LONG-TERM RESULTS IN SYNDROMIC CRANIOSYNOSTOSIS

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Sien
“Home is wherever I am with you.”
Edward sharpe & the magnetic zeros

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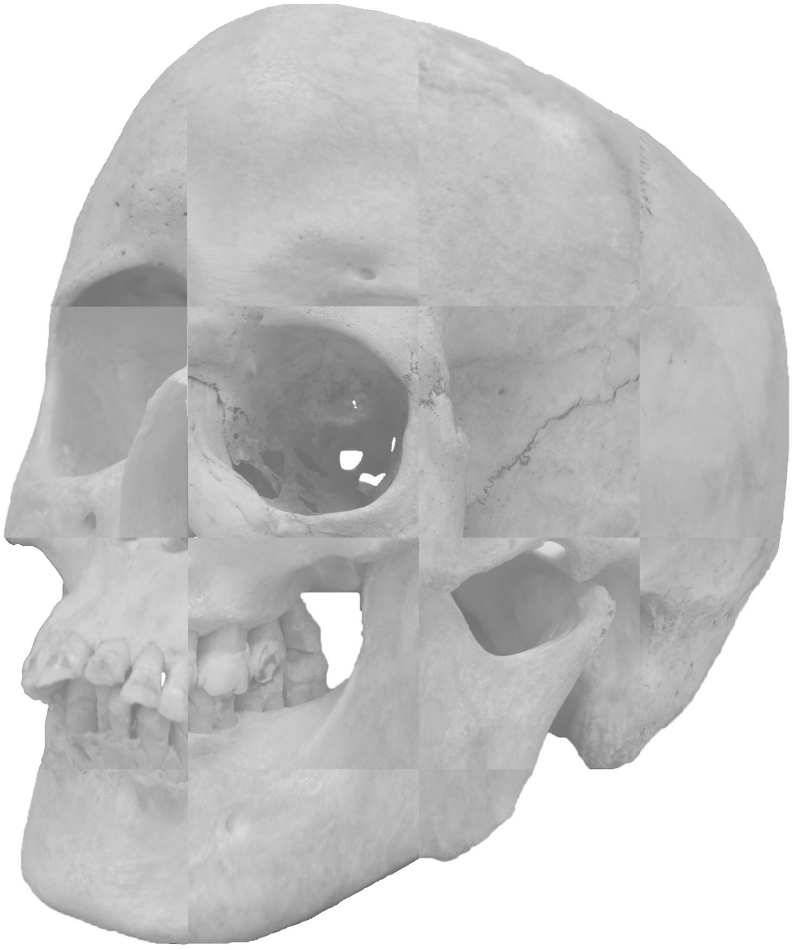
Chapter 1

General introduction

T. de Jong



INTRODUCTION

Skull sutures are fibrous joints between the different bones of the skull. In adult life they have no function but in the foetus they allow the bones to move during the birth process and are involved in skull growth till the age of six years. After the age of six years skull growth takes place by apposition of bone at the outer site of the skull and resorption of bone on the inner site of the skull.

Craniosynostosis is a condition in which one or more sutures of the skull prematurely fuse. The term craniosynostosis was first used by Otto in 1830.[1] The word "Cranio" refers to cranium, "Syn" to together and "ostosis" to the genesis of bone. But the first description of craniosynostosis dates back to Hippocrates and Galen[2] and it is a disorder that occurs in the human species since ancient times.[3] When craniosynostosis is caused by a mutation or deletion we speak of syndromic craniosynostosis. This is the case in at least 20% of the patients with craniosynostosis.[4] The most prevalent syndromes are Apert, Crouzon, Muenke and Saethre-Chotzen.

In 1851 Virchow was the first to describe how skull growth is restricted in the plane perpendicular to the prematurely fused suture and is enhanced in the plane parallel to it.[5] Skull growth is necessary to provide space for the growing brain, but in case of craniosynostosis this results in an abnormal skull shape and possibly a restricted intracranial volume. In patients with syndromic craniosynostosis not only the neurocranium is affected but also the viscerocranium which affects the growth of the orbits, maxilla and mandible. This abnormal growth results in functional and morphological problems, of which the most important are raised intracranial pressure (ICP), ventricular dilatation, obstructive sleep apnea (OSA), Chiari I malformation, visual impairments, hearing disorders, malocclusion and exophthalmus.

The prevalence of raised ICP varies per syndrome, between 60% in Crouzon syndrome, 45% in Apert syndrome and 30 % in all other syndromes.[6] There are many hypotheses for the cause of raised ICP in craniosynostosis, all of them can be related to the Monro-Kellie hypothesis stating that the cranium and its constituents (blood, cerebrospinal fluid and brain tissue) create a state of volume equilibrium. Intracranial pressure is stable as long as volume added is balanced by volume displaced or in case of children increase of the intracranial volume. In patients with craniosynostosis the displacement can be obstructed by limited growth of the intracranial volume, obstructed venous outflow caused by OSA or jugular foramen stenosis and by liquor resorption problems.[7-9] Diagnosis of raised ICP can be difficult because it is not always symptomatic in patients with craniosynostosis, and papilledema can be the only clini-

cal sign.[10] Raised ICP causes papilledema because the pressure is transmitted to the optic nerve, causing nerve head swelling, or optic disc oedema. This can lead to loss of fibers of the optic nerve and permanent visual impairment. The sensitivity and specificity of fundoscopy for the detection of papilledema depends on experience of the investigator. In one study it has a high specificity (98%). Its sensitivity howeer is age-dependent, being 100% sensitive in children older than 8 years, with only 22% sensitivity in younger patients.[11]

Ventricular dilatation has a high prevalence in syndromic craniosynostosis. It has been reported in 30% to 70% in Crouzon and Pfeiffer syndrome and in 40% to 90% in Apert syndrome,[12] while most cases with Muenke and Saethre-Chotzen syndrome seem not to be affected. Enlarged ventricles can either be progressive, known as hydrocephalus, or non-progressive, known as ventriculomegaly. Ventriculomegaly may be related to primary brain development. Hydrocephalus on the other hand can be caused by cerebrospinal fluid outflow problems or malabsorption. Outflow problems could to be related to Chiari I malformation and to a small fossa posterior. Hydrocephalus can be one of the causes of raised ICP in craniosynostosis.

Obstructive sleep apnea is characterized by repetitive pauses in breathing during sleep, despite the effort to breathe. In children with craniosynostosis it is associated with midfacial hypoplasia, micrognathia, tracheamalacie, intranasal airway obstruction and muscular hypotonia.[13] Potential complications of OSA are failure to thrive, behavioral problems, cor pulmonale, and sudden death.[14-15] Screening for the presence of OSA can reliably be done with the Brouillette questionnaire[16] and polysomnography (PSG) is generally accepted as the gold standard to diagnose and determine the severity of OSA.

In this thesis a Chiari I malformation is considered to be present when the cerebral tonsils herniate 5 mm or more downward through the foramen magnum. In craniosynostosis a Chiari I malformation appears to be acquired, due to several factors such as; a disproportion between the cerebellum and a small posterior fossa, hydrocephalus and raised ICP.[17] A Chiari I malformation remains symptom free in most patients with craniosynostosis but can cause severe problems such as; central sleep apnea, non-communicating hydrocephalus, muscle weakness in the head and face, difficulty swallowing, impaired coordination, paralysis and autonomic dysregulation. Diagnosis is in most cases based on MRI.

SYNDROMES

The Apert syndrome was first described by the French Pediatrician dr. Eugène Charles Apert in 1906.[18] The syndrome is characterized by synostosis of the coronal sutures, midface hypoplasia, symmetrical complex (osseous and soft-tissue) syndactyly of hand and feet and mental retardation. The most used classification system of the hand anomalies in Apert syndrome is that of Upton,[19] classifying the Apert hand into three types according to increasing severity; type I consists of complex syndactyly of digits two through four with a free thumb and a simple syndactyly of the small finger, type II consists of complex syndactyly of digits two through five with an associated simple syndactyly of the thumb, type III consists of complex syndactyly of all the digits. Apert syndrome has an incidence of around 1 per 60.000 births.[20-21] In 99% of the cases it is caused by the S252W or the P253R mutation in the FGFR2 gene.[22] The mode of transmission is autosomal dominant, but most cases are sporadic.

The Crouzon syndrome was first described by Octave Crouzon in 1912.[23] The syndrome is characterized by bicoronal synostosis, but other sutures can be affected. In some cases the craniosynostosis develops postnataly.[24] Other features that can be appreciated are exopthalmus, midface hypoplasia and hypertelorism. Crouzon syndrome is in most cases caused by mutations on the FGFR2 gene, but can also be caused by a distinct mutation on the FGFR3 gene. This mutation is associated with acanthosis nigricans.[25] Crouzon syndrome has an incidence of around 1 per 25.000 births. The mode of transmission is autosomal dominant, and it is familiar in about 50% of the cases.

Pfeiffer syndrome was first described by Rudolf Arthur Pfeiffer in 1964.[26] Phenotypically Pfeiffer is very similar to Crouzon syndrome, but is distinguished by the presence of broad thumbs and halluces. Genetically the syndromes can often not be distinguished from each other.[27] Therefore we assume that both syndromes belong to the same broad spectrum of the same disease.

The Muenke syndrome was first described by Glass et al. in 1994[28] but named after the one who discovered the mutation rather than the one who first described the phenotype. The Muenke syndrome is characterized by bilateral or unilateral synostosis of the coronal sutures, but synostosis of other sutures or the absence of craniosynostosis can be seen in this syndrome. Other findings include hypertelorism, ptosis, midface hypoplasia, a highly arched palate, strabismus, sensorineural hearing loss, developmental delay, carpal bone and/or tarsal bone fusions and brachydactyly. The estimated birth prevalence is 1 per 30.000 births, but is probably higher because not all cases come to clinical attention.[29-30] The Muenke syndrome is caused by the

P250R mutation in the FGFR3 gene.[31] The mutation rate at this locus is one of the highest known in human genome.[29] The mode of transmission is autosomal dominant with an incomplete penetrance and a varying expression.

The Saethre-Chotzen syndrome was first described by dr. Haakon Saethre in 1931 and by dr. F. Chotzen of Breslau in 1932.[32-33] In Saethre-Chotzen syndrome, the coronal sutures can be bilateral or unilateral affected. Other features of this syndrome are upper eyelid ptosis, hypertelorism, strabismus, tear duct stenosis, brachydactyly, and cutaneous syndactyly of hand and feet. The estimated birth prevalence is around 1 per 25.000 births. It is caused by several mutations and deletions in the TWIST1 gene.[34-35] The mode of transmission is autosomal dominant with a varying expression.[36]

There are many other syndromes associated with craniosynostosis that are not covered in this thesis. These are the craniofrontonasal syndrome (EFNB1 gene),[37] Antley-Bixler syndrome (POR gene),[38] Carpenter syndrome (RAB23 gene),[39] Roberts syndrome (ESCO2 gene),[40] Greig syndrome (GLI3 gene),[41] Alagille syndrome (JAG1 gene),[42] Noonan syndrome (KRAS gene),[43] Baller Gerold syndrome (RECQL4 gene),[44] Loeys-Dietz syndrome (TGFBR1 and TGFBR2 gene)[45] and craniosynostosis caused by MSX2.[46]

If no mutation can be found and two or more sutures are closed, the term complex craniosynostosis is used. Patients with complex craniosynostosis are a heterogeneous group, which can present with a mild to a very severe phenotype. This group is getting increasingly smaller as more mutations are found.

