.38, p = 0.001), also after exclusion of the patients without OSA (r = 0.55, p = 0.008) (figure 3).

Overall, there is a significant correlation between the total OSA-18 score and the total CBCL score in children between 1.5 and 5 years and 6 and 18 years (figure 4), also after exclusion of the patients without OSA (r = 0.73, p = 0.000).

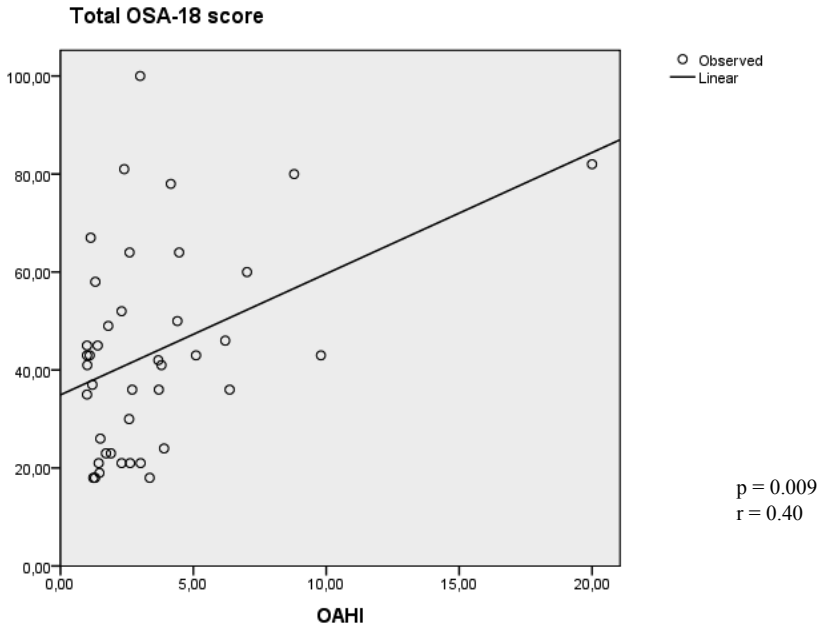


Figure 1: Correlation between total OSA-18 score and the OAHI in the total group after exclusion of children without obstructive sleep apnea
OAHI obstructive apnea hypopnea index

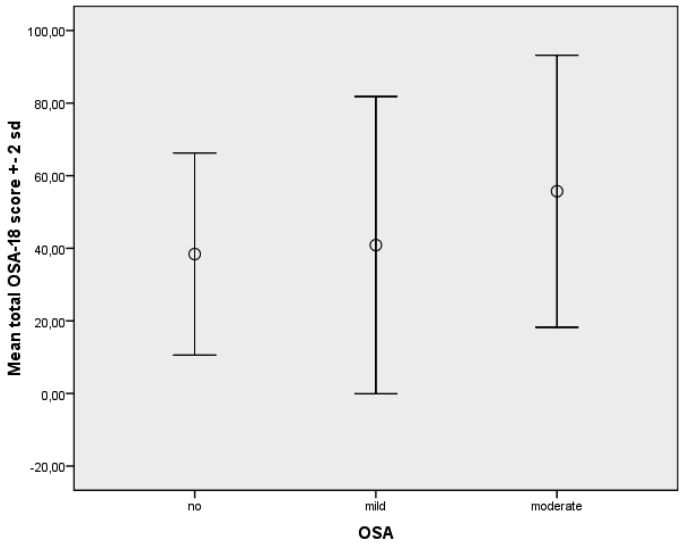


Figure 2: Mean total OSA-18 scores with standard deviation over three groups with no, mild and moderate obstructive sleep apnea
sd standard deviation

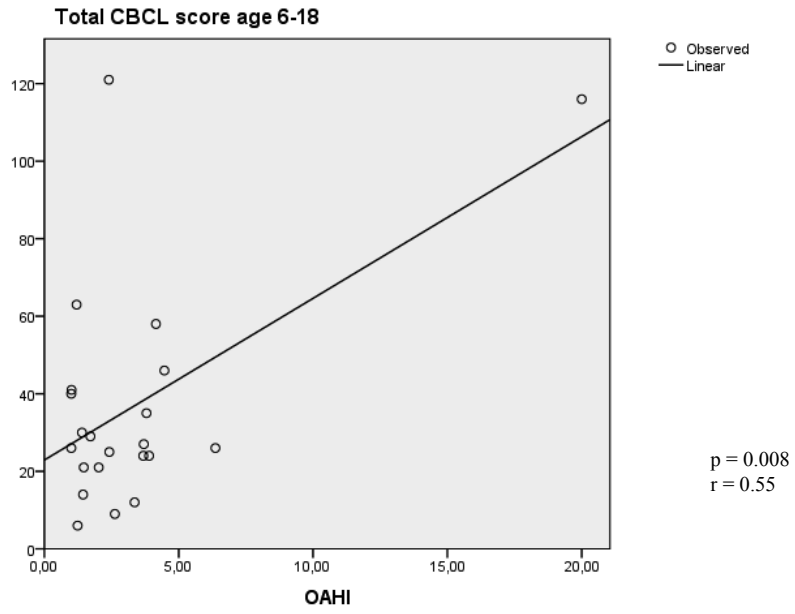


Figure 3: Correlation between total CBCL score and the OAHI in the children between the age of 6 and 18 after exclusion of children without OSA
OAHI obstructive apnea hypopnea index

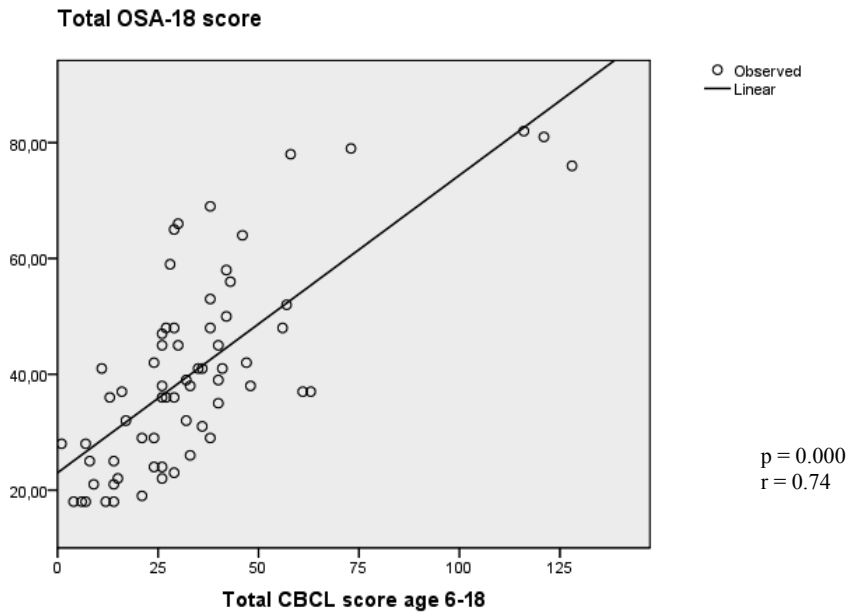


Figure 4: Correlation between the total CBCL score of the children between the age of 6 and 18 and the total OSA-18 score

DISCUSSION

This is the first study using a disease-specific quality of life score (OSA-18) in which comparison is made between children with syndromic or complex craniosynostosis suffering from obstructive sleep apnea and a general healthy population of Dutch children. The total OSA-18 score was significantly higher in the syndromic craniosynostosis population than in the general population (table 2), which meant a lower quality of life. Explanations can be the higher prevalence of OSA in this group compared to the low prevalence (2-5%) in the general population[15] and the impact of having syndromic or complex craniosynostosis independent of the presence of OSA[18]. In the craniosynostosis population the total OSA-18 score (mean 43.4) of the OSA group was higher in comparison with the non OSA group (mean 38.0). Per domain the scores on 'sleep disturbance', 'physical suffering', and 'caregiver concerns' were significantly higher in the craniosynostosis than in the general population.

Within the group of children with syndromic or complex craniosynostosis, children with Apert syndrome showed the highest total OSA-18 score (table 2). This is in accordance with the lowest health-related quality of life in comparison with the other syndromes[18] and a high prevalence of OSA (42%) seen in Apert syndrome.

There was a significant positive correlation between the total OSA-18 score and the OAHI. However, within the group of children with mild OSA a considerable number of children had a high OSA-18 score. This could be due to high scores on some specific items within the domains, which can be related to syndromic craniosynostosis. These items are snoring, mouth breathing, nasal discharge, aggressive or hyperactive behavior and poor attention span or concentration. These items were also higher scored in children with syndromic craniosynostosis without OSA. Overall the domains 'sleep disturbance' and 'physical suffering' were scored significantly higher in children with moderate OSA and these two domains might be used in clinical practice for evaluating the severity of OSA. A significant correlation between the mean OSA-18 score and the severity of OSA was also found in healthy children with OSA due to adenotonsillar hypertrophy[10].

We found a high prevalence of behavioral problems, especially in boys with syndromic or complex craniosynostosis. Furthermore we found a positive correlation between the total CBCL score and the OAHI and the total OSA-18 score. Within the group of children with syndromic or complex craniosynostosis it was remarkable that boys with Apert and Muenke syndrome showed the highest prevalence of behavioral problems, whereas none of the girls with Apert syndrome scored these problems. In Apert syndrome OSA is much more present in boys (78%) than in girls (10%) and the intelligence of boys with Apert syndrome is significantly lower than that of girls, which can influence the behavior (Maliepaard et al., unpublished data). In Muenke syndrome the behavioral problems may be more intrinsic and possibly related to their P250R mutation than be associated with OSA. The prevalence of OSA in Muenke syndrome is with 28% low in comparison with the other syndromes. Previously, studies on behavioral problems were mostly performed in children with isolated craniosynostosis. Boltshauser et al.[19] reported in 30 children with isolated sagittal craniosynostosis a normal behavior whereas Kelleher et al.[20] reported in 63 children with trigonocephaly that 37% of the parents expressed concerns about their child's behavior. In children with Apert syndrome Sarimski et al.[5, 6] reported in the majority of the children clinically significant social problems and attention deficit, the total CBCL scores were only in 8 out of 25 children with Apert in the clinical range.