CAUSES

A part of the mutations are inherited especially in cases with a mild phenotype, such as seen in Saethre-Chotzen and Muenke syndrome. However most cases are de novo mutations. The observations that the mutations have an almost exclusively paternal origin and that the paternal age of patients with de novo mutation tends to be 2 to 5 years older30,[47-48] have lead to the hypothesis known as the paternal age effect mutations.[49] Paternal age effect mutations encode for proteins with a gain-of-function property. Spermatogonia with these mutations are positively selected and expand clonally, this leads to an enrichment of sperm with mutations over time. Therefore unaffected fathers of a child with syndromic craniosynostosis have a slightly higher change of getting a second affected child, compared to diseases originated from de novo mutations.

TREATMENT

In 1890 Lennelongue was the first to report on surgical treatment for craniosynostosis. He used strip craniotomies to release the cranial sutures in an attempt to expand intracranial volume.[50] This treatment was halted in 1894 after reviewing the first 33 cases of whom 15 died.[51] By the mid-1940s the strip craniotomies were again widely accepted. But it took till the end of the 1960s that Paul Tessier reported his techniques which are now regarded as the principles of modern craniofacial surgery.

The most commonly performed expansion for bicoronal craniosynostosis is the frontal orbital advancement. The general principle of this procedure is the mobilization and advancement of the supraorbital bar with the forehead. This results in an increased volume of the anterior fossa and the orbits.

A posterior vault expansion is indicated in the youngest patients with Apert and Crouzon syndrome were a second surgery may be needed at a later age. When a posterior vault expansion is performed as primary surgery this leaves the face untouched. This makes it easier to perform a monobloc at a later age. An exception is the presence of severe exorbitism or obstructive sleep apnea. In these cases a frontal orbital advancement together with a midface advancement or monoblock may be needed, to prevent vision loss or prevent the need of a tracheal cannula. During surgery a large posterior bony flap is raised. It is thought that posterior vault expansion offers a larger volumetric increase than the frontal orbital advancement.[20, 52] An alternative for the conventional posterior vault expansions is the spring assisted posterior vault expansion. The use of springs were introduced by professor Lauritzen in 1997.[53] They have since been used for various indications and forms of craniosynostosis.[54-56] The main advantage of springs is that they can be custom made per patient, are covered under the skin and need a smaller dissection.[57] These properties make them less sensitive to mechanical failure, as is seen with internal distractors.[58-59]

The Le Fort III procedure is used for midface advancement. During this procedure the midface is mobilized along the Le Fort III fracture lines. This procedure is used for the treatment of midface hypoplasia and it's related problems, such as obstructive sleep apnea and exorbitism and malocclusion.[60] If necessary the advancement of the midface can be combined with advancement of the orbits, in a single segment. This procedure was first described by Ortiz- Monasterio in 1978 and is known as a monobloc advancement. Another modification was proposed by van der Meulen in 1979, known as the bipartition.[61] During this procedure the midface is divided in the middle with a V-shaped resection. This makes it possible to combine a monobloc advancement with a correction of hypertelorism.

If hydrocephalus is the main cause of raised ICP a ventriculoperitoneal (VP) shunt may be indicated. This is predominantly the case in Crouzon syndrome, while in Apert syndrome most cases of enlarged ventricles remain stable over time.[12] Because VP-shunts are associated with complications, shunt placement must be done only if there are no other treatment options left. Complications that are encountered are infection, obstruction, overdrainage and intraventricular haemorrhage.

Besides a vault expansion patients with Apert syndrome need hand surgery for the complex syndactyly of the hands associated with this syndrome. To limit the number of procedures the first procedure is preferably done bilaterally, followed by two unilateral procedures. How hand surgery in Apert syndrome improves long-term hand function, quality of life and participation is unknown.

THESIS AIM AND OBJECTIVES

The Dutch craniofacial center in Rotterdam is the single referral center for syndromal craniosynostosis in the Netherlands and active since 1972. Therefore we have a large and unique population. The aim of this thesis is to give a better perspective of the most prevalent syndromes associated with craniosynostosis including Crouzon, Muenke, Saethre-Chotzen and Apert syndrome.

The first part of this thesis presents long-term results of raised ICP, OSA, hearing and vision and intelligence. In **chapter 2** this is done with a large retrospective study, where we present functional problems in patients with syndromic craniosynostosis. This will give a better understanding of the syndrome specific problems, which is needed for patient tailored treatment and follow-up. Besides the functional problems we report on the age at time of first onset of raised ICP.

In **chapter 3** we report the long-term intellectual and visual outcome of the treatment protocol used in Paris and Rotterdam, were a routine vault expansion is performed before the age of one year if patients are referred on time. The aim of this protocol is to treat or prevent early episodes of raised ICP, and with that improve long-term intellectual and visual outcome. In the future these baseline results could be compared with results of other treatment protocols, e.g. the treatment protocol used in the craniofacial unit from London. We hope that this will improve the treatment of patients with syndromic craniosynostosis.

Furthermore, hearing loss is a much encountered problem in syndromic craniosynostosis, which we think needs more attention. At this moment there are only a

limited number of publications on this topic with in most cases a small sample size.[63-67] Syndrome specific type, severity, and prevalence of hearing loss are presented in **chapter 4** on which follow-up and treatment of patients should be guided.

The second part of this thesis focuses on quality of life, and variables that influence quality of life. Patients with syndromic craniosynostosis have several functional problems that can negatively influence their quality of life. However there is only one report on quality of life in syndromic craniosynostosis.[68] In **chapter 5** we report the Health Utility Index mark 3 to give a better understanding on which and how much functional problems influence the quality of life. With this knowledge functional problems that have the largest negative influence on quality of life can get more attention during treatment and follow-up.

Hand function is one of the functional outcomes that can have a large negatively influences on quality of life in patients with Apert syndrome. There are however no reports on long-term hand function in this syndrome. In **chapter 6** we report on hand function, and the influence of hand function on quality of life and participation in Apert syndrome based on several questionnaires completed by patients, parents or care givers.

The last part of this thesis reports on ventricular and brain volumes and a new surgical technique; the spring assisted posterior vault expansion.

The growth curve of brain and ventricles in syndromic craniosynostosis could provide a better understanding of the development of raised ICP. Craniocerebral disproportion is thought to be an important cause for the development of raised ICP. However cranial volume is not always too small and there are no reports on brain volumes of patients with syndromic craniosynostsis.[62] Therefore in **chapter 7** we report on brain and ventricle volume in patients with syndromic and complex craniosynostosis.

In an aim to improve the results of occipital vault expansions, springs were introduced in 2009. Springs are thought to give a larger increase in intracranial volume. In **chapter 8** we demonstrate the efficacy of spring-assisted posterior vault expansion by comparing this technique with the conventional method.

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Part II
Long-term outcome

Chapter 2

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

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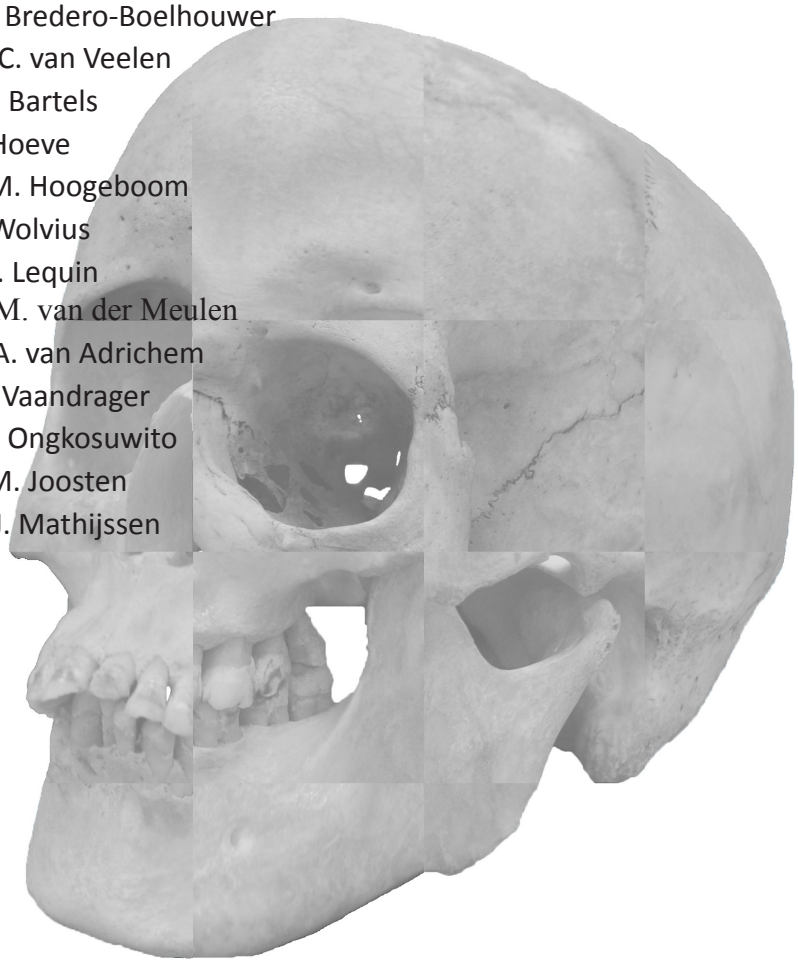

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ABSTRACT

Objective Little is known about the long-term prevalence of elevated intracranial pressure (ICP), obstructive sleep apnoea (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 syndromes 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 (21%). 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 ICP has a high prevalence in patients with Apert and Crouzon/Pfeiffer syndrome[1, 2] but its prevalence in Muenke en Saethre-Chotzen syndrome is unclear. One of the factors that is related to elevated ICP is 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 this data, guidelines for follow-up of patients per syndrome are suggested.

PATIENTS AND 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 that 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, pediatrician, radiologist, psychologist and a nurse practitioner. All patients were offered a genetic analysis. Depending on their phenotype exons of FGFR1, 2 and 3 and Twist were tested. Routine diagnostic tests besides a complete physical examination were skull X-rays, cephalograms, photographs, fundoscopy, and a 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 to 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 remodel-

ling. 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 a Le Fort I
osteotomy at 18 is the resulting consequence. Follow-up visits of these patients are once every 3 to 6 months during their first two-and-a-half year. Thereafter, check ups are 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 that have no functional problems requiring extra attention. During follow-up visits, patients and their parents were specifically asked about complaints suggestive for elevated intracranial pressure, 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 impressiones 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 increased ICP, decline in growth curve of skull circumference, presence of papiledema or indication for surgery (vault remodelling, Le Fort III or monobloc).

Intracranial pressure (ICP)

Papilledema was used as an indicator of elevated ICP. A pediatric 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 margins of the optic disc 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 1 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 3 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)

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 analysed 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 to 5, moderate OSA with an ODI of 6 to 24 and severe OSA with an ODI higher than 24. [14, 15]

Sight and hearing

Sight was assessed based on the test results done by an orthoptist or ophthalmologist. Sight was scored as normal, myopic, hyperopic, astigmatic, anisometropic or blind. Hearing was assessed based on the results of hearing tests peformed 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. All numbers are expressed as average and range. The Pearson Chi-square was used or when a table contained numbers smaller than 5 the Fisher's exact test was used to compare proportions. A 2-sided p-value of 0.05 or less was considered significant.