In this study it can be questioned what the additional influence of OSA is next to having syndromic craniosynostosis on the presence of behavioral problems in the different syndromes. Goldstein et al.[9] reported that non-syndromic healthy children with OSA demonstrated a high prevalence of behavioral and emotional problems measured by the standardized CBCL, which changed after adenotonsillectomy. A positive correlation was found between the OSA-18 total scores and the CBCL scores[9]. After adenotonsillectomy both scores improved[21]. In children with the diagnosis ADHD in combination with mild OSA the apnea hypopnea index, the OSA-18 'sleep disturbance' domain and the ADHD-rating scale total and inattentive scores improved significantly more in the group treated for OSA by adenotonsillectomy than the group treated for their ADHD by methylphe-

nidate[22]. Concerning children with syndromic or complex craniosynostosis future studies have to elaborate the impact of OSA treatment on the OSA-18 score and CBCL score for each specific syndrome separately.

In conclusion, children with syndromic craniosynostosis reported a lower quality of life measured with the OSA-18 compared to healthy controls. Behavioral problems were highly prevalent and most common in boys with Apert and Muenke syndrome. Obstructive sleep apnea reduced the quality of life of children with syndromic craniosynostosis. The OSA-18 and CBCL scores are correlated with the severity of OSA, but the additional influence of OSA on behavior is unclear in craniosynostosis.

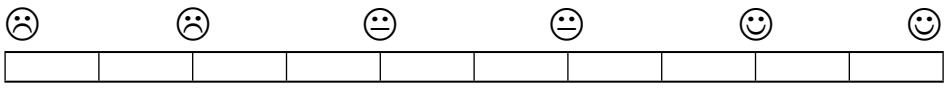
APPENDIX 1

OSA-18 Quality of Life Survey

Instructions. For each question below, please circle the number that best describes how often each symptom or problem has occurred during the past 4 weeks. Please circle only one number per question. Thank you.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Sleep Disturbance							
During the past *4 weeks*, how often has your child had…							
…loud snoring?	1	2	3	4	5	6	7
…breath holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
…choking or gasping sounds while asleep?	1	2	3	4	5	6	7
…restless sleep or frequent awakenings from sleep?	1	2	3	4	5	6	7
Physical Symptoms							
During the past *4 weeks*, how often has your child had…							
…mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
…frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
…nasal discharge or runny nose?	1	2	3	4	5	6	7
…difficulty in swallowing foods?	1	2	3	4	5	6	7
Emotional Distress							
During the past *4 weeks*, how often has your child had…							
…mood swings or temper tantrums?	1	2	3	4	5	6	7
…aggressive or hyperactive behavior?	1	2	3	4	5	6	7
…discipline problems?	1	2	3	4	5	6	7
Daytime Problems							
During the past *4 weeks*, how often has your child had…							
…excessive daytime drowsiness or sleepiness?	1	2	3	4	5	6	7
…poor attention span or concentration?	1	2	3	4	5	6	7
…difficulty getting out of bed in the morning?	1	2	3	4	5	6	7
Caregiver Concerns							
During the past *4 weeks*, how often have the above problems…							
…caused you to worry about your child's general health?	1	2	3	4	5	6	7
…created concern that your child is not getting enough air?	1	2	3	4	5	6	7
…interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
…made you frustrated?	1	2	3	4	5	6	7

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF THE ABOVE PROBLEMS?
(Circle one number)



0 1 2 3 4 5 6 7 8 9 10

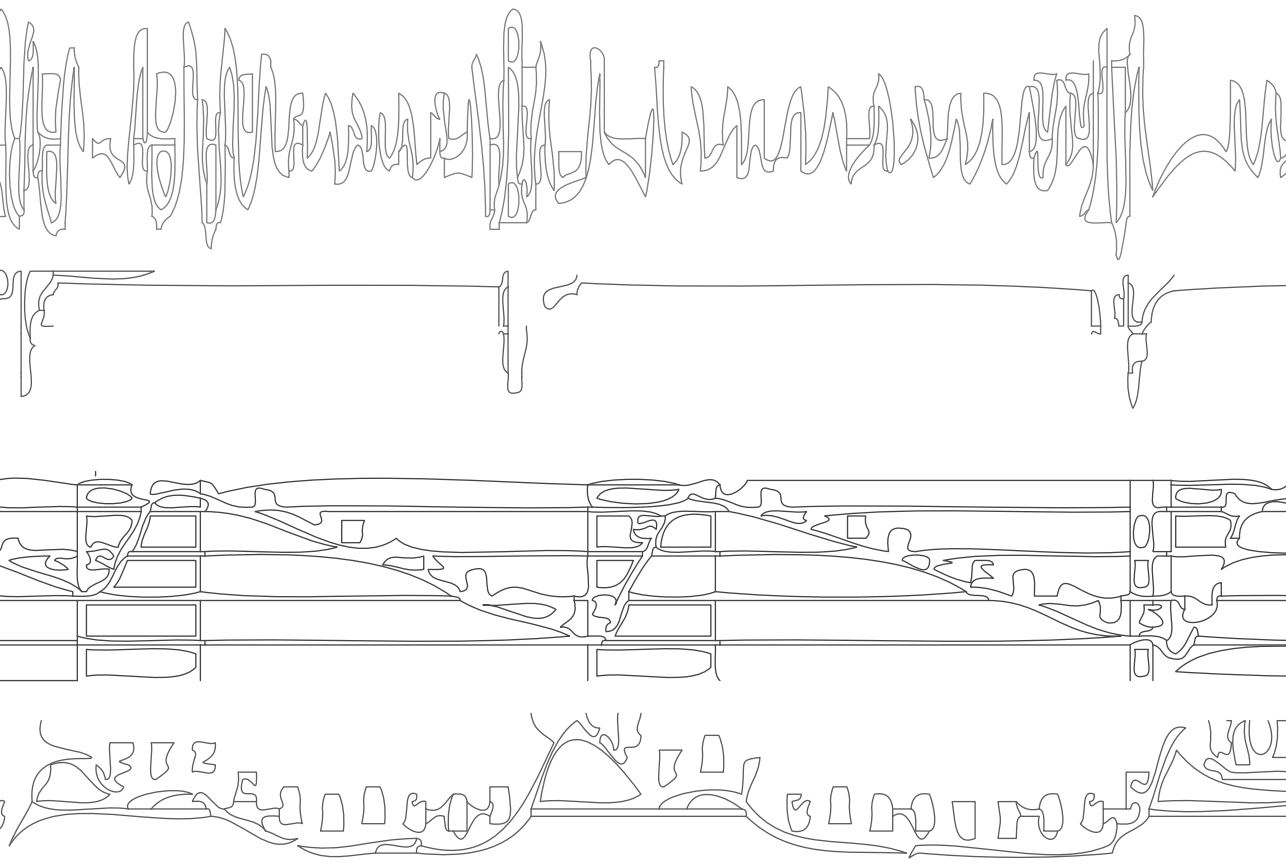
Worst Possible Quality-of-Life — Half-way Between Worst and Best — Best Possible Quality-of-Life

REFERENCES

1. Kress W, Schropp C, Lieb G, et al. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet 2006;14:39-48.
2. Lajeunie E, Heuertz S, El Ghouzzi V, et al. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet 2006;14:289-298.
3. Hoeve HL, Joosten KF, van den Berg S. Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol 1999;49 Suppl 1:S59-61.
4. Lo LJ, Chen YR. Airway obstruction in severe syndromic craniosynostosis. Ann Plast Surg 1999;43:258-264.
5. Sarimski K. Children with Apert syndrome: behavioral problems and family stress. Developmental medicine and child neurology 1998;40:44-49.
6. Sarimski K. Social adjustment of children with a severe craniofacial anomaly (Apert syndrome). Child: care, health and development 2001;27:583-590.
7. Nixon GM, Brouillette RT. Sleep. 8: paediatric obstructive sleep apnoea. Thorax 2005;60:511-516.
8. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;109:704-712.
9. Goldstein NA, Fatima M, Campbell TF, et al. Child behavior and quality of life before and after tonsillectomy and adenoidectomy. Arch Otolaryngol Head Neck Surg 2002;128:770-775.
10. Franco RA, Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg 2000;123:9-16.
11. Rescorla LA. Assessment of young children using the Achenbach System of Empirically Based Assessment (ASEBA). Mental retardation and developmental disabilities research reviews 2005;11:226-237.
12. Achenbach TM, Edelbrock CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. Monographs of the Society for Research in Child Development 1981;46:1-82.
13. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Archives of pediatrics & adolescent medicine 2005;159:775-785.
14. Preutthipan A, Chantarojanasiri T, Suwanjutha S, et al. Can parents predict the severity of childhood obstructive sleep apnoea? Acta Paediatr 2000;89:708-712.
15. Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 1996;13:198-207.
16. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
17. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
18. Bannink N, Maliepaard M, Raat H, et al. Health-related quality of life in children and adolescents with syndromic craniosynostosis. J Plast Reconstr Aesthet Surg
19. Boltshauser E, Ludwig S, Dietrich F, et al. Sagittal craniosynostosis: cognitive development, behavior, and quality of life in unoperated children. Neuropediatrics 2003;34:293-300.
20. Kelleher MO, Murray DJ, McGillivary A, et al. Behavioral, developmental, and educational problems in children with nonsyndromic trigonocephaly. J Neurosurg 2006;105:382-384.
21. Tran KD, Nguyen CD, Weedon J, et al. Child behavior and quality of life in pediatric obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 2005;131:52-57.
22. Huang YS, Guilleminault C, Li HY, et al. Attention-deficit/hyperactivity disorder with obstructive sleep apnea: a treatment outcome study. Sleep Med 2007;8:18-30.

Part V

Discussion and summary







Chapter 10

Discussion and future perspectives

DISCUSSION

The main aim of this thesis was to assess the importance and impact of obstructive sleep apnea (OSA) in children with syndromic or complex craniosynostosis. **Main findings** are:

- The prevalence of obstructive sleep apnea in children with syndromic or complex craniosynostosis is 42%.
- When parents do not notice difficulty in breathing of their child during sleep the presence of moderate or severe obstructive sleep apnea can almost be excluded.
- Home cardiorespiratory monitoring is feasible to diagnose obstructive sleep apnea; nevertheless there are concerns about the nasal flow recordings. Analysis of the X flow signal gives additional information.
- Endoscopy before midface advancement in patients with obstructive sleep apnea is recommended to identify level of airway obstruction and to help predict respiratory improvement after midface advancement.
- There is a high (52-56%) prevalence of functional problems such as refractive errors and hearing loss in all types of syndromic or complex craniosynostosis. The prevalence of papilledema in Crouzon/ Pfeiffer syndrome is 53%; in Apert syndrome it is 33%.
- Syndromic craniosynostosis has a large impact on the health-related quality of life of these children and their parents, both physical and psychosocial.
- The OSA-18, a disease-specific quality of life questionnaire, has good reliability and validity for patients with syndromic craniosynostosisis. Obstructive sleep apnea reduced the quality of life of children with syndromic craniosynostosis and the OSA-18 scores are correlated with disease severity.
- The prevalence of behavioral problems in boys with syndromic or complex craniosynostosis is 32%; in girls it is 16%. Boys with Apert syndrome (67%) or Muenke syndrome (50%) had more behavioral problems than children with the other syndromes.

COMMENTS ON FINDINGS

This thesis describes a large study in children with syndromic or complex craniosynostosis, who were treated by the multidisciplinary team at the craniofacial center in Rotterdam. It is divided into a retrospective and prospective part. Prospectively, 190 children and their parents were approached consecutively, and 164 gave informed consent. Thus the participation rate was 86%. This high rate made it possible to differentiate the outcomes per syndrome. The records of 167 children with syndromic craniosynostosis were reviewed retrospectively regarding the presence of elevated intracranial pressure (ICP), obstructive sleep apnea, functional problems and the different treatments.

Prevalence of obstructive sleep apnea

Obstructive sleep apnea is an important feature in children with syndromic craniosynostosis. On the basis of an obstructive apnea hypopnea index ≥ 1 the prevalence of OSA was 42% in the total prospective study group, 47% in Apert syndrome, 42% in Crouzon/Pfeiffer, 35% in Muenke, 28% in Saethre-Chotzen syndrome, and 50% in complex craniosynostosis. This is in accordance with the 40% risk to develop OSA in children with Apert, Crouzon and Pfeiffer syndrome reported in the literature[1-3]. Of the OSA patients 82% had mild and 18% had moderate OSA. Apert syndrome occurred in half of those with moderate OSA; each of the other syndromes in 12.5% of the other half. The prospective study revealed no new cases with severe OSA. On the other hand, some cases of severe OSA were described in the group of patients studied retrospectively in **chapter 4**. The latter patients were older than 18 years at the time of the study and therefore not included in the prospective study.

Polysomnography in the prospective study resulted in a higher prevalence of OSA than that found previously in the retrospective analyzed patients, of whom the majority had undergone nocturnal pulse oximetry only (**chapter 6**). Obstructive and mixed apneas without desaturation were not registered with pulse oximetry, as this technique only records desaturation.

After informed consent all children aged between 0 and 18 years underwent a polysomnography. The mean age at inclusion and thus the age at OSA diagnosis with polysomnography differed between the children with OSA and the children without OSA: 5.5 and 9.7 years, respectively. This would seem to imply that in the majority of children with syndromic craniosynostosis OSA will develop at a young age. The older patients did not develop OSA or had already been treated. The exact age of OSA onset is currently not clear; yearly follow up from the first year of life during at least six years might provide a clue.

Screening tool

In the past, parents and physicians of children with syndromic or complex craniosynostosis did not recognize respiratory difficulties as separate entity. Parents or caregivers did not report and physicians did not ask for breathing problems at the outpatient clinic. We evaluated the use of an established screening tool for OSA, the Brouillette score, which is based on three questions[4] (**chapter 2**). This study showed that informing of difficulty in breathing in itself is sensitive to screen for moderate or severe OSA. This single question is a simplification of the Brouillette score. Information about snoring is not specific due to its high prevalence (77%). The question about presence of apneas is specific but not sensitive and thus may result in missing cases.

In conclusion, if the child has no difficulty in breathing moderate or severe OSA is not very likely to be present. If difficulties in breathing are reported a polysomnography is recommended.

Diagnostic method

Polysomnography

There are four levels of polysomnography[5, 6].

Level 1, full polysomnography, is the gold standard and this is performed in a sleep laboratory with a technician in attendance. It records sleep stages (REM and non-REM sleep and arousals), respiratory effort, airflow, oxygen saturation, electrocardiogram, body position and limb movements.

Level 2 records the same variables, but can be performed outside of the sleep laboratory without a technician.

Level 3 is the method used in the prospective study described in this thesis. A portable monitor records four physiologic variables, i.e. two respiratory variables (respiratory movement and airflow), a cardiac variable (heart rate or an electrocardiogram), and arterial oxyhemoglobin saturation via pulse oximetry. Sleep stages and arousals cannot be recorded[5, 6].

Level 4 is the simplest portable monitor, which records arterial oxyhemoglobin saturation and/ or airflow[5, 6]. Brouillette et al.[7] used nocturnal pulse oximetry to diagnose OSA in healthy children with a high positive predictive value, but a negative oximetry result could not rule out the presence of OSA. In children with syndromic craniosynostosis moderate or severe OSA is almost unlikely with a negative oximetry.

Chapter 3 described the use of level 3 polysomnography in children with syndromic or complex craniosynostosis. OSA was diagnosed with 40.5% successful recordings (minimal total sleep time of 360 minutes with artefact-free signals). This is a better result than that of a previous study performed in children who snore, in whom only 29% of the home cardiorespiratory recordings were successful[8]. Moss et al.[9] studied the use of abbreviated home polysomnography in 50 primary school children. In 89% of the recordings the total sleep time without movement or artifacts was at least four hours. However, it is two hours less than our definition of a successful measurement. In general, a polysomnography lasting a minimum of six hours is advocated for the accurate diagnosis of OSA.

Limitations in the use of ambulatory polysomnography

- Use of nasal cannula

The nasal cannula is the most important limitation of polysomnography in children with syndromic craniosynostosis. Shifting during sleep or intolerance may cause failure. Another causative factor is the absence of nasal passage when the nasal cavity is severely malformed[10].

- X flow as alternative for nasal flow

We showed that the X flow can be helpful to diagnose OSA in the absence of nasal flow. We were the first to report this use of the X flow in ambulatory polysomnography in children.

A limitation of this method is underestimation of the degree of OSA by missing a part of the obstructive apneas, possibly due to shifting of the trace belts. This method should be properly validated in comparison with level 1 polysomnography. An alternative solution to bypass the nasal obstruction is the use of a mouth thermistor to record oral airflow.

- Additional measurements

Guilleminault et al.[11, 12] recommended to measure esophageal pressure (indirect measure of the intrathoracic pressure, which gives information on respiratory efforts) and the transcutaneous or end tidal CO_2 next to arousal and sleep stages detection. This method allows to distinguish OSA from upper airway resistance syndrome (UARS)[12]. Furthermore the relation between elevated intracranial pressure and OSA or UARS can be determined more accurately.

- Uniform definitions for polysomnography in children

Another limitation in children is the lack of a uniform definition to analyze a polysomnography (table 1)[7, 8, 13-15]. The common definition of OSA is an AHI ≥ 1 based on the number of obstructive apneas and hypopneas followed by desaturation for at least two breaths. In our studies this definition was used as well. There is less consensus about the definitions of mild, moderate and severe OSA (table 2). In our study we used the definition of Guilleminault et al.[16] Children were classified as having mild obstructive sleep apnea if they had an AHI of 1 to 5 events per hour of sleep, as moderate OSA with an AHI of between 6 and 25 events per hour of sleep, and as severe with more than 25 events per hour.

Central apneas were not included in the AHI, because many children, especially the very young, show central irregularity of breathing[17, 18], which has no association with OSA.

Another definition is the lowest observed saturation in addition to the number of apneas and hypopneas per hour[19, 20]. There are however no studies in children who showed a higher morbidity using these criteria. It might be argued that very low saturations warrant more or earlier treatment than mild desaturations, but this has to be determined.

Treatment

Patients who underwent a polysomnography are discussed by a multidisciplinary team consisting of a pediatrician, plastic surgeon, otorhinolaryngologist, oral and maxillofacial surgeon, and nurse specialist. If OSA is not diagnosed, a strategy of annual screening is decided on, unless symptoms of OSA developed in between.

If OSA is diagnosed, the otorhinolaryngologist is asked to inspect the adenoid and tonsils. In mild or moderate cases conservative medical therapy (e.g. xylometazolin, antibiotics, nasal corticosteroids) or adenotonsillectomy (ATE) are the first treatment options.

If these do not improve OSA or in severe OSA, continuous or bi-level positive airway pressure (CPAP or BiPAP) can be initiated. In some children oxygen therapy might be helpful. A tracheostomy might be necessary in very young children with severe OSA who present with breathing problems throughout the day.

Table 1: Overview of different studies about definitions to analyze a polysomnography

	N of patients, diagnosis	Mean age (yrs) ± sd (range)	TST in hrs	Obstructive apnea (O)	Central apnea (C)	Mixed apnea (M)	Hypopnea (H)	Obstructive sleep apnea	Desaturation
Brouillette et al.[7], 2000	349 patients referred for PSG	median 4.5 (2.9-7.1)	8.1 ± 1.4	≥ 1 breath	≥ 1 breath	≥ 1 breath	associated with desaturation	O+M+H ≥ 1	≥ 4%
Guilleminault et al.[13], 2004	400 patients suspected for OSA + 60 controls	6.5 ± 4.0 (2.0-12.1)	≥ 8.5	> 2 breaths, independent of desaturation/ EEG arousal	> 2 breaths independent of desaturation/ EEG arousal	> 2 breaths independent of desaturation/ EEG arousal	≥ 2 breaths independent of desaturation/ EEG arousal	O+M+H > 1.5	≥ 3%
Marcus et al.[14], 1992	50 healthy children	9.7 ± 4.6 (1.1-17.4)	6.0 ± 1.6	any length	associated with desaturation < 90%, irrespective of length	central component: ≥ 4 sec/ ≥ 2 breaths, obstructive: any length	-	O > 1	> 4%
Poels et al.[8], 2003	24 patients scheduled for ATE	4.2 ± 1.6	≥ 6.5	≥ 10 sec	≥ 10 sec	≥ 10 sec	≥ 10 sec	O+C+M+H ≥ 1	≥ 4%
Verhulst et al.[15], 2007	60 healthy children	11.7 ± 2.6 (7.1-16.6)	7.8 ± 0.8	> 2 breaths independent of desaturation	≥ 10 sec or of any length associated with desaturation	central and obstructive component	associated with desaturation/ EEG arousal	O+M+H > 1	> 3%
This study: Bannink et al., 2010	65 patients syndromic/ complex craniosynostosis	median 8.5 (0.2-18.7)	≥ 6	> 2 breaths independent of desaturation	> 2 breaths associated with desaturation	> 2 breaths independent of desaturation	> 2 breaths associated with desaturation	O+M+H ≥ 1	≥ 4%

Table 2: Overview of different studies about the severity of OSA

	Mild (events/hour)	Moderate (events/hour)	Severe (events/hour)
Guilleminault et al.[16], 1995			
AHI	1-5	6-24	>25
Guideline New Zealand*, 2005			
Apnea index	1-4	5-9	>10
Saturation in association with obstruction	Nadir 87-91%	Nadir 76-85%	Nadir <75%
Hypoventilation	10-24% of total sleep time	25-49% of total sleep time	>50% of total sleep time
Goroza et al.[16], 2009			
AHI	5-15	16-30	>30
Lowest saturation	Nadir 81-90%	Nadir 71-80%	Nadir ≤ 70%
This study, Bannink et al, 2010			
AHI	1-5	6-25	>25

* best practice evidence based guideline, assessment of sleep disordered breathing in childhood, 2005, Pediatric Society of New Zealand

Surgical treatment to enlarge the upper airway with midface advancement can also be valuable to treat OSA. Patients with Apert, Crouzon and Pfeiffer syndrome have an intrinsic growth retardation of the maxilla[21] and restriction of normal transverse growth of the mandible, possibly secondary to cranial base abnormalities[22]. However, midface advancement does not always result in improvement of OSA[21, 23, 24].