RESULTS

Baseline

Of the 167patients 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 years 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 8 the P253R mutation. In 9 of the tested patients with Crouzon/Pfeiffer no mutation was found. No TWIST mutation or deletion was found in eleven patients with Saethre-Chotzen, in whom a FGFR2 or 3 mutation was excluded. In these patients we sticked to the clinical diagnoses made by the geneticist. All patients with the Muenke syndrome had the FGFR3 P250R mutation. Type of primary surgery is described in **table 2**. No surgery was performed in 10 patients because they were relatively old at time of referral and didn't have signs of elevated ICP or because their parents did not give their consent. The mean age at primary vault expansion was 14 months (2 months -9 years). A total of 92 (55%) patients underwent surgery before the age of 1 year. The main reason for performing primary skull remodellation after the age of 1 year was a delay in referral. In 14 of the 167 (8%) a second vault expansion was needed and in one a third vault expansion was needed. The indication for this secondary surgery was elevated ICP in 8, 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 14 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] Type and timing of the midface advancements are described in **table 3**. A ventricular peritoneal shunt was placed in 13 patients (3 Apert, 9 Crouzon/Pfeiffer, and 1 Muenke syndrome) because progressive ventricular dilatation was present and intracranial volume was more than appropriate.

Table 1 overview of genetic diagnosis

	Apert N=36	Crouzon/ Pfeiffer N = 55	Muenke N=38	Saethre-Chotzen N=38
FGFR2				
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		1		
S 354 C		1		
S 267 P		3		
W 290 R		3		
A 362 T		3		
C 342 R		2		
C 342 W		1		
S 351 C		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		9		11
Not tested	12	7		7

Table 2 Overview of primary vault expansion per syndrome

Syndrome	Primary expansion	Secondary expansion	Midface advancement
Apert	35 (95%)	5 (14%)	16 (43%)
Crouzon/Pfeiffer	46 (81%)	10 (22%)	21 (37%)
Muenke	39 (100%)	2 (5%)	0
Saethre-Chotzen	34 (89%)	5 (15%)	0
Total	154	22 (14%)	37

Intracranial pressure

A complete fundoscopic assessment was performed in 164 patients, of them 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 (5 months-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 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**).

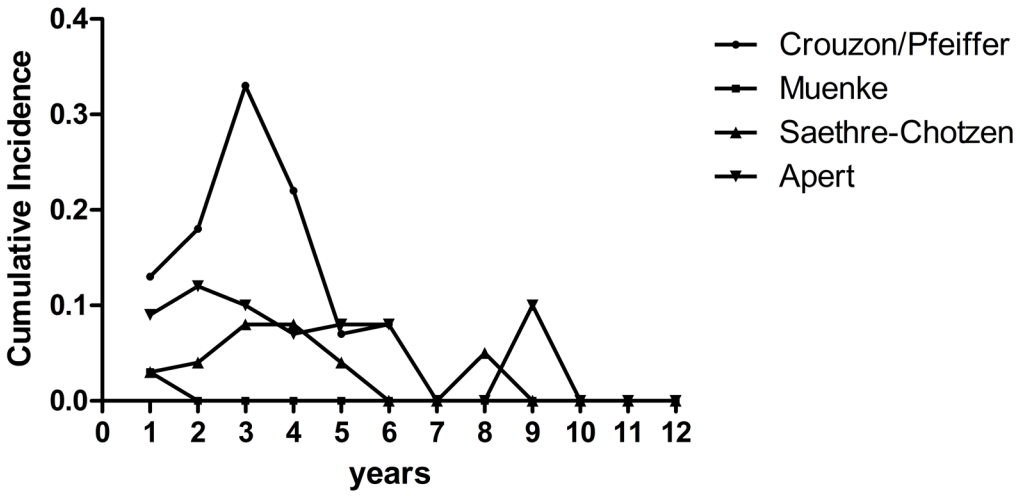

Figure 1 1-year cumulative incidence of first occurrence of papilloedema per syndrome. Includes only patients checked for papilloedema at least once every 3 years, Apert syndrome n= 32, Crouzon/Pfeiffer syndrome n=47, Muenke syndrome n=36 and Saethre-Chotzen syndrome n=36

Table 3 Type and timing of first midface advancement

	Average age of first midface advancement (years)	Apert (n=12)	Crouzon/Pfeifer (n=17)
Monoblock	2.3	5	6
Le fort III	10.3	6	9
Le fort II	10.3	1	2

Table 4 Prevalence of papilloedema before and after the first vault expansion

	preoperative[a]	postoperative[b]	total
Apert syndrome	2/22 (9%)	11/31 (35%)	12/36 (33%)
Crouzon/Pfeiffer syndrome			
Muenke syndrome			
Saethre-Chotzen syndrome			

[a] Number of patients with papilloedema divided by the number of patients tested for papilloedema

[b] Includes new onset and recurrent cases of papilloedema

Obstructive sleep apnea

Because of a high suspicion for respiratory problems (e.g., snoring, difficulty in breathing during sleep or apnoeas 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 syndromes had a much higher prevalence of OSA than patients with Muenke and Saethre-Chotzen syndromes, and if OSA was present in patients with Muenke and Saethre-Chotzen syndromes it was only mild (**Table 5**).

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**).

earing

Hearing loss was reported in 65 of 119 (55%) patients. Conductive hearing loss was reported in 62 (45%), 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 syndromes (**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.

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%)[a]	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%)

[a] Statistical significant compared to all other syndromes.

DISCUSSION

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

All patients need genetic analysis to establish the diagnosis, for selective

screening on related abnormalities, genetic counselling and research. Given the fact that we never encountered a mutation in the FGFR1 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 syndromes, 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 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 increased 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 syndromes.[18,23] The craniofacial group from London has presented similar findings in patients with 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 increased ICP at about 5 years of age. Apparently, expansion of the skull does prevent and treat increased 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 SaethreeChotzen syndromes up to the age of 6 and for Muenke up to the age of 2. If papilloedema 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 Apert and Crouzon/Pfeiffer syndromes and in 5% of the children with Saethre-Chotzen and Muenke syndromes. Because of the high prevalence of OSA in Apert and Crouzon/Pfeiffer syndromes, we advocate yearly screening for OSA with polysomnography. Children with Saethre-Chotzen or Muenke syndromes should be tested when difficulties with 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 mid-face advancement (Bannink 2009 submitted). Treatment of OSA should be individualised 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 counselling 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.

Conflict of interest statement

None of the authors has financial or personal relations with persons or companies that could inappropriately influence the outcome of this study.

Table 7 Overview of diagnosis-specific screening and treatment protocol

Clinical diagnosis	Apert	Crouzon/Pfeiffer	Muenke	Saethre-Chotzen	Comments
Genetic research	FGFR2	FGFR2	1st. P250R FGFR3 2nd TWIST	1st TWIST 2nd P250R FGFR3	No FGFR1 analysis included
Fundoscopy	Yearly up till 6 years	Yearly up till 6 years In patients without craniosynostosis every 3 months during the first two years	At age of 2 years	Yearly up till 6 years	At first visit and pre-surgery in all patients. Papilloedema 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 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	At age 0 and 4	-	-	If papilloedema is present
First cranial vault remodelling	Occipital expansion between 6 and 9 months (if synostosis is present) If Severe OSA or severe exorbitism present: monobloc + distraction		Fronto-orbital advancement between 6 and 9 months		
Raised 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 istraction)	Relative indication: Between age 9 to 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				

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Chapter 3

Long-term intellectual and visual outcome in patients with syndromic craniosynostosis

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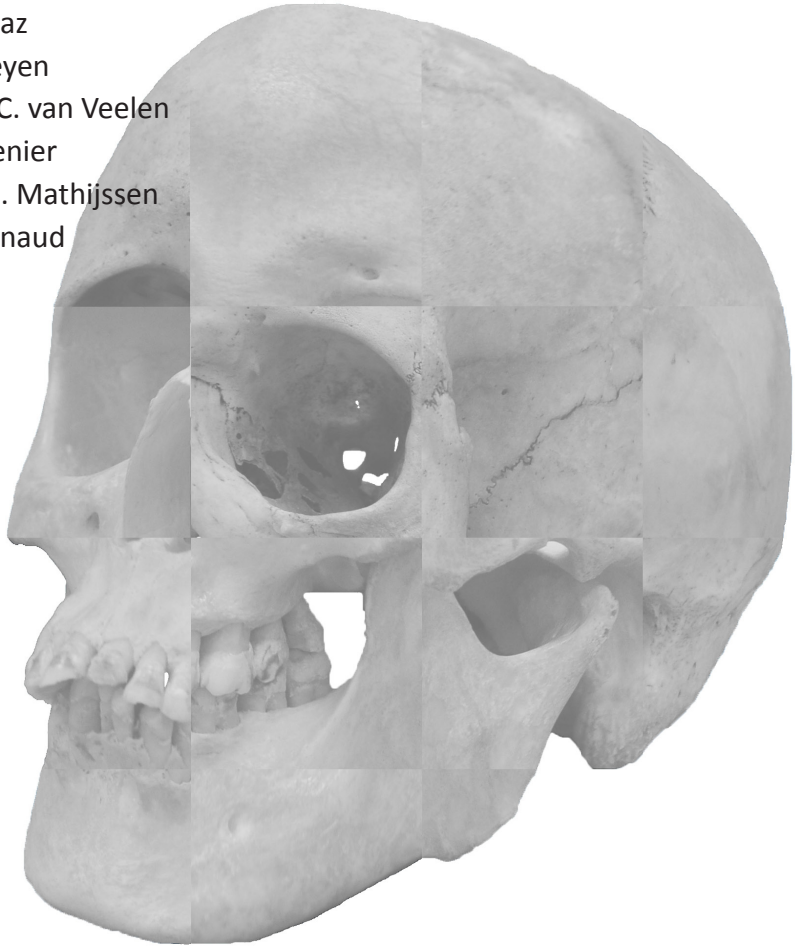

ABSTRACT

Background The current literature provides no data on long-term intellectual outcome of patients with syndromic craniosynostosis. This information is needed to evaluate treatment protocols and find predictors for intellectual functioning at an adult age.

Objective To report on the long-term intellectual and visual outcome in patients with syndromic craniosynostosis of two major craniofacial units.

Methods A total of 147 patients were included: 95 from Paris and 52 from Rotterdam. Patients with Crouzon, Saethre-Chotzen and Apert syndrome who had received a vault expansion were included if they had an IQ test at the age of 6 years or older. Both units routinely perform vault expansions between the age of 6-9 months. Data of visual acuity are reported for a subgroup of 39 patients from the Rotterdam cohort.

Results There was a good long-term intellectual outcome in patients with Crouzon and Saethre-Chotzen. Patients with Apert syndrome had a significantly lower IQ compared to both other syndromes ($p<0.001$). However, in all three syndromes a significantly larger proportion had an IQ lower than -2 sd compared to the normal population (46% Apert, 16% Crouzon, 12% Saethre-Chotzen, 2.3% norm). On average, a good vision was found in all syndromes. Nevertheless, the visual acuity of the best corrected eye was ≤ 0.5 in 8% of the patients.

Conclusion With our current policy to perform early vault expansions a good long-term intelligence and visual acuity could be achieved. However, despite early vault expansion a number of cases will still have a low IQ.

INTRODUCTION

The most common syndromes associated with craniosynostosis are Crouzon, Saethre-Chotzen, Apert and Pfeiffer syndrome.[1-2] Intelligence levels in patients with syndromic craniosynostosis can be within normal limits, but also severely compromised. The current literature provides no data on long-term intellectual outcome. This information is needed to evaluate treatment protocols and find predictors for intellectual functioning at an adult age. Some studies with a short follow-up report on variables that may relate to intelligence and development; syndrome diagnosis probably has the largest influence. Another potential variable is age at time of first vault expansion. In addition, family environment, parental education, associated hydrocephalus and brain malformations might also be related to intelligence.[3-8] A vault expansion is needed to correct functional and morphologic problems due to growth restriction caused by craniosynostosis. In the most severe cases several surgical procedures are required over time. The main indication for vault expansion is raised intracranial pressure (ICP).[2, 9] If left untreated, raised ICP may lead to visual impairment and may have a negative influence on neurocognitive development.[2, 10-11] Therefore, IQ and visual acuity are two important long-term outcome parameters for the assessment of treatment protocols in syndromic craniosynostosis. The treatment protocol of both the participating units consists of a routine vault expansion between the ages of 6-9 months, if patients are referred on time. Screening for raised ICP is done at first presentation of the patient. If papilledema is present, the vault expansion will be planned before the age of 6 months. Patients with Apert, Crouzon and Pfeiffer syndrome will receive a posterior vault expansion as initial surgery in most instances. This to preserve the facial profile in case of midface hypoplasia, and to leave the frontal part of the skeleton untouched for a monobloc or facial bipartition at a later age. A monobloc is only done as primary surgery in cases with severe OSA and/or exorbitism. Patients with Saethre-Chotzen syndrome will receive a frontal-orbital advancement as they never need a midface advancement. After the vault expansion, annual screening for raised ICP will be done until age 6 years. After this age screening continues regularly until age 18 years. The current treatment protocol is based on previous studies, with short-term results on mental outcome.[2, 4] The aim of this study is to report on longterm intellectual and visual outcome of two craniofacial units who perform vault expansions before the age of 1 year.

METHODS

Patients with Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndrome were included from prospective cohorts in Hôpital Necker Enfants Malades (Paris, France) and the Sophia Children's Hospital (Rotterdam, the Netherlands). Patients were included if they received a vault expansion and had an IQ test at the age of 6 years or older. In both units intelligence was tested with the Wechsler Intelligence Scale for Children (WISC),[12] by a pediatric psychologist. In the normal population, the WISC has an average value of 100 and a standard deviation (sd) of 15. Patients with an IQ ≤ 50 cannot be reliably tested with the WISC and were considered to have an IQ too low to test. We defined an IQ of 85 or higher as normal based on the 10th edition of the World Health Organization International Classification of Diseases. Syndrome diagnosis was based on genetic testing and/or a clinical diagnosis. Because Crouzon and Pfeiffer syndrome often cannot be distinguished from each other, even from a genetic point of view,[13] they were considered to be a homogenous group. All patients were seen by a pediatric ophthalmologist to screen for the presence of raised ICP and to test visual acuity. The diagnosis of raised ICP was based on the presence of papilledema seen with fundoscopy. Visual acuity was tested with the help of a Snellen chart, and the best corrected visual acuity at the last visit was used for analysis. All charts of the Rotterdam patients were reviewed.

Predictors of intelligence were tested with the help of an ordinal regression model. The IQ data were divided into four strata to prevent the exclusion of patients who were not able to complete the test due to low intelligence; those patients would automatically fall into the first stratum. Predictors of visual acuity were tested with the help of a linear regression model. All analyses were done with SPSS 16.0 for Windows. Differences were considered statistically significant with a 2-sided p-value of 0.05 or less.

RESULTS

A total of 147 patients were included (95 from Paris and 52 from Rotterdam), their characteristics are presented in **Table 1**. Intelligence was too low to test in 10 (7%) patients; these included 4 (11%) patients with Apert syndrome, 4 (6%) with Crouzon syndrome, and 2 (4%) with Saethre-Chotzen syndrome. After excluding these 10 patients, the average IQ was 75 in Apert syndrome, 98 in Crouzon and 102 in Saethre-Chotzen syndrome. There was no difference in mean IQ between both centers.

Vault expansions were performed between age 0.13 and 3.85 (median 0.78) years. In the entire group, there was no relation between age at time of surgery and IQ (p=0.188). **Table 2** presents the percentage of patients with a normal IQ (≥85), stratified by age at time of vault expansion. **Table 3** presents the distribution of the IQ per syndrome stratified by early (before age 1 year) and late surgery. Patients with Apert syndrome had a significantly lower IQ (p<0.001). Gender had no influence on IQ (p=0.319).

Visual acuity was tested in 39 patients with an average age of 9.4 years at the latest test (this could not be tested in 11 patients due to low intelligence and was missing in 4). These 39 patients included 7 patients with Apert, 19 with Crouzon, and 13 with Saethre-Chotzen syndrome. The average visual acuity was 0.80 in Apert syndrome, 0.82 in Crouzon syndrome, and 0.93 in Saethre-Chotzen syndrome. Visual acuity was ≤0.5 in 3 (8%) patients, all with Crouzon syndrome. Low visual acuity was due to myopia gravior in 1 patient; the other two patients had severe papilledema earlier in life, leading to optic disc atrophy and therefore low visual acuity (0.3 and no light perception, respectively).

Table 1 Patient characteristics

	Paris	Rotterdam	Total
Patients	95	52	147
Gender M/F	49/46	27/25	76/71
Apert	26	11	37
Crouzon/Pfeiffer	42	20	62
Saethre-Chotzen	27	21	48
Median age at vault expansion, in years (range)	0.6 (0.1 - 3.9)	1.0 (0.2 - 3.5)	0.78 (0.1 - 3.9)
median age at IQ test, in years (range)	11.4 (6.0 - 18.7)	9.1 (6.2 - 13.3)	10.7 (6.0 - 18.7)

Table 2 Patients with a normal IQ (≥ 85) stratified by age at time of surgery

	0 - 6 months at surgery	6 - 12 months at surgery	12 months - 4 years at surgery
Apert	7/16 (44%)	7/17 (41%)	1/4 (25%)
Crouzon/Pfeiffer	7/12 (58%)	9/11 (82%)	30/39 (77%)
Saethre-Chotzen	12/14 (86%)	14/20 (70%)	11/14 (79%)

Table 3 Distribution of IQ per syndrome

	IQ<-3sd (<55)	-3sd< IQ <-2sd (55-70)	2sd< IQ <-1sd (70-85)	-1sd< IQ <0sd (85-100)	0sd< IQ <+1sd (100-115)	+1sd <IQ (>115)
Apert	24%	22%	14%	37%	3%	0%
Crouzon/Pfeiffer	11%	5%	10%	42%	16%	16%
Saethre-Chotzen	8%	4%	13%	25%	29%	21%
Normal population	0.1%	2.2%	13.6%	34.1%	34.1%	15.9%

sd = standard deviation

DISCUSSION

The current study is not a comparative study for early versus late surgery but a long-term follow-up analysis of IQ and visual acuity after a protocol with the intention to treat early. We found that long-term intelligence is within the normal limits in most patients with Crouzon and Saethre-Chotzen, and in some patients with Apert syndrome. However, despite early surgical intervention some patients will end up with a low IQ. In the normal population, 2.3% of the patients have an IQ of ≤ -2 sd (≤70). We found an IQ of ≤ -2 sd in 16% of the patients with Crouzon, 12% with Saethre-Chotzen and in 46% with Apert syndrome. People with an IQ of ≤ -2 sd are unable to live and work independently. Therefore, parents should be told that there is a risk that their child's intelligence might be low even when the child has a mild phenotype, as can been seen in Crouzon and Saethre-Chotzen syndromes.

On average good visual acuity was observed in all syndromes. However, visual impairment (defined as a visual acuity ≤0.5 in the best corrected eye) was found in 8% of the patients, all with Crouzon syndrome. This is a smaller proportion compared to the literature where visual impairment is reported in 17%-35%

of the patients with these syndromes.[14-17] Thus, early management of children with syndromic craniosynostosis might improve the ophthalmological outcome. The main reasons for suboptimal visual acuity are ametropia and amblyopia. Risk factors for amblyopia seen in syndromic craniosynostosis include strabismus, ametropia, astigmatism and ptosis.[16-17] Optic nerve atrophy is reported in 5%-16% of the patients with Apert and Crouzon syndrome[15, 17-18] and in about 10% of the patients with Saethre-Chotzen syndrome.[19-20] However, this finding was not observed in our children with Saethre-Chotzen syndrome. In our series, two patients (5%) had a low visual acuity due to previous papilledema leading to optic atrophy before they were referred to our unit, and one patient (3%) had low visual acuity caused by myopia gravior.

We found no relation between age at time of surgery and long-term IQ. This could be related to the fact that biases which influence age of surgery probably also influence IQ. In fact, patients with a more severe phenotype are generally diagnosed early and receive surgery before the age of 1 year, while patients with a mild phenotype have a higher chance to be referred late and have surgery after the age of 1 year. The question whether age at time of vault expansions influences long-term intelligence in syndromic craniosynostosis cannot be answered without a randomized clinical trial, or at least comparison with data from a center with a protocol to operate late. To our knowledge there are reports from three different centers on the timing of surgery and early intellectual outcome in syndromic craniosynostosis. Of these, two did not find a relation,[3, 6-7] while the center in Paris did find such a relation, including nonsyndromic brachycephaly.[2, 4-5, 21] However, most patients with unisutural non-syndromic craniosynostosis have a satisfactory mental development irrespective of the age at time of surgery.[22-23] The main predictive factor of long-term mental outcome in non-syndromic and syndromic craniosynostosis appears to be the initial level of development.[2, 23-24]

One study has described another treatment protocol, where a vault expansion in Apert patients is performed only when signs of raised ICP are present.[25] A total of 90% of the patients treated with this protocol needed a surgical intervention for raised ICP, of which 67% received a vault expansion at a mean age of 2.2 years. In patients with Crouzon syndrome the prevalence of raised ICP is even higher, and probably all patients will need a surgical intervention.[2, 9] Therefore, this latter protocol probably prevents surgery in only a very small group. At the ages of 3-4 years a similar increase of raised ICP is detected for both treatment protocols.[9, 25] Furthermore, there are no reports on long-term intellectual and visual outcome of such a protocol; additional studies are needed to determine its safety.

Conclusion

With the policy to perform vault expansions before the age of 1 year and with a strict follow-up, a good long-term IQ and visual acuity can be achieved. However, despite early vault expansion a limited number of cases will still have only low neurocognitive development.