Chapter 4 showed a favorable short-term effect of monobloc or le Fort III with distraction in only six of eleven (55%) patients with Apert, Crouzon or Pfeiffer syndrome. In a study by Witherow et al.[24], severe OSA treated with tracheostomy or CPAP was resolved after monobloc with external distraction in six of fourteen (43%) patients suffering from Apert, Crouzon or Pfeiffer syndrome. The other eight patients remained dependent on tracheostomy or CPAP. Arnaud et al.[21] showed that removal of tracheostomy was possible after monobloc with internal distraction in four of six (67%) severe cases with Apert, Crouzon or Pfeiffer syndromes. Nelson et al.[23] studied eighteen patients with syndromic bilateral coronal synostosis and OSA; respiratory support was discontinued after midface advancement in eleven patients (73%). Five patients were decanulated and CPAP was stopped in six. With a monobloc the midface (including the maxilla) and the forehead are advanced; with a le Fort III the midface is advanced, which resulted in improvement of the naso- and oropharynx (figure 1)[25]. A lower obstruction at the level of the hypopharynx may be responsible for unsuccessful midface advancement. Other treatment modalities should be considered as well, such as an advancement of the mandible.

Endoscopy of the upper airways by the otorhinolaryngologist before starting OSA treatment is recommended. In adults endoscopy is possible under propofol to induce the obstructive sleep situation. Children need to be in lying position at the outpatient clinic. When this is not possible, usually in very young children, it might be done under general anesthesia.

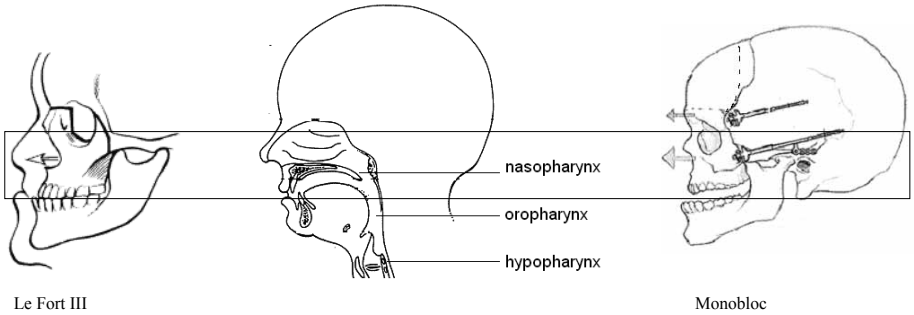


Figure 1: Le Fort III and monobloc as treatment modalities to improve the upper airway volume

Furthermore, the age at which the midface is advanced is essential, seeing that due to persistent maxillar growth retardation this intervention has only a temporary effect when performed at young age[26]. Then, at the age of 18, a second but simpler advancement (le Fort I) is needed. During adolescence it will be better to postpone the midface advancement if possible, because of the psychological consequences of this large surgical intervention, the period of distraction and the change of the child's face.

Other treatment options for OSA are a mandibular repositioning appliance (MRA), a surgically assisted rapid maxillary expansion (SARME) or a correction of the nasal septum. The treatment of OSA must be individualized, dependent on age, severity of OSA, craniofacial syndrome and level of obstruction (table 3).

Multidisciplinary approach

In this prospective study all children underwent at least one polysomnography; children below the age of seven more frequently on a yearly basis. In 35 multidisciplinary meetings 321 polysomnographies were evaluated. In 246 polysomnographies (77%) no or mild OSA without clinical symptoms was diagnosed and follow-up was arranged. In 78 polysomnographies (24%) mild OSA with clinical symptoms or moderate OSA was diagnosed and treatment was scheduled (table 4). Treatments were mostly (81%) needed in patients with Apert, Crouzon or Pfeiffer syndrome. This study also includes patients who were treated for OSA in the past and underwent a PSG in the follow-up program. In the past few years a new treatment was needed in 24% of those.

Airway volume measurements

In **chapter 4** we showed that it was possible to analyze computed tomography (CT) scans and measure volumes of two separate anatomical defined areas, the nasal cavity and rhinopharynx, and the oro- and hypopharynx. These airway volume measurements can show the improvement in airway after midface advancement and can determine the narrowest point of the airway. Volume changes in the pharyngeal airway were also found after

Table 3: Policy of the multidisciplinary team after performing a polysomnography

Age	Mild OSA	Moderate/ severe OSA	Remarks
0-1 yr	Conservative medical therapy	Nasal corticosteroids, nocturnal oxygen, NPT, tracheostomy	
1-6 yrs	Conservative medical therapy	ATE, nasal corticosteroids, nocturnal oxygen, CPAP/ BiPAP, monobloc (as first vault expansion or in presence of elevated ICP)	PSG 6 weeks post ATE, 3 months post monobloc, repeat PSG yearly
6-12 yrs	Conservative medical therapy	ATE, nasal corticosteroids, nocturnal oxygen, CPAP/ BiPAP, monobloc (in presence of elevated ICP)/ le Fort III	PSG 6 weeks post ATE, 3 months post advancement, repeat PSG yearly
12-15 yrs	Conservative medical therapy	Nasal corticosteroids, nocturnal oxygen, CPAP/ BiPAP, monobloc* (in presence of elevated ICP)/ le Fort III*, other options	PSG 3 months post advancement, repeat PSG yearly
15-18 yrs	Conservative medical therapy	Nasal corticosteroids, nocturnal oxygen, CPAP/ BiPAP, monobloc (in presence of elevated ICP)/ le Fort III, mandibular advancement, other options	PSG 3 months post advancement, repeat PSG yearly

Table 4: Treatment protocol of obstructive sleep apnea

Policy after 321 polysomnographies	n (%)
Follow-up	246 (76.6)
Consultation of otorhinolaryngologist	17 (5.3)
Endoscopy of upper airways	20 (6.2)
Nasal corticosteroids	7 (2.2)
Adenotonsillectomy	11 (3.4)
CPAP	4 (1.2)
Midface/ mandibular advancement	7 (2.2)
Correction of nasal septum	1 (0.3)
Diagnostics for elevated ICP	8 (2.5)

mandibular advancement[27]. Per surgical treatment this method can reproduce the level of improvement in the upper airway and it will be possible to choose the best treatment for each patient individually.

Functional problems

In **chapters 5 and 6** functional problems in syndromic craniosynostosis were discussed. The prevalence of papilledema in patients with Apert, Crouzon, or Pfeiffer syndrome is high, not only before but also after vault expansion. From 4% of patients with Muenke syndrome to 53% of patients with Crouzon/ Pfeiffer syndrome showed a first, preoperative episode of elevated intracranial pressure. It can be related to craniocerebral disproportion and can be adequately treated or prevented with early vault expansion. However,

the second episode is also frequently seen at the age of about 4 years, but its causative factors are less clear. It can be related to OSA, hydrocephalus or venous hypertension[28-30]. The prevalence of papilledema after the first vault expansion was 17% in Saethre-Chotzen syndrome, 20% in Crouzon/ Pfeiffer and 35% in Apert syndrome. Marucci et al.[31] reported the same prevalence in Apert syndrome. Only in Muenke syndrome there is a low risk of papilledema, i.e. 4%. Annual fundoscopy is recommended to screen for papilledema. If found present, a CT angiography can be performed to evaluate the ventricles and the venous outflow. A polysomnography to exclude OSA is needed to explore the possible cause of elevated ICP. Fundoscopy is of particular importance given the low reliability of clinical symptoms related to elevated ICP[32].

Other functional problems, such as refractive errors and hearing loss, should be diagnosed early, through screening. Treatment of hearing loss is necessary for an adequate development of speech.

Quality of life

Syndromic craniosynostosis has a large impact on the health-related quality of life of the children and their parents, both physical and psychosocial. This phenomenon was explored in **chapter 7**. Apert syndrome has the largest impact. But also patients with Muenke syndrome scored significantly lower than the norm, despite the lower risk for elevated ICP and OSA in comparison with Apert and Crouzon or Pfeiffer syndrome. OSA was an independent predictor for the domain 'change in health' on the Child Health Questionnaire (CHQ) only, possibly associated with the improvement after OSA treatment. Furthermore, elevated ICP was an independent predictor for lower scores on several domains: 'parental impact: emotional', 'family activity' and 'change in health' on the Infant Toddler Quality of Life questionnaire (ITQoL) and 'physical functioning', 'general behavior', 'general health perceptions', 'parental impact: time' and 'family activity' on the CHQ. This might be explained by the fact that elevated ICP could result in behavioral changes that influence these scores.

Chapter 8 showed the reliability and validity of the OSA-18, a disease-specific quality of life questionnaire, in children with syndromic or complex craniosynostosis. Its use is described in **chapter 9**. OSA seems to have consequences for quality of life. In these patients the OSA-18 score is also correlated with the severity of OSA. The domains 'sleep disturbance' and 'physical suffering' can be used to evaluate the impact of OSA on quality of life. In future research we will ask parents to complete the OSA-18 before and after treatment. Comparing these scores with polysomnography results we could measure the exact impact of OSA in syndromic craniosynostosis.

The OSA-18 showed no correlation with the presence of elevated ICP. Patients with papilledema scored not significantly higher at the different domains than those without papilledema.