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Chapter 4

Audiological profile of children and young adults with syndromic and complex craniosynostosis

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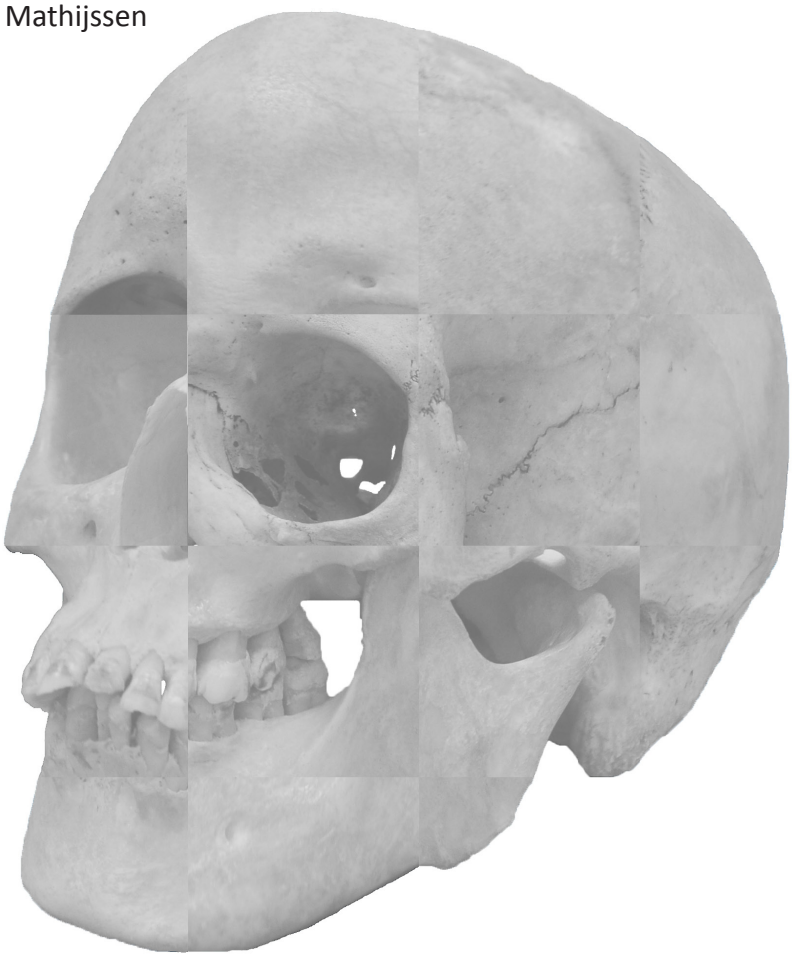

Arch Otolaryngol Head Neck Surg. 2011 Aug;137(8):775-8

ABSTRACT

Objectives To determine syndrome-specific type, severity, and prevalence of hearing loss to facilitate follow-up and treatment.

Design Tertiary pediatric hospital craniofacial clinic survey study. If insufficient or no data were available for a child, he or she was referred to an audiologist for puretone audiometry.

Setting Academic research facility.

Patients Information was gathered regarding 132 children and young adults with craniosynostosis.

Main Outcome Measures The primary outcome was hearing assessment of children and young adults with various types of craniosynostosis. A secondary outcome was inference regarding the incidence of otitis media among children and young adults with craniosynostosis.

Results We found mild or moderate hearing loss in 44.0% of patients with Apert syndrome, in 28.5% with Crouzon syndrome, in 62.1% with Muenke syndrome, in 28.6% with Saethre-Chotzen syndrome, and in 6.7% with complex craniosynostosis. Hearing loss was conductive in most patients with Apert, Crouzon, and Saethre-Chotzen syndromes and it was predominantly sensorineural in patients with Muenke syndrome. Sensorineural hearing loss at lower frequencies was found only in patients with Muenke syndrome.

Conclusions Most patients with syndromic and complex craniosynostosis have recurrent otitis media with effusion, causing episodes of conductive hearing loss throughout their lives. Sensorineural hearing loss can occur in all 4 syndromes studied but is the primary cause of hearing loss in children and young adults with Muenke syndrome. For patients with these syndromes, we recommend routine visits to the general practitioner or otolaryngologist, depending on national standards of care, to screen for otitis media with effusion throughout life. We also advise early screening for sensorineural hearing loss among children and young adults with these syndromes.

INTRODUCTION

Children with syndromic craniosynostosis are at high risk of developing hearing loss. An earlier retrospective study[1] found that the prevalence of hearing loss varied from 37% among children with Saethre-Chotzen syndrome to 72% among children with Apert syndrome. Despite the high prevalence, research on this topic is limited, especially for syndromes other than Apert syndrome. Current knowledge is based on data from few studies,[2-6] with small sample sizes. Furthermore, only 1 study[7] mentioned the severity of associated hearing loss. If syndrome-specific type, severity, and prevalence of hearing loss are known, appropriate follow-up and treatment can be implemented. The best possible hearing is necessary to optimize language development, which is already compromised in many children with syndromic craniosynostosis.[8]

MEDTHODS

A cross-sectional survey was conducted among 146 patients aged 4 to 18 years with syndromic or complex craniosynostosis treated at the Dutch Craniofacial Center, Erasmus Medical Center–Sophia, Rotterdam, the Netherlands. All diagnoses were made by a geneticist based on the results of genetic analysis. If no syndrome diagnosis could be made and 2 or more sutures were closed, craniosynostosis was defined as complex. Because Crouzon and Pfeiffer syndromes often cannot be distinguished genetically, we considered them a homogeneous group in this study. If no audiological information was available at our center, we contacted the parents or their child by mail to inquire about the results of testing performed elsewhere. In the Netherlands, hearing screening is performed in the first week of life, in primary school, and in secondary school. If screening results are aberrant, the child will be referred to an otolaryngologist or audiologist. If a patient had been seen by an otolaryngologist or audiologist, informed consent was obtained to acquire audiological data. Information was gathered regarding audiometric results, episodes of otitis media, inserted ear plugs, and the use of hearing aids. If the patient never had been seen by an otolaryngologist or audiologist, he or she was referred to an audiologist for single pure-tone audiometry. Patients were excluded if no audiological information was available and if they did not respond to or consent to our inquiry. A pure-tone average (with average losses at 0.5, 1.0, and 2.0 kHz) of 20- to 40-dB hearing loss was classified as mild and 41- to 70-dB hearing loss as moderate.

RESULTS

Of 146 patients aged 4 to 18 years with syndromic or complex craniosynostosis, audiological information was available at our center for 27 patients. The other 119 patients were contacted by mail, of whom 105 (88.2%) responded. Of 105 respondents, 62 had previously visited an otolaryngologist or audiologist and 43 had not. Of 43 who were referred for single pure-tone audiometry, we received information regarding 19 patients. The total group forwhomaudiological information was sought consisted of 132 children and young adults (**Table 1**). Of these 132 children, 25 had Apert syndrome, 42 had Crouzon syndrome, 29 had Muenke syndrome, 21 had Saethre-Chotzen syndrome, and 15 had complex craniosynostosis. The mean age at the time of review was 11.5 years, and the mean age at the last hearing test was 8.8 years. Sixtysix patients (50.0%) were male. Of 132 children and young adults, 108 (81.8%) had been seen at least once by an otolaryngologist or audiologist, and 88 (66.7%) had undergone audiometry at least once. Among those who underwent audiometry, 19 patients had Apert syndrome, 29 had Crouzon syndrome, 23 had Muenke syndrome, 10 had Saethre-Chotzen syndrome, and 7 had complex craniosynostosis. The distribution of hearing loss severity in the ear with better hearing is given in the **Table 1**. The average hearing loss severity in the ear with better hearing across patients per frequency was calculated for those with Apert, Crouzon, and Muenke syndromes (**Figure 1**). Audiological data were insufficient to calculate the frequency of hearing loss for patients with Saethre-Chotzen syndrome and for those with complex craniosynostosis. Hearing loss in patients with Apert, Crouzon, and Saethre-Chotzen syndromes was mainly of conductive origin. Hearing loss in patients with Muenke syndrome was mostly sensorineural at lower frequencies, sometimes occurring in combination with conductive hearing loss. This pattern of hearing loss was found only in patients with Muenke syndrome. Two patients with Saethre-Chotzen syndrome had unilateral sensorineural hearing loss, with pure-tone averages of 65- and 70-dB hearing loss. Recurrent otitis media with effusion was seen in 22 of 25 patients (88.0%) with Apert syndrome, 20 of 42 patients (47.6%) with Crouzon syndrome, 14 of 29 patients (48.3%) with Muenke syndrome, 8 of 21 patients (38.1%) with Saethre-Chotzen syndrome, and none with complex craniosynostosis. Of 132 patients, 19 (14.4%) were treated with a hearing aid. These included 5 of 25 (20.0%) with Apert syndrome, 5 of 42 (11.9%) with Crouzon syndrome, 7 of 29 (24.1%) with Muenke syndrome, and 2 of 21 (9.5%) with Saethre-Chotzen syndrome.

Table 1 Severity of Hearing Loss in the Better Ear

	Patient Group, No. (%)				
Hearing loss	Apert syndrome (n=25)	Crouzon syndrome (n=42)	Muenke syndrome (n=29)	Saethre-Chotzen syndrome (n=21)	Complex craniosynostosis (n=15)
None	14 (56.0)	30 (71.4)	11 (37.9)	15 (71.4)	14 (93.3)
Mild	6 (24.0)	8 (19.0)	14 (48.3)	6 (28.6)	1 (6.7)
Moderate	5 (20.0)	4 (9.5)	4 (13.8)	0	0

DISCUSSION

There is a high prevalence of hearing loss among children with syndromic craniosynostosis; this is reflected in the high proportion (66.7%) of patients who had visited an otolaryngologist or audiologist at least once before this study. In most cases, recurrent otitis media with effusion has resulted in conductive hearing loss. Sensorineural hearing loss or mixed hearing loss occurred in all syndromes but especially among patients with Muenke syndrome. If present, hearing loss in patients with Saethre-Chotzen syndrome is mild and hearing loss is absent in most patients with complex craniosynostosis. Small studies[2,9] show a high prevalence of congenital hearing loss due to ossicular chain fixation and constricted or absent external ear canals; larger studies[3,7,10-12] show amuch lower prevalence of congenital hearing loss and indicate that recurrent otitis media with effusion is the main cause of conductive hearing loss in syndromic craniosynostosis. Several risk factors for the development of recurrent otitis media with effusion are present in patients with syndromic craniosynostosis, including small nasopharynx,[13,14] short and dysfunctional eustachian tube,[2,10,15] obstructive sleep apnea,[16] and cleft palate.[17]

Apert syndrome is caused by an S252W or P253R mutation in the FGFR2 gene (OMIM 176943). This syndrome is characterized by craniosynostosis of coronal sutures, midface hypoplasia, obstructive sleep apnea, complex syndactyly of hands and feet, and mental retardation. Studies[7,9,10,18,19] of patients with Apert syndrome describe a high incidence of conductive hearing loss, predominantly caused by recurrent otitis media with effusion and congenital stapes fixation. Superior semicircular channel dehiscence has been described in Apert syndrome as a cause of conductive hearing loss with larger air-bone gaps at lower frequencies.[20,21] In effect, superior semicircular channel dehiscence creates a third window, which causes pseudoconductive hearing loss.

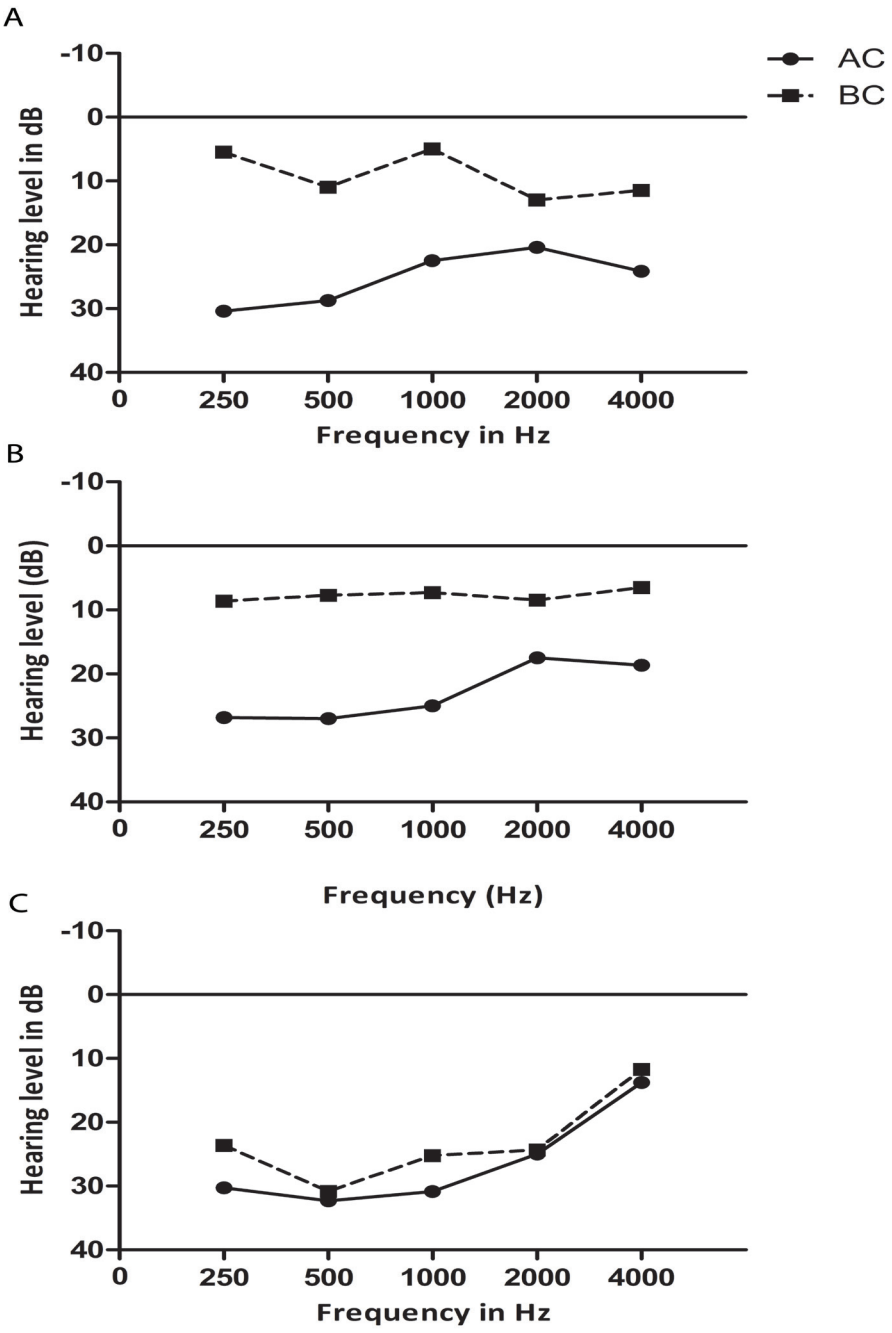

Figure 1 Average hearing level in the better ear among patients with syndromic and complex craniosynostosis. Twenty-five with Apert syndrome (A); 42 with Crouzon syndrome (B); and 29 with Muenke syndrome (C). AC indicates air conduction threshold; BC, bone conduction threshold.

Crouzon syndrome is caused by several mutations in FGFR2 that differ from those in Apert syndrome. All sutures can be affected. Children with Crouzon syndrome have exophthalmus, midface hypoplasia, and a high prevalence of obstructive sleep apnea and raised intracranial pressure; however, their mental development is nearly normal in most cases. Among patients with Crouzon syndrome, studies[2-4] describe conductive hearing loss, sensorineural hearing loss, and mixed hearing loss, caused by recurrent otitis media with effusion, ossicular chain fixation, and external auditory canal atresia. Although Crouzon syndrome has the lowest prevalence of hearing loss, 35.0% of patients have mild or moderate hearing loss. The same air-bone gaps as in Apert syndrome are seen, but they are larger at lower frequencies. Muenke syndrome is caused by a P250R mutation in FGFR3 (OMIM 134934). In most cases, 1 or 2 coronal sutures are affected.

Muenke syndrome is associated with a mild phenotype, but patients can have developmental and behavioral problems. A high prevalence of hearing loss is reported in Muenke syndrome, predominantly of the sensorineural type and worse at lower frequencies.[11,22,23] Sensorineural hearing loss probably results from an influence of the FGFR3 mutation on development of the inner ear.[24] This hearing loss was not found in patients with other forms of craniosynostosis, making it specific to Muenke syndrome. This is relevant for counseling; because the phenotype of Muenke syndrome varies, low-frequency sensorineural hearing loss may be the sole expression of the syndrome.

Saethre-Chotzen syndrome has a mild phenotype and is caused by deletions or mutations in the TWIST1 gene (OMIM 601622). In most cases, coronal sutures are affected. This syndrome is characterized by ptosis of the upper eyelid. The literature pertaining to hearing in patients with Saethre-Chotzen syndrome is limited. A high prevalence of recurrent otitis media with effusion is described, and hearing loss (if present) was mostly conductive.[5,11] One patient with Saethre-Chotzen syndrome was described as having sensorineural hearing loss.[6] Herein, 2 patients with Saethre-Chotzen syndrome had unilateral sensorineural hearing loss, both of whom profited from the use of a hearing aid.

The prevalence of hearing loss is low among patients with Saethre-Chotzen syndrome and among those with complex craniosynostosis. Because patients are routinely screened for hearing loss throughout their childhood, we can assume that they do not have clinically relevant hearing loss if they have never been examined by an otolaryngologist or audiologist.

Of the 108 children and young adults studied herein, only 19 were treated with a hearing aid, although more than 50% had mild or moderate hearing loss in

their better ear. This likely occurred because hearing loss is caused by recurrent otitis media with effusion in most instances and this condition was initially treated with grommets. Insertion of grommets does not prevent the development of permanent hearing loss, especially if ear discharge is present. Therefore, early management of hearing loss with a hearing aid always should be considered.[19] Doing so will optimize auditory access and speech and language, since many developmental problems are seen in children with these syndromes.[8,22,25]

In conclusion, regular checkups for middle ear function and hearing are indicated at least until age 18 years for patients with Apert syndrome and those with Crouzon syndrome. Depending on national standards of care, these checkups can be performed by an otolaryngologist or general practitioner. Patients with persistent otitis media with effusion or significant hearing loss should be referred to an otolaryngologist. Patients with Apert, Crouzon, Muenke, and Saethre-Chotzen syndromes. should be screened for sensorineural hearing loss early in life. Treatment of hearing loss with grommets or hearing aids is needed in children and young adults with syndromic craniosynostosis for optimization of speech and language development.

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Part III
Quality of life

Chapter 5

Health-related problems and quality of life in patients with syndromic craniosynostosis

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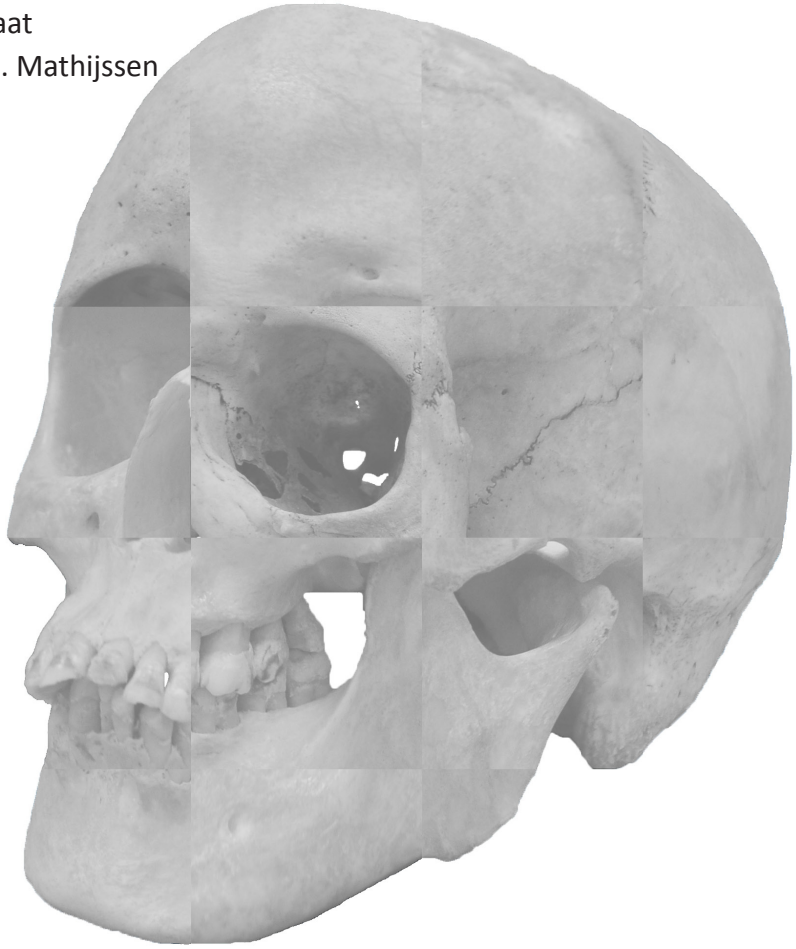

Childs Nerv Syst. 2012 Jun;28(6):879-82

ABSTRACT

Purpose We conducted this study to gauge the health-related problems, quality of life and the performance of the Health Utility Index Mark 3 (HUI-3) in patients with syndromic and complex craniosynostosis. Patients with syndromic and complex craniosynostosis have various physical and mental problems. More insight on these problems, per syndrome, could provide guidance to improve patient treatment and follow-up.

Methods A cross-sectional, comparative study on 131 patients and their parents was performed. Health-related quality of life was measured with the HUI-3 and the Visual Analogue Scale (VAS). All data were compared to a normative Dutch population. Vision, hearing and intelligence were objectively measured.

Results The HUI-3 and the VAS were significant lower compared to the normative Dutch population. All syndromes have a high prevalence of vision and speech problems. Cognitive problems were mainly reported in patients with Apert, Crouzon and Muenke syndrome. Ambulation and dexterity problems were seen in Apert, Crouzon, Saethre–Chotzen and complex craniosynostosis. Only patients with Apert syndrome scored significantly worse on pain. The HUI-3 had a medium to strong correlation with the objectively measured outcomes.

Conclusions The overall quality of life is lower in patients with syndromic and complex craniosynostosis. To improve quality of life, more attention is needed for problems with vision and speech.

INTRODUCTION

Craniosynostosis involves the premature closure of the cranial sutures. In about 40% of the patients, it is part of a syndrome such as Apert, Crouzon, Muenke and Saethre–Chotzen. Patients with syndromic and complex craniosynostosis have a lower health related quality of life (HRQoL), while patients with isolated craniosynostosis score within the normal range for quality of life and behavioral problems.[1] Reasons for the lower HRQoL are problems concerning physical functioning, bodily pain and mental health.[2] Commonly reported healthrelated problems in syndromic craniosynostosis are hearing and visual disorders, sleep apnea and hand and foot anomalies.[3] The prevalence and severity of these problems vary per syndrome, and it is unknown to what extent they influence the HRQoL and parents perceived quality of life. The aim of this study was to evaluate health related problems, quality of life and the performance of the Health Utility Index Mark 3 (HUI-3) in patients with syndromic craniosynostosis.