Behavior

Behavioral problems were common in children with syndromic or complex craniosynostosis, as presented in **chapter 9**. The prevalence of behavioral problems is 32% in boys and 16% in girls. Sixty-seven percent of the boys with Apert syndrome scored in the (borderline) clinical range versus none of the girls. In Muenke syndrome also half of the boys scored in the (borderline) clinical range. In Apert syndrome OSA occurs more in boys (78%) than in girls (10%). Further the intelligence of boys with Apert syndrome is significantly lower than that of girls with Apert syndrome (Maliepaard et al., unpublished data); this can influence behavior. In Muenke syndrome the behavioral problems may be more intrinsic and are possibly related to the P250R FGFR3 mutation rather than associated with OSA. Previous studies were mostly performed in isolated craniosynostosis, only Sarimski[33, 34] reported behavioral problems in patients with Apert syndrome.

The total Child Behavior Checklist (CBCL) score of the children between the ages of 6 and 18 clearly correlated with the total OSA-18 score ($p = 0.000$). Boys aged 2-18 years with total CBCL scores in the abnormal range had significantly higher mean scores ($p < 0.05$) on all domains of the OSA-18 and the total OSA-18 score, girls only on the domains 'emotional distress' and 'daytime problems'. In boys the same was found for the externalizing CBCL scores in the abnormal range and for internalizing CBCL scores in the abnormal range: significantly higher means were found on the domains 'sleep disturbance', 'emotional distress', 'caregiver concerns' and the total OSA-18 score. In girls with abnormal internalizing and externalizing CBCL scores only the domain 'emotional distress' had significantly higher scores.

From the above results we may deduce that the 'emotional distress' domain can serve as a first screening for the presence of behavioral problems in children with syndromic or complex craniosynostosis. Dependent on age and sex we can formulate cut-off points for the 'emotional distress' score. Only above these points the complete CBCL questionnaire is needed. Setting a cut-off point of 6, for example, would imply that 45 CBCLs were indicated in this study population, of which 24 were scored in the (borderline) clinical range. The negative predictive value is 93% in boys and 91% in girls; six were missed. For externalizing scores in the abnormal range the domain 'emotional distress' had a negative predictive value of 100% in both boys and girls. Seventy-seven questionnaires could have been saved, and thus efficiency at the outpatient clinic in tracing behavioral problems could have been higher.

The CBCL showed no correlation with the presence of elevated ICP. Only one of seven boys and one of twelve girls with papilledema scored in the (borderline) clinical range on the total CBCL score. After this analysis with a small number of patients with papilledema we cannot confirm that elevated ICP resulted in behavioral problems.

Overall, obstructive sleep apnea in children with syndromic or complex craniosynostosis is characterized by difficulty in breathing during sleep and an obstructive apnea hypopnea index (OAHI) ≥ 1. But complaints during the day, such as frequent colds, and the consequences for behavior and quality of life are also important for evaluation of the severity in specific patients and for the decision how to treat.

FUTURE PERSPECTIVES

- Improved recognition of the clinical symptoms of mild obstructive sleep apnea

The presence of OSA must be suspected in each child with syndromic or complex craniosynostosis. Information from parents about difficulty in breathing is a good screening tool to exclude moderate or severe OSA in these children, but not mild OSA. There is a need for a screening tool that can be used to detect mild OSA.

- Better definition of mild, moderate and severe obstructive sleep apnea

The clinical consequences of mild obstructive sleep apnea are not well understood in children with syndromic and complex craniosynostosis. To gain more insight into the (patho) physiologic consequences of OSA, future studies should address the relations of OSA severity with heart rate variability, pulse transit time, sleep quality and arousal detection. Furthermore, markers of inflammation and oxidative stress will have to be determined to find a relation with the severity of OSA.

- Improvement of ambulatory polysomnography as diagnostic method

Polysomnography carried out at home is a great step forward. However, nasal flow is difficult to register. As alternative methods may serve the X flow or a mouth thermistor for recording of oral airflow. In ambulatory polysomnography, professionals could remotely monitor parents attaching the sensors with the use of a webcam rather than going to the patients' home themselves to attach the sensors. In case monitoring raises doubt about the procedure or when the diagnosis OSA is made, a full polysomnography in the hospital is necessary.

- Further determination of the relation between obstructive sleep apnea, elevated intracranial pressure and functional problems

The detection of elevated intracranial pressure is difficult. Papilledema is a late sign[32]. Transorbital sonography of the optic nerve can show dilatation of the optic nerve sheath diameter. A rise in ICP directly affects the perioptic nerve space resulting in an increase of the diameter[35-37]. Ultrasounds were performed in the craniosynostosis group and these will be analyzed in relation to the presence of papilledema. We will study the value of this method to detect elevated ICP more early in comparison with the development of papilledema.

The cause for elevated ICP is not only craniocerebral disproportion. The possible relationship between elevated ICP and Chiari malformation or ventricular dilatation is evaluated in these children with syndromic or complex craniosynostosis. To explore the venous hypertension hypothesis the size of the jugular foramen[38] will be measured on CT angiography scan in our study population. In addition, the natural course of ICP in craniosynostosis and the exact relationship with OSA will be studied by combining polysomnography with intracranial pressure monitoring.

- Further evaluation of the relation between physical sequelae, obstructive sleep apnea, elevated intracranial pressure and quality of life and behavior

Quality of life was measured using the Child Health Questionnaire Parental Form 50 (CHQ-PF50) above the age of 4 and the Infant Toddler Quality of Life questionnaire below 4 years. To compare the health-related quality of life in these children after a few years and to evaluate the impact of momentous events such as going to school we will ask the parents, who completed the ITQoL in this study, to complete the CHQ-PF 50. As teachers may note problems from comparison with classmates, parents are unaware of before. Teachers will also be asked to complete the CBCL to compare behavioral problems reported by parents and teachers.

Muenke syndrome is not well understood. This syndrome was recognized recently. Until now it was seen as a mild anomaly, but our studies brought out many problems in these children. Not all persons with the P250R FGFR3 mutation have craniosynostosis and it is not clear if they have the same problems as the patients with craniosynostosis. Maybe we can use them as controls to see the impact of the premature fusion of the calvarial sutures. The health-related quality of life of children with Muenke syndrome is lower and behavioral problems were frequently seen. Perhaps there is a relation between these two findings. The risk for elevated ICP is very low, but a third of patients will develop OSA in a mild form. It might well be that the behavioral problems are intrinsic. On the other hand mild OSA might be underestimated and the condition could then also result in behavioral problems and a lower quality of life. Psychological tests will help to unravel the sort of behavioral problems and the need for treatment.

Mental development in all children with syndromic or complex craniosynostosis will be determined by psychological tests. More attention to quality of life and behavior is needed at the outpatient clinic and support of children and their parents is necessary. Each child with syndromic or complex craniosynostosis should be seen by a psychologist minimally once. The best age for testing seems to be eight years; at that age accurate testing is possible. Furthermore, in most children any problems, such as anxiety, behavioral problems and learning disabilities will have developed before that age, so there is time for intervention.

- Longitudinal follow-up of treatment for OSA

Treatment should be individualized and the level of obstruction must be the determining factor. The effect of each treatment should be analyzed by change and hopefully improvement of the OAHI, the functional outcome and quality of life measured by the ITQoL or CHQ and by the OSA-18. Enlargement of the upper airway volume after surgical treatment, such as midface advancement, should be evaluated with three dimensional volume measurements before and after surgery.

With the initiation of this large prospective study in 2006, a lot of these future aims can be explored as part of the ongoing research in our center. The aim of this study and the ongoing studies is to improve the care of patients with syndromic and complex craniosynostosis. The early recognition of possible problems related to their syndrome is important. This enables to start with treatment as soon as possible, thus diminishing the negative consequences and offering these children optimal chances in life.

REFERENCES

1. Hoeve LJ, Pijpers M, Joosten KF. OSAS in craniofacial syndromes: an unsolved problem. Int J Pediatr Otorhinolaryngol 2003;67 Suppl 1:S111-113.
2. Lo LJ, Chen YR. Airway obstruction in severe syndromic craniosynostosis. Ann Plast Surg 1999;43:258-264.
3. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 2004;15:670-674.
4. Brouilette R, Hanson D, David R, et al. A diagnostic approach to suspected obstructive sleep apnea in children. J Pediatr 1984;105:10-14.
5. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2007;3:737-747.
6. Ferber R, Millman R, Coppola M, et al. Portable recording in the assessment of obstructive sleep apnea. ASDA standards of practice. Sleep 1994;17:378-392.
7. Brouillette RT, Morielli A, Leimanis A, et al. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000;105:405-412.
8. Poels PJ, Schilder AG, van den Berg S, et al. Evaluation of a new device for home cardiorespiratory recording in children. Arch Otolaryngol Head Neck Surg 2003;129:1281-1284.
9. Moss D, Urschitz MS, von Bodman A, et al. Reference values for nocturnal home polysomnography in primary schoolchildren. Pediatric research 2005;58:958-965.
10. Lowe LH, Booth TN, Joglar JM, et al. Midface anomalies in children. Radiographics 2000;20:907-922; quiz 1106-1107, 1112.
11. Guilleminault C, Lee JH, Chan A. Pediatric obstructive sleep apnea syndrome. Arch Pediatr Adolesc Med 2005;159:775-785.
12. Guilleminault C, Pelayo R, Leger D, et al. Recognition of sleep-disordered breathing in children. Pediatrics 1996;98:871-882.
13. Guilleminault C, Li K, Khramtsov A, et al. Breathing patterns in prepubertal children with sleep-related breathing disorders. Arch Pediatr Adolesc Med 2004;158:153-161.
14. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146:1235-1239.
15. Verhulst SL, Schrauwen N, Haentjens D, et al. Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. Pediatric pulmonology 2007;42:159-167.
16. Guilleminault C, Pelayo R, Clerk A, et al. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 1995;127:905-912.
17. Oliveira AJ, Nunes ML, Fojo-Olmos A, et al. Clinical correlates of periodic breathing in neonatal polysomnography. Clin Neurophysiol 2004;115:2247-2251.
18. Weintraub Z, Cates D, Kwiatkowski K, et al. The morphology of periodic breathing in infants and adults. Respiration physiology 2001;127:173-184.
19. Goroza E, Sagy M, Sagy N, et al. Severity assessment of obstructive sleep apnea syndrome (OSAS) in pediatric patients. Clinical pediatrics 2009;48:528-533.
20. Matsumoto E, Tanaka E, Tabe H, et al. Sleep architecture and the apnoea-hypopnoea index in children with obstructive-sleep apnoea syndrome. Journal of oral rehabilitation 2007;34:112-120.
21. Arnaud E, Marchac D, Renier D. Reduction of morbidity of the frontofacial monobloc advancement in children by the use of internal distraction. Plastic and reconstructive surgery 2007;120:1009-1026.

22. Boutros S, Shetye PR, Ghali S, et al. Morphology and growth of the mandible in Crouzon, Apert, and Pfeiffer syndromes. J Craniofac Surg 2007;18:146-150.
23. Nelson TE, Mulliken JB, Padwa BL. Effect of midfacial distraction on the obstructed airway in patients with syndromic bilateral coronal synostosis. J Oral Maxillofac Surg 2008;66:2318-2321.
24. Witherow H, Dunaway D, Evans R, et al. Functional outcomes in monobloc advancement by distraction using the rigid external distractor device. Plastic and reconstructive surgery 2008;121:1311-1322.
25. Burstein FD, Cohen SR, Scott PH, et al. Surgical therapy for severe refractory sleep apnea in infants and children: application of the airway zone concept. Plastic and reconstructive surgery 1995;96:34-41.
26. Fearon JA. Halo distraction of the Le Fort III in syndromic craniosynostosis: a long-term assessment. Plastic and reconstructive surgery 2005;115:1524-1536.
27. Vos WG, De Backer WA, Verhulst SL. Correlation between the severity of sleep apnea and upper airway morphology in pediatric and adult patients. Current opinion in allergy and clinical immunology;10:26-33.
28. Hayward R. Venous hypertension and craniosynostosis. Childs Nerv Syst 2005;21:880-888.
29. Hayward R, Gonsalez S. How low can you go? Intracranial pressure, cerebral perfusion pressure, and respiratory obstruction in children with complex craniosynostosis. J Neurosurg 2005;102:16-22.
30. Taylor WJ, Hayward RD, Lasjaunias P, et al. Enigma of raised intracranial pressure in patients with complex craniosynostosis: the role of abnormal intracranial venous drainage. J Neurosurg 2001;94:377-385.
31. Marucci DD, Dunaway DJ, Jones BM, et al. Raised intracranial pressure in Apert syndrome. Plastic and reconstructive surgery 2008;122:1162-1168; discussion 1169-1170.
32. Tuite GF, Chong WK, Evanson J, et al. The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. Neurosurgery 1996;38:272-278.
33. Sarimski K. Children with Apert syndrome: behavioral problems and family stress. Developmental medicine and child neurology 1998;40:44-49.
34. Sarimski K. Social adjustment of children with a severe craniofacial anomaly (Apert syndrome). Child: care, health and development 2001;27:583-590.
35. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension II. Patient study. Pediatr Radiol 1996;26:706-710.
36. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension. I. Experimental study. Pediatr Radiol 1996;26:701-705.
37. Wiegand C, Richards P. Measurement of intracranial pressure in children: a critical review of current methods. Developmental medicine and child neurology 2007;49:935-941.
38. Rich PM, Cox TC, Hayward RD. The jugular foramen in complex and syndromic craniosynostosis and its relationship to raised intracranial pressure. AJNR Am J Neuroradiol 2003;24:45-51.





Chapter 11

Summary

SUMMARY

The aim of this thesis is to assess the importance and impact of obstructive sleep apnea in children with syndromic or complex craniosynostosis. The topics of interest are the prevalence, diagnostics and treatment outcome of obstructive sleep apnea and the influence on prevalence of papilledema, health-related quality of life and general behavior.

Background information on syndromic craniosynostosis is given in **chapter 1**. Craniosynostosis is characterized by the premature fusion or agenesis of calvarial sutures and in about 40% of the cases (1:6.250) the craniosynostosis is part of a syndrome, such as Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome. Complex craniosynostosis is defined as fusion of two or more cranial sutures without known FGFR (fibroblast growth factor receptor) or TWIST mutation.

Patients with syndromic and complex craniosynostosis are at risk for elevated intracranial pressure (ICP) and obstructive sleep apnea (OSA). Factors suggested to contribute to elevated ICP in craniosynostosis are craniocerebral disproportion, ventriculomegaly or hydrocephalus, venous hypertension and obstructive sleep apnea. In craniosynostosis the first treatment or prevention of elevated ICP is surgical decompression to expand the skull within the first year of life.

Obstructive sleep apnea is a clinical syndrome due to partial or complete upper airway obstruction characterized by difficulty in breathing, snoring and apneas during sleep resulting in sleep fragmentation, hypoxia and hypercapnia. A questionnaire on presence of symptoms can be helpful to screen for OSA, but the gold standard to diagnose presence and severity of OSA is polysomnography (PSG). The obstructive apnea hypopnea index (OAHI) is used to differentiate in severity. OSA treatment is dependent on its severity, cause and level of obstruction.

Chapter 2 described the prediction of the presence of OSA in children with syndromic or complex craniosynostosis by their parents. The OSA score, known as Brouillette score, can be used to screen for the presence of OSA and consists of the three items: breathing difficulty, apnea and snoring. The single question 'difficulty in breathing during sleep' showed a sensitivity of 64% and a high negative predictive value of 91% in comparison with polysomnography. So, if the child has no difficulty in breathing during sleep, the presence of moderate or severe OSAS can almost certainly be excluded and polysomnography is not necessary. The question about snoring does not have any additional value, because it was shown that 77% of the children snore. This is mainly due to a narrow nasal cavity.

The feasibility of a home cardiorespiratory monitor in these children to diagnose OSA at home is presented in **chapter 3**. Overall, 40.5% of the recordings were suitable for calculating an OAHI with all signals being present. The most important limitation is the absence of nasal flow. In children with syndromic or complex craniosynostosis we speculate that

the main reason for the failing signal of the nasal cannula is the absence of nasal passage due to the severe anatomical malformations of the nasal cavity, leading to almost complete obstruction of the upper airway and as a consequence preferred mouth breathing. Another important reason for absence of nasal flow is that not all children accept the nasal cannula. The sum of the amplitudes of the thoracic and abdominal movements (X flow) seems a valuable alternative assessment, when complete recording of the nasal flow signal was not achieved. Using X flow as screening method raised the overall success rate from 40.5% to 75%.

The long-term respiratory outcome of midface advancement in patients with Apert, Crouzon or Pfeiffer syndrome suffering from moderate or severe OSA, requiring oxygen, continuous positive airway pressure (CPAP), or tracheostomy is assessed in **chapter 4**. Despite midface advancement, long-term respiratory support (dependency on CPAP or tracheostomy) was maintained in five of the eleven studied patients. In all patients without respiratory improvement or with relapse after surgery, endoscopy showed obstruction at the level of the rhino- or hypopharynx. Dynamic pharyngeal collapse can affect the respiratory outcome of midface advancement. Therefore endoscopy of the upper airway before midface advancement is recommended to identify any level of airway obstruction that may interfere with respiratory improvement after midface advancement.

The prevalence of functional problems in children with syndromic craniosynostosis is reported in **chapter 5 and 6**. The prevalence of papilledema in patients with Apert, Crouzon or Pfeiffer syndrome is high (51%), not only before cranial decompression (38%) but also after surgery (43%). Clinical symptoms, such as headache and vomiting, were poor predictors for the presence of papilledema. Complex craniosynostosis, exorbitism and ventricular dilatation were factors associated with papilledema. Given the high prevalence of papilledema annual fundoscopy is highly recommended (chapter 5). Other functional problems such as refractive errors and hearing loss are highly prevalent (52-56%) in all types of syndromic or complex craniosynostosis. Genetic analysis is necessary for counseling and screening on syndrome specific anomalies and functional deficits. Follow-up by a multidisciplinary team is needed till the age of 18 years to obtain the best possible outcome. A diagnosis-specific screening and treatment protocol is given (chapter 6).

Chapter 7 describes the health-related quality of life in children and adolescents with syndromic or complex craniosynostosis. Parents' scores for these patients were significant lower than those for the norm population; syndromic craniosynostosis has a large impact on the health-related quality of life, both physical and psychosocial. Apert syndrome had the largest impact on the different domains.

To evaluate the disease-specific impact of obstructive sleep apnea in the general population and also in children with syndromic or complex craniosynostosis, a disease-specific quality of life questionnaire, the OSA-18 survey, is tested. The internal consistency, test-retest reliability and discriminative validity of the OSA-18 in the craniosynostosis popula-

tion are assessed in **chapter 8**. The OSA-18 was found to be a reliable and valid method. It can be used in future studies.

Chapter 9 reports the impact of OSA on quality of life in syndromic and complex craniosynostosis and the prevalence of behavioral problems. The correlation between OAHI and the total OSA-18 and CBCL scores was significant. The domains 'sleep disturbance' and 'physical suffering' were significantly higher in patients with moderate OSA and can be used to evaluate the impact of OSA on their quality of life. Within the craniosynostosis group children with Apert syndrome showed the highest total OSA-18 score. A high prevalence of behavioral problems was found, especially in boys with Apert and Muenke syndrome.

The main findings of this thesis and comments on these findings are discussed in **chapter 10**, including future perspectives on research. Future studies are needed to improve the recognition of the clinical symptoms of mild, moderate and severe OSA and the consequences of the severity of OSA on growth and development, intracranial pressure, behavior and quality of life. Concerning ambulatory polysomnography the use of X flow should be validated in comparison with full polysomnography in the hospital.

A multidisciplinary team should take care of all the different clinical features known in these craniosynostosis patients and centralization of care is highly recommended.





Chapter 12

Nederlandse samenvatting

Abbreviations

Dankwoord

Curriculum vitae

List of publications

PhD portfolio

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift betreft het in kaart brengen van het belang en de impact van het obstructief slaap apneu syndroom bij kinderen met een syndromale of complexe vorm van craniosynostose. Aandachtsgebieden zijn prevalentie, diagnostiek en behandelingsuitkomst van het obstructief slaap apneu syndroom (OSAS) en de invloed van OSAS op de prevalentie van papiloedeem, de gezondheidsgerelateerde kwaliteit van leven en het gedrag.

Achtergrondinformatie over syndromale craniosynostose wordt gegeven in **hoofdstuk 1**. Craniosynostose wordt gekenmerkt door vroegtijdige sluiting of agenesie van de schedelnaden en is in 40% van de gevallen (1:6.250) onderdeel van een syndroom, zoals het syndroom van Apert, Crouzon, Pfeiffer, Muenke of Saethre-Chotzen. Complexe craniosynostose wordt gedefinieerd als sluiting van twee of meer schedelnaden zonder bekende mutatie in de fibroblast groeifactor receptor (FGFR) of in het TWIST gen.