MATERIAL AND METHODS

A cross-sectional comparative study was performed in patients 4–18 years of age, with a diagnosis of syndromic or complex craniosynostosis. All patients were treated at the craniofacial unit of a tertiary pediatric hospital. Patients were included in the study if they had craniosynostosis associated with Apert, Crouzon, Pfeiffer, Saethre–Chotzen, Muenke syndrome or complex craniosynostosis. Syndrome diagnosis was based on genetic testing. Complex craniosynostosis was defined as the premature closure of two or more sutures in the absence of a genetic mutation. Because Crouzon and Pfeiffer syndrome cannot be distinguished from each other genetically, they were considered a homogeneous group in this study. The health-related quality of life was assessed using the HUI-3 questionnaire.[4-5] The HUI is developed to measure health-related quality of life and is applicable in clinical studies. The HUI is suitable for patients of 5 years and older, and for children under the age of 8 years a proxy assessment is recommended. Because we approached a large group of patients younger than 8 years and there is a high prevalence of cognitive impairment in patients with syndromic craniosynostosis, we requested the parents to complete the questionnaire. Patients were compared to normative data from a general Dutch population survey.[6] It were also the parents who completed the questionnaire in the Dutch population survey. Based on the questionnaire, subjects were classified according to the HUI-3 classification system. The HUI is a utility (preference) based scoring system for

measuring comprehensive health status and health-related quality of life, consisting of eight attributes. Each attribute was scored from 1 (no limitations) to 4, 5 or 6 (severe limitations). Single attribute utility scores range from 1.00 to 0.00, where perfect health is 1.00 and dead is 0.00. Multi-attribute utility scores, indicating overall health, are calculated based on single attribute scores.[7-8] The multi-attribute HUI score can be negative, which indicates a state described as worse than dead. Next to the HUI, the Visual Analogue Scale (VAS) was used to rate parent-perceived overall health of the child, with a score ranging from 0 (worst health) to 100 (best health). The questionnaire was once sent by mail once. From the eight attributes of the HUI-3, vision, hearing and intelligence can be measured objectively. Therefore, we collected data of vision, hearing and intelligence to compare to the corresponding HUI-3 attributes. Data of vision was retrospectively collected. Vision is routinely checked with a Snellen chart by our pediatric ophthalmologist. Data of hearing was cross-sectionally gathered as part of another study.[9] Hearing was tested by a pediatric audiologist with pure tone audiometry. Hearing loss was expressed as the average hearing loss at 500, 1.000 and 2.000 Hz of the best ear. Intelligence was tested by a pediatric psychologist with the Wechsler Intelligence Scale for Children (WISC)-III, as part of a prospective study.

Statistical analysis

Mann–Whitney U-test was used to compare means within the syndrome groups and between the syndrome groups and the normative population. Pearson's chi-square test was used to test correlation. A two-sided $p \leq 0.05$ was considered significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 173 patients were approached, of whom 131 responded (76%). Of the 131 patients, 20 had Apert, 39 Crouzon/Pfeiffer, 25 Muenke, 18 Saethre–Chotzen and 29 complex craniosynostosis. The mean age of the patients at the time of this review was 9.6 years, and 45% were female. The average age of the respondents was 41.6 years, and 73% were female (see **Table 1**). There was no significant difference between how mothers and fathers scored the HUI-3 and VAS, in the normative Dutch population and craniosynostosis groups. Age and gender did not influence quality of life, except for Apert syndrome, were the males had a significant lower HUI-3. The percentage of patients who are not affected and the mean single attribute HUI-3 scores are shown in **Table 2**. Patients were considered to be not affected if they had the best possible

score for that specific attribute. Vision, speech and cognition were the most affected attributes in patients with syndromic craniosynostosis. Speech was significant associated with hearing (p<0.001) and cognition (p<0.001). The mean VAS and multi-attribute HUI-3 score are shown in **Table 3**. There was no significant difference between the multi-attribute score and the VAS except for the Apert syndrome, in whom the HUI-3 was significant lower. This difference indicates that parents subjectively experience a higher quality of life for their child than their objective scoring indicates. The correlation between the multi-attribute HUI-3 and the VAS was 0.476 (p<0.001) in patients with craniosynostosis. Of the 131 included patients, 68 (52%) had data on vision, 63 (48%) on hearing and 60 (46%) were tested with the WISC-III. The correlation between the objective measurements and the single-attributes was 0.558 (p<0.001) for vision, −0.345 (p=0.006) for hearing and 0.418 (p=0.001) for intelligence.

Table 1 Characteristics of patients and the normative population

	Apert (n=20)	Crouzon (n=39)	Muenke (n=25)	Saethre-Chotzen (n=18)	Complex (n=29)	Norm group (n=1435)
Sex patient M/F	8/12	18/21	11/14	5/13	17/12	708/727
Age patients in years, mean (sd)	10.6 (4.9)	9.5 (3.9)	9.3 (4.1)	10.4 (3.9)	8.7 (4.0)	8.1 (2.4)
Sex parent M/F	6/14	9/30	6/19	4/14	7/22	206/1229
Age parent in years, mean (sd)	41.6 (8.0)	41.8 (5.3)	40.5 (6.3)	43.3 (7.9)	41.3 (6.0)	37.7 (5.2)

DISCUSSION

The multi-attribute HUI-3 and the VAS are significantly lower in patients with craniosynostosis compared to the normative Dutch population. Themain reasons for this are problems with vision and speech, and cognition in Apert and Crouzon syndrome. Ambulation, emotional problems and pain have no or limited influence on the HRQoL in syndromic craniosynostosis. In general, age and gender did not influence the quality of life. The overall correlation between the objective measurements and the HUI-3 attributes is medium to strong. Most problems were found in the attributes vision, speech and cognition, despite routine screening for these impairments in our patients. This screening and treatment is thus essential but cannot prevent or overcome all restrictions. Problems with vision affect about half the patients and can be

due to refractive error, strabismus, astigmatism and persistent elevated intracranial pressure.[10-13] Speech problems have previous been reported in Apert, Muenke and Saethre–Chotzen syndrome.[14-16] Causes for speech problems are hearing deficits, oral anomalies, learning disabilities and impaired social interaction.[16] The impaired cognition is probably not the main reason for speech problems but will contribute to a worse language development.[16] The level of intelligence varies strongly per syndrome but also within every syndrome, especially patients with Apert syndrome can have a low intelligence.[17-20]

The single-attribute HUI-3 had a medium to strong correlation with the objectively measured vision, hearing and intelligence. However, in individual cases, there were large differences between how parents scored the vision, hearing or intelligence and the objective measurements. It is known that parents have difficulty judging their child's hearing.[21] Therefore, we conclude that the HUI-3 is less suitable in individual patients for follow-up, but can be used on a group level for patients with syndromic craniosynostosis. A limitation of this study is that although this is one of the largest reported groups of children with syndromic craniosynostosis, the syndrome-specific groups still have a small sample size, making comparisons within groups not more than explanatory. Another limitation is the crosssectional design of this study. In conclusion, the overall quality of life is lower in patients with syndromic and complex craniosynostosis. To improve quality of life more attention is needed for problems with vision and speech. As there can be a big discrepancy between objective measures and how parents score the HUI-3, this questionnaire is more suitable for groups than for individual follow-up. The Erasmus Medical Center medical ethical review board approved the study under reference number: MEC-2005-273.

Table 3 Mean multi-attribute score of the HUI-3 and VAS

	HUI-3	VAS
Apert (n=20), mean (SD)	0.44* (0.30)	0.77 (0.20)
Crouzon (n=39), mean (SD)	0.76 (0.23)	0.79 (0.18)
Muenke (n=25), mean (SD)	0.81 (0.22)	0.81 (0.16)
Saethre–Chotzen (n=18), mean (SD)	0.87 (0.14)	0.88 (0.11)
Complex (n=29), mean (SD)	0.83 (0.24)	0.87 (0.10)
Total craniosynostosis group (n=132), mean (SD)	0.75 (0.27)[±]	0.82 (0.16)[±]
Norm group (n=1435), mean (SD)	0.91 (0.12)	0.93 (0.09)

*Significantly lower compared to VAS, $p<0.05$

[±]Significantly lower compared to norm group, $p<0.001$

Table 2 Mean single-attribute HUI-3 of patients and the normative population

	Apert (n=20)		Crouzon (n=39)		Muenke (n=25)		Saethre-Chotzen (n=18)		Complex (n=29)		Norm group (n=1435)	
	% not affected	Mean	% not affected	Mean	% not affected	Mean	% not affected	Mean	% not affected	Mean	% not affected	Mean
Vision	50	0.90 $^{\pm}$	50	0.90 $^{\pm}$	60	0.97 $^{\pm}$	31	0.96 $^{\pm}$	72	0.99 $^{\pm}$	93	0.99
Hearing	85	0.93 $^{\pm}$	79	0.93 $^{\pm}$	76	0.93 $^{\pm}$	89	0.96$^{\#}$	93	0.98*	98	1.00
Speech	20	0.68 $^{\pm}$	56	0.84 $^{\pm}$	56	0.84 $^{\pm}$	71	0.95*	66	0.87 $^{\pm}$	88	0.97
Ambulation	85	0.97 $^{\pm}$	90	0.96 $^{\pm}$	100	1.00	100	1.00	93	0.96 $^{\pm}$	99	1.00
Dexterity	0	0.58 $^{\pm}$	90	0.95 $^{\pm}$	100	1.00	94	0.98$^{\#}$	93	0.96 $^{\pm}$	99	1.00
Emotion	80	0.97	71	0.97	71	0.97	76	0.98	83	0.98	81	0.98
Cognition	25	0.77 $^{\pm}$	61	0.93 $^{\pm}$	72	0.89*	78	0.97	72	0.94	84	0.97
Pain	55	0.93 $^{\pm}$	73	0.97	76	0.96	76	0.98	79	0.97	81	0.98