Patiënten met een syndromale en complexe craniosynostose hebben een verhoogd risico op de ontwikkeling van verhoogde intracraniële (hersen)druk (ICP) en van het obstructief slaap apneu syndroom. Mogelijke factoren die bijdragen aan de verhoogde ICP bij craniosynostose zijn craniocerebrale disproportie, ventriculomegalie of hydrocephalus, veneuze hypertensie en OSAS. De eerste behandeling of preventie van verhoogde ICP bij deze kinderen betreft een operatie in het eerste levensjaar waarbij de schedel groter wordt gemaakt.

Het obstructief slaap apneu syndroom is een klinisch syndroom waarbij een gedeeltelijke of complete obstructie van de bovenste luchtweg optreedt, die wordt gekenmerkt door moeilijkheden met ademhalen, snurken en apneus (stoppen met ademhalen) tijdens de slaap en die leidt tot slaapfragmentatie, hypoxie (zuurstoftekort) en hypercapnie (teveel koolstofdioxide). Een vragenlijst over de aanwezigheid van symptomen kan handig zijn in de screening naar OSAS, maar de gouden standaard om de aanwezigheid en de ernst van OSAS vast te stellen is polysomnografie (PSG). De obstructieve apneu hypopneu index (OAHI) wordt gebruikt om te differentiëren in ernst. De behandeling van OSAS is afhankelijk van de ernst, de oorzaak en het niveau van obstructie.

Hoofdstuk 2 beschrijft de vraag of ouders de aanwezigheid van OSAS bij hun kinderen met een syndromale of complexe craniosynostose kunnen voorspellen. De OSAS score, bekend als Brouillette score, kan gebruikt worden bij de screening op de aanwezigheid van OSAS en bestaat uit drie items, namelijk ademhalingsmoeilijkheden, apneus en snurken. In de craniosynostose populatie heeft de vraag naar moeilijkheden met ademhalen tijdens de slaap een sensitiviteit van 64% en een hoge negatief voorspellende waarde van 91% in vergelijking met polysomnografie. Kortom, als het kind geen moeilijkheden met ademhalen tijdens de slaap heeft kan de aanwezigheid van matige en ernstige OSAS zo goed als

zeker uitgesloten worden en is een polysomnografie onnodig. De vraag over snurken heeft geen toegevoegde waarde, daar vastgesteld is dat 77% van de kinderen snurkt. Dit komt voornamelijk door een nauwe neusholte.

Het gebruik van een cardiorespiratoire thuismonitor (polysomnograaf) voor het stellen van de diagnose OSAS bij deze kinderen wordt besproken in **hoofdstuk 3**. Totaal is 40.5% van de registraties te gebruiken om een OAHI te berekenen aan de hand van alle signalen. De belangrijkste beperking is de afwezigheid van de neusflow, geregistreerd door de neusbril. Bij kinderen met een syndromale of complexe craniosynostose lijkt de belangrijkste reden voor het ontbreken van het neusflowsignaal de afwezigheid van neuspassage te zijn. Dit laatste komt door de anatomische afwijkingen van de neusholte, die leiden tot een bijna complete obstructie van de bovenste luchtweg met als gevolg mondademhaling. Een andere belangrijke reden voor de afwezigheid van de neusflow is het feit dat niet alle kinderen de neusbril accepteren. De som van de amplitudes van de borst- en buikademhalingsbewegingen (X flow) lijkt een waardevol alternatief, wanneer complete registratie van de neusflow niet gelukt is. Het gebruik van de X flow als screeningsmethode zorgt voor een stijging van het succespercentage van 40.5% naar 75%.

De respiratoire uitkomst van een aangezichtscorrectie op de lange termijn bij patiënten met het syndroom van Apert, Crouzon of Pfeiffer met matige of ernstige OSAS, waarvoor ze zuurstof, neuskapbeademing (CPAP) of een tracheacanule nodig hebben, wordt besproken in **hoofdstuk 4**. Ondanks de aangezichtscorrectie bleef respiratoire ondersteuning (afhankelijkheid van CPAP of een tracheacanule) op de lange termijn gehandhaafd bij vijf van de elf onderzochte patiënten. Bij alle patiënten zonder respiratoire verbetering of met een recidief na chirurgie toonde de endoscopie een obstructie op het niveau van de rhino- of hypopharynx (neus-keelholte of het onderste deel van de keelholte). Een dynamische collaps van de pharynx kan de respiratoire uitkomst van de aangezichtscorrectie beïnvloeden. Daarom wordt voor deze operatie een endoscopie van de bovenste luchtweg geadviseerd om elk niveau van luchtwegobstructie vast te stellen, dat invloed kan hebben op de respiratoire verbetering na de correctie.

De prevalentie van functionele problemen voorkomend bij kinderen met een syndromale craniosynostose komt aan de orde in **hoofdstuk 5 en 6**. De prevalentie van papiloedeem bij patiënten met het syndroom van Apert, Crouzon of Pfeiffer is hoog (51%), niet alleen voor de chirurgische decompressie (38%), maar ook na de operatie (43%). Klinische symptomen, zoals hoofdpijn en braken, zijn slechte voorspellers voor de aanwezigheid van papiloedeem. Complexe craniosynostose, exorbitisme en ventrikeldilatatie zijn factoren die geassocieerd zijn met papiloedeem. Jaarlijkse funduscopie is sterk aan te raden gezien de hoge prevalentie van papiloedeem (hoofdstuk 5). Andere functionele problemen, zoals refractieafwijkingen en gehoorverlies komen veel voor (52-56%) bij alle typen syndromale en complexe craniosynostose. Genetische analyse is noodzakelijk voor counseling en screening op syndroom-specifieke afwijkingen en functionele stoornissen. Follow-up door een

multidisciplinair team is nodig tot de leeftijd van 18 jaar om de best mogelijke uitkomst te bieden. Een voorstel voor een diagnose-specifieke screening en een behandelprotocol wordt gedaan (hoofdstuk 6).

Hoofdstuk 7 beschrijft de gezondheidsgerelateerde kwaliteit van leven van kinderen en adolescenten met syndromale of complexe craniosynostose. De door ouders gerapporteerde scores voor deze patiënten waren significant lager dan die voor de normpopulatie; syndromale craniosynostose heeft een grote impact op de gezondheidsgerelateerde kwaliteit van leven, zowel fysiek als psychosociaal. Het syndroom van Apert heeft de grootste impact op verscheidene domeinen.

Om de ziekte-specifieke impact van het obstructief slaap apneu syndroom in de gewone populatie en bij kinderen met een syndromale of complexe craniosynostose te evalueren, is een ziekte-specifieke kwaliteit van leven vragenlijst, de OSA-18, getoetst. De interne consistentie, de test-hertest betrouwbaarheid en de discriminatieve validiteit van de OSA-18 in de craniosynostose populatie zijn onderzocht in **hoofdstuk 8**. De OSA-18 vragenlijst is als een betrouwbaar en valide instrument getest en kan in toekomstige studies gebruikt worden.

Hoofdstuk 9 rapporteert de impact van OSAS op de kwaliteit van leven bij syndromale en complexe craniosynostose en de prevalentie van gedragsproblemen. De correlatie tussen de OAHI en de totale OSA-18 en CBCL scores is significant. De domeinen 'slaapproblemen' en 'lichamelijke verschijnselen' scoren significant hoger bij patiënten met matige OSAS en kunnen gebruikt worden om de impact van OSAS op hun kwaliteit van leven te bepalen. Binnen de craniosynostose groep wordt bij kinderen met het syndroom van Apert de hoogste totale OSA-18 score gemeten. De prevalentie van gedragsproblemen is hoog, voornamelijk bij jongens met het syndroom van Apert en Muenke.

De belangrijkste bevindingen van dit proefschrift en opmerkingen naar aanleiding van deze bevindingen worden bediscussieerd in **hoofdstuk 10**, dat ook de toekomstplannen op onderzoeksgebied bespreekt. Toekomstige studies zijn nodig om de herkenning van klinische symptomen van milde, matige en ernstige OSAS en de consequenties van de mate van ernst op groei en ontwikkeling, hersendruk, gedrag en kwaliteit van leven te verbeteren. Wat de ambulante polysomnografie betreft, het gebruik van de X flow behoeft validatie in vergelijking met volledige polysomnografie uitgevoerd in het ziekenhuis.

Een multidisciplinair team dient zorg te dragen voor alle verschillende klinische aspecten voorkomend bij deze craniosynostose patiënten en centralisatie van de zorg wordt sterk aangeraden.

ABBREVIATIONS

ATE	adenotonsillectomy
BiPAP	bi-level positive airway pressure
Br score	Brouillette score
CBCL	child behavior checklist
CHQ-PF	child health questionnaire parent form
CHQ-CF	child health questionnaire child form
CI	confidence interval
CPAP	continuous positive airway pressure
CT scan	computed tomography scan
FGFR	fibroblast growth factor receptor
ICP	intracranial pressure
ITQoL	infant toddler quality of life questionnaire
MRA	mandibular repositioning appliance
NPT	nasopharyngeal tube
NPV	negative predictive value
OAHI	obstructive apnea hypopnea index
ODI	oxygenation desaturation index
OSA	obstructive sleep apnea
PSG	polysomnography
SARME	surgically assisted rapid maxillary expansion
Sens	sensitivity
sd	standard deviation
VP	ventriculoperitoneal

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Natalja

CURRICULUM VITAE

Natalja Bannink was born on 1st January 1980 in The Hague. She finished high school at the Gymnasium Haganum in The Hague in 1998. From her youngest years she knew she wanted to become a pediatrician. She obtained her medical degree at the Erasmus University in Rotterdam in 2004 (cum laude). At the outpatient clinic of the Erasmus MC-Sophia Children's Hospital in Rotterdam she finished her research project about learning problems in children with Neurofibromatosis type 1 in 2002. She worked as a pediatric resident (ANIOS) at the department of pediatrics in the Albert Schweitzer Hospital in Dordrecht during six months. In March 2005 she worked for a year in the Erasmus MC-Sophia Children's Hospital at the medium care unit and the neonatal intensive care unit.

Between March 2006 and April 2010 she performed her PhD on 'Obstructive sleep apnea in children with syndromic craniosynostosis' at the Dutch Craniofacial Center in the Erasmus MC-Sophia Children's Hospital under the supervision of dr. Irene M.J. Mathijssen and dr. Koen F.M. Joosten (promoter prof. dr. S.E.R. Hovius).

In April 2010 she started as a pediatric resident (AIOS) at the Maasstad Hospital in Rotterdam (dr. C.R. Lincke) and at the Erasmus MC-Sophia Children's Hospital in Rotterdam (dr. M. de Hoog and prof. dr. A.J. van der Heijden).

Natalja lives with her husband Arno and daughter Nouschka in Rijswijk.

LIST OF PUBLICATIONS

- Bannink N, Joosten KFM, van Veelen MLC, Bartels MC, Tasker RC, van Adrichem LNA, van der Meulen JJNM, Vaandrager JM, de Jong THR, Mathijssen IMJ. Papilledema in patients with Apert, Crouzon and Pfeiffer syndrome; prevalence, efficacy of treatment and risk factors. J Craniofac Surgery 19: 121-127, 2008
- De Jong T, Bannink N, Bredero-Boelhouwer HH, van Veelen ML, Bartels MC, Hoeve LJ, Hoogeboom AJ, Wolvius EB, Lequin MH, van der Meulen JJ, van Adrichem LN, Vaandrager JM, Ongkosuwito EM, Joosten KFM, Mathijssen IMJ. Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. J Plast Reconstr Aesthet Surg Epub ahead of print, 2009
- Florisson JMG, van Veelen MLC, Bannink N, van Adrichem LNA, van der Meulen JJNM, Bartels MC, Mathijssen IMJ. Papilledema in isolated single-suture craniosynostosis: prevalence and predictive factors. J Craniofac Surgery 21(1): 20-24, 2010
- Bannink N, Nout E, Wolvius EB, Hoeve LJ, Joosten KFM, Mathijssen IMJ. Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement. Int J Oral Maxillofac Surgery 39(2): 115-121, 2010
- Bannink N, Mathijssen IMJ, Joosten KFM. Can parents predict obstructive sleep apnea in children with syndromic or complex craniosynostosis? Int J Oral Maxillofac Surgery 39(5): 421-423, 2010
- Bannink N, Mathijssen IMJ, Joosten KFM. Use of ambulatory polysomnography in children with syndromic craniosynostosis. J Craniofacial Surgery In press, 2010
- Bannink N, Maliepaard M, Raat H, Joosten KFM, Mathijssen IMJ. Health-related quality of life in children and adolescents with syndromic craniosynostosis. J Plast Reconstr Aesthet Surg Epub ahead of print, 2010

- De Carolien Bijl Stichting financiert onderzoek bij craniofaciale patiënten. Face Nieuwsbrief van Laposa, nr 2, 2009
- Speciale groep kinderen heeft een vergrote kans op OSAS. Apneu magazine, nr 2, juni 2009

PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Erasmus MC Department: Pediatrics/ Plastic Surgery
PhD period: 01-03-2006 – 01-04-2010
Promoter: Prof. dr. S.E.R. Hovius
Supervisor: Dr. I.M.J Mathijssen/ Dr K.F.M. Joosten

1. PhD training

	Date	Workload (ECTS)
General academic skills		
- Introduction for beginning PhD candidates	08-06-06	0.1
- How to write and read a medical paper?	12-08-06, 19-08-06	0.7
- Biomedical English Writing and Communication	04-09-07 – 18-12-07, 15-01-08	4.0
Research skills		
- Statistics		
Introduction to data-analysis	07-08-06 – 11-08-06	0.9
Regression analysis	14-08-06 – 18-08-06	1.3
- Methodology		
Minicursus Methodologie van patiëntgebonden onderzoek Rotterdam	16-03-06	0.3

Oral presentations		
- Obstructive sleep apnea and intracranial pressure in children with syndromic craniosynostosis. Meeting Tyco Healthcare Rotterdam	19-04-07	1.4
- Obstructief slaap apneu syndroom en intracraniële drukverhoging bij kinderen met een syndromale craniosynostosis. Onderzoeksdag Sophia Kinderziekenhuis Rotterdam	18-10-07	1.4
- De effecten van chirurgische behandeling van het obstructief slaap apneu syndroom bij kinderen met een syndromale craniosynostosis. Vergadering Nederlandse Vereniging van Schisis en Craniofaciale Afwijkingen Zwolle	17-11-07	1.4
- Obstructive sleep apnea and intracranial pressure in children with syndromic craniosynostosis. Craniofacial Meeting Rotterdam	18-01-08	1.4
- Obstructief slaap apneu syndroom en verhoogde intracraniële druk bij kinderen met syndromale craniosynostosis. Refereerbijeenkomst Plastische Chirurgie Rotterdam	02-04-08	1.4
- Lange termijn resultaat van midface advancement voor obstructief slaap apneu syndroom bij kinderen met syndromale craniosynostosis. Vergadering Nederlandse Vereniging van Plastische Chirurgie Zeist	24-04-08	1.4
- Obstructive sleep apnea in children with syndromic craniosynostosis: unsatisfactory long-term respiratory outcome of midface advancement. European Society of Craniofacial Surgery Lille, France	20-09-08	1.4
- Kunnen ouders van kinderen met syndromale craniosynostosis de aanwezigheid van obstructief slaap apneu syndroom voorspellen? Vergadering Nederlandse Vereniging van Schisis en Craniofaciale Afwijkingen Nijmegen	15-11-08	1.4
- Obstructive sleep apnea in children with syndromic craniosynostosis: respiratory outcome of midface advancement. 9th World Congress on Sleep Apnea Seoul	26-03-09	1.4
- Health-related quality of life in children with syndromic or complex craniosynostosis and obstructive sleep apnea. 9th World Congress on Sleep Apnea Seoul	28-03-09	1.4
- Gezondheids gerelateerde kwaliteit van leven van kinderen met een syndromale of complexe craniosynostosis. Vergadering Nederlandse Vereniging van Plastische Chirurgie Utrecht	03-04-09	1.4
Poster presentations		
- Elevated ICP in patients with Apert, Crouzon and Pfeiffer syndrome. Wetenschapsdag Erasmus MC Rotterdam	01-02-07	1.0
- Kunnen ouders van kinderen met syndromale craniosynostosis de aanwezigheid van obstructief slaap apneu syndroom voorspellen? Dag voor de jonge onderzoeker Nederlandse Vereniging Kindergeneeskunde Veldhoven	04-11-08	1.0
- Kunnen ouders de aanwezigheid van obstructief slaap apneu syndroom voorspellen? Posterprijs 30e congres Nederlandse Vereniging voor Kindergeneeskunde Veldhoven	07-11-08	1.0
- Can parents predict the presence of obstructive sleep apnea in children with syndromic or complex craniosynostosis? 9th World Congress on Sleep Apnea Seoul	26-03-09	1.0

International conferences		
- Sleep and the cardiovascular system Marburg, Germany	07-04-06	0.3
- 8th International Neurotrauma Symposium Rotterdam	23-05-06	0.2
- 8th World Congress on Sleep Apnea Montréal, Canada	28-09-06 – 30-09-06	0.7
- Benelux Sleep Congress Mondorf-les-Bains, Luxembourg	11-05-07	0.2
- European Society of Craniofacial Surgery Lille, France	19-09-08 – 20-09-08	0.4
- Benelux meeting Nederlandse Vereniging van Plastische Chirurgie/ Royal Belgian Society for Plastic Surgery Den Bosch	04-10-08	0.3
- Symposium on sleep-disordered breathing in children Antwerpen, Belgium	21-11-08 – 22-11-08	0.4
- 9th World Congress on Sleep Apnea Seoul, Korea	25-03-09 – 28-03-09	1.0
Seminars and workshops		
- INVOS Paediatric Master Class Paris, France	10-04-06 – 11-04-06	0.3
- Wetenschapsdag Erasmus MC Rotterdam	01-02-07	0.2
- Embletta trainingsdag Embla/ Medcare Amsterdam	14-02-07	0.2
- Brain RT klinische polysomnografie trainingsdag Universitair Ziekenhuis Antwerpen, Belgium	02-07-07	0.1
- Onderzoeksdag Kindergeneeskunde Sophia Kinderziekenhuis Rotterdam	18-10-07	0.2
- Najaarsvergadering Nederlandse Vereniging van Schisis en Craniofaciale Afwijkingen Zwolle	17-11-07	0.3
- Craniofacial Meeting Rotterdam	18-01-08	0.3
- Wetenschapsdag Erasmus MC Rotterdam	07-02-08	0.2
- Refereerbijeenkomst Plastische Chirurgie Rotterdam	02-04-08	0.1
- Voorjaarsvergadering Nederlandse Vereniging van Plastische Chirurgie Zeist	24-04-08	0.3
- The Generation R Symposium Imaging and early brain development Rotterdam	19-06-08	0.1
- Najaarsvergadering Nederlandse Vereniging van Schisis en Craniofaciale Afwijkingen Nijmegen	15-11-08	0.3
- Refereerbijeenkomst Plastische Chirurgie Rotterdam	17-09-08	0.1
- Dag voor jonge onderzoekers Nederlandse Vereniging voor Kindergeneeskunde Veldhoven	04-11-08	0.3
- 30c congres Nederlandse Vereniging voor Kindergeneeskunde Veldhoven	07-11-08	0.3
- Symposium Cognitive deficits in children with Neurofibromatosis type 1: from recognition to treatment Rotterdam	26-11-08	0.1
- Symposium Quality of life and quality of care Rotterdam	02-12-08	0.1
- Onderzoeksdag Kindergeneeskunde Sophia Kinderziekenhuis Rotterdam	18-12-08	0.1
- Refereerbijeenkomst Plastische Chirurgie Rotterdam	21-01-09	0.1
- Workshop grant writing Nijmegen	29-01-09	0.1
- Workshop TULIPS subsidieaanvraag schrijven Rotterdam	02-03-09	0.1
- Voorjaarsvergadering Nederlandse Vereniging van Plastische Chirurgie Utrecht	03-04-09	0.3
- Seminar Epidemiology Success in research: learn from the experts Rotterdam	15-04-09	0.1
- Symposium Infant feeding, early growth patterns, and long-term risk for metabolic and cardiovascular disease Rotterdam	06-05-09	0.2

2. Teaching activities		
Lecturing		
- Wetenschappelijk onderzoek OSAS en ICP bij syndromale craniosynostosis. Kinderartsenweek Sophia Kinderziekenhuis Rotterdam	29-01-07	1.4
- Het obstructief slaap apneu syndroom bij kinderen. Keuzeonderwijs plastische chirurgie studenten geneeskunde Rotterdam	12-02-07, 30-01-08, 26-01-09, 28-01-10	2.8
Supervising Master's theses		
- Supervising Tim de Jong, medical student, retrospective research and article writing	2008	3.6