*$p<0.05$, $^{\#}p<0.01$, $^{\pm}p<0.001$ compared to norm group

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Chapter 6

Activity limitations and quality of life in Apert syndrome

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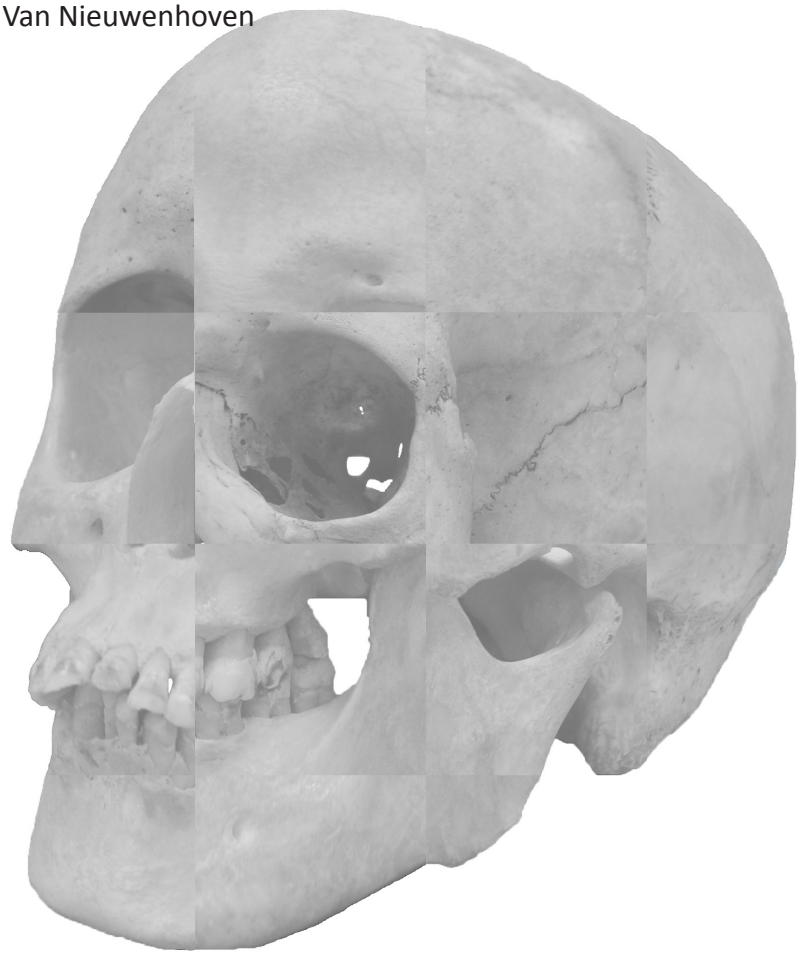

ABSTRACT

Background Apert syndrome is a rare condition characterized by craniosynostosis, cerebral anomalies, complex syndactyly of hands and feet, and a low to near normal mental development. There are no reports on long-term outcome of upper and lower extremity, and the impact on quality of life. The aim of this study is to report on activity limitation of the upper and lower extremity, and its impact on quality of life in patients with Apert syndrome.

Methods Questionnaires were sent to all patients of 6 years and older. Patients from 6 until 16 years received the Abilhand-Kids, Lower Extremity Functional Scale (LEFS), Child Health Questionnaire Parental Form 50 (CHQ-PF50), and Health Utility Index (HUI)-3. Patients aged 16 years or older received the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire, LEFS, and Short Form 36 health survey (SF-36). All patients received a Visual Analogue Scale (VAS) to grade overall health, function and appearance of the hands. Results were compared to normative data from the literature, also the correlation between activity limitation and quality of life was tested.

Results Forty of the 45 eligible patients (response rate 89%) returned the questionnaires. Patients with Apert syndrome scored significantly lower compared to normative data. However, more than 60% of the patients with Apert syndrome scored within the normal range for the SF-36, CHQ-PF50, VAS quality of life and the DASH. A lower limitation of activity was associated with a higher quality of life. Activity limitations of the upper and lower extremities had a similar relation with quality of life. Caregivers scored similar compared to persons with Apert syndrome for quality of life but significantly lower for activity limitation ($p<0.01$).

Conclusions More than 60% of the patients with Apert syndrome and their caregivers report a quality of life and activity limitation within the normal range. However, about one-third of the patients may perceive a low quality of life and high activity limitation. A higher limitation of activity should be considered as a risk factor for a lower quality of life in these patients.

INTRODUCTION

Apert syndrome is a rare condition affecting around 1 in every 65.000 live birth, characterized by craniosynostosis of the coronal sutures, cerebral anomalies, mid-face hypoplasia, symmetric complex syndactyly of hands and feet, and a low to near normal mental development. In more than 98% of the cases it is caused by a S252W or P253R mutation in the FGFR2 gene.[1 2-3] The mode of transmission is autosomal dominant, but almost all cases are sporadic. Most of the de novo mutations occur during spermatogenesis and are related to an advanced paternal age.[4]

The commonly used classification system of the hand anomalies in Apert syndrome is that of Upton,[5] classifying the Apert hand into three types according to increasing severity; type I hands ("spade hand") consist of complex syndactyly of digits two through four with a free thumb and a simple syndactyly of the fourth web, or a separate fifth finger; type II hands ("mitten or spoon hand") consist of complex syndactyly of digits two through five with an associated simple (incomplete) syndactyly of the thumb; and type III hands ("rosebud hand") consist of complex syndactyly of all digits. In all cases a brachyclinodactyly of the thumb is present. Furthermore a synostosis between the fourth and fifth metacarpal bones can be possible. The P253R mutation is associated with the more severe complex syndactyly of the hands.[6-7]

The feet in Apert syndrome are characterized by a medial deviation of the great toe and fusion of the two phalanges with a minimal motion at the metatarsophalangeal joint. The midfoot and hindfoot will characteristically fuse in a supinated position. There is prominence of the fifth and third metatarsal heads with callus formation in most patients.[8]

Besides complex syndactyly of hands and feet, other malformations of the extremities may occur. These may be present at birth or manifest at a later age. In the upper extremity this results in limited shoulder anteflexion and abduction.[9] Elbow motion is mostly not a significant problem unless elbow fusion (9%) occurs.[10-11] In the lower extremity, acetabular, femoral head and neck alterations, and genua valga are incidentally reported, causing limitations of activity.[11]

Previously, two studies from our department have demonstrated a lower quality of life in patients with Apert syndrome compared to other craniosynostosis syndromes and normal controls.[12-13] They found that parents reported problems specifically regarding vision, speech, dexterity and cognition measured with the Health Utility Index-3 (HUI-3). Furthermore, lower scores for physical functioning, parental impact and family activities measured with the Child Health Questionnaire

Parental Form 50 (CHQ-PF50) have been reported. Lower scores on dexterity and physical functioning are probably the result of activity limitations of the extremities. Apert syndrome has various effects on a person's functioning and well-being. Therefore, knowing the impact of this syndrome on physical functioning and quality of life is clinically important. To our knowledge scientific reports on patients with Apert syndrome have mainly focussed on surgical techniques and short-term outcome. However, no reports have been published on long-term outcome of physical functioning of the upper and lower extremities, and the impact on quality of life in patients with Apert syndrome. Therefore the aims of this study are to 1) report on perceived physical functioning of the upper and lower extremities, and quality of life in patients with Apert syndrome of 6 years or older, and 2) present data which can be employed for comparison in future surgical and non-surgical research.

METHODS

We performed a cross-sectional study in patients with Apert syndrome treated for their hand differences at the Sophia's Children's Hospital of the Erasmus MC Universty Medical Center (Rotterdam, the Netherlands). Questionnaires were sent through mail to all patients aged 6 years and older. Caregivers of 6-16 years-old patients were asked to complete the Abilhand-Kids, Lower Extremity Functional Scale (LEFS), Child Health Questionnaire Parental Form (CHQ-PF50) and Health Utility Index (HUI)-3. Patients of 16 years and older were asked to complete the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire, LEFS, and Short Form 36 health survey (SF-36). In all patients a Visual Analogue Scale (VAS) was used to grade overall health, function and appearance of the hands. In patients aged 6-16 year all questionnaires were completed by a caregiver. When patients aged >16 years experienced difficulty completing the questionnaires, they were filled out with help of a caregiver or by a caregiver alone.

Questionnaires (Table 1)

The Abilhand-Kids evaluates a child's manual ability in bimanual activities performed by patients aged 6-15 years.[14-15] This questionnaire is developed for children with cerebral palsy, no normative data are present in the current literature. It measures the parent's perceptions of the difficulty in performing a bimanual daily activity on a three level scale: impossible (0), difficult (1), easy (2). The sum score range is 0-42. A higher score indicates lower difficulty.

The DASH is designed to measure physical functioning and symptoms of the upper extremities in persons 18 till 65 years of age.[16] Normative data are available

for the general American population.[17] For each question, patients or caregivers were asked to provide their perceived difficulty in performing an activity on a five level scale: no difficulty (1), mild difficulty (2), moderate difficulty (3), severe difficulty (4) and unable (5). The sum score range is 0-100, with higher scores indicating greater disability.[18]

The LEFS measures overall function of the lower extremities. The questionnaire consists of 20 questions. For each question, patients or caregivers were asked to provide their perceived difficulty on five level scale: extreme difficulty or unable to perform activity (0), quite a bit of difficulty (1), moderate difficulty (2), a little bit of difficulty (3) and no difficulty (4). The range of the total score is 0-80, with higher scores indicating better function.[19] Normative data are missing in the current literature.

The CHQ-PF50 is a generic health survey that measures parental perception of their child's overall health and is appropriate for parents or caregivers of patients 5-18 years of age. Dutch normative data are available.[12] It contains 12 health-domains and gives a summary score for physical and psychosocial functioning. Scales have a mean of 50, with a standard deviation of 10. Higher scores indicate a higher level of well-being.

The SF-36 is a short generic health survey, designed for adults for which Dutch normative data are available.[20] It measures 8 health domains and gives a summary score for the physical and mental component. Scales range from 0 to 100 with higher scores indicating higher level of well-being.

The HUI-3 is a utility or preference-based scoring system added to the survey to measure health-related quality of life. This questionnaire is suitable for patients of 5 years and older. Dutch normative data are available for children aged 5 to 13 years of age.[21-22] Single attribute utility scores range from 0.00 to 1.00, where perfect health is 1.00 and dead is 0.00. The multi-attribute HUI score can be negative, indicating states described as worse than dead.[23]

The VAS is a line from 0 "not affected" to 100 "severely affected". Patients were asked to put a point on the line corresponding to how they felt to be affected. If 10% of the items of any scale were missing, that individual's scale score was treated as missing values.

Statistical analysis

Differences between patients and caregivers were tested with the Mann-Whitney U test. The student-t test was used to compare our results to normative data from the literature. The correlation between different questionnaire outcomes was assessed

with the Spearman correlation coefficient. The correlation was considered to be small with a rho of 0.3-0.5, moderate with a rho of 0.5-0.8 and strong with a rho of ≥0.8. A two-sided p-value of 0.05 or smaller was considered to be significant. All analyses were performed in SPSS 16.0 for windows.

Table 1 Summary of the questionnaires

	Measures	Best score	Worst score	6-16 year	> 16 year
Abilhand-Kids	bimanual ability	42	0	x	-
LEFS	overall function of the lower extremity	80	0	x	x
CHQ-PF	parental perception of their child's generic quality of life	100	0	x	-
SF-36	generic quality of life	100	0	-	x
HUI-3	health-related quality of life	1.0	-0.37	x	x
VAS	overall health, function and appearnace of the hands	100	0	x	x

RESULTS

The database consisted of 59 patients, of whom 6 were too young to participate, 3 deceased and 5 were lost to follow up. Of the 45 eligible patients for this study, 40 (89%) returned the questionnaires. Non-responders were not different regarding age (p=0.71) and gender (p=0.23). Since 5 patients did not participate in the study, only age and gender were known. Severity of the Apert syndrome or education could therefore not be compared. Patient characteristics are presented in **Table 2**. Of the 24 patients aged > 16 year, 11 (56%) completed the questionnaire themselves, 5 (21%) with help of a caregiver and 8 (33%) were solely completed by a caregiver. Several caregivers reported difficulties with answering the questionnaires because they found that a number of activities were not applicable due to physical or mental impairment of their child. As a result, missing data were present in these instances.

Table 2 patient characteristics

Age, mean ± sd, range (y)	21.6±10.4 (6.1-53.6)
Age 6-16 y, n (%)	16 (40%)
Age > 16 y, n (%)	24 (60%)
Sex, n (%)	
Male	15 (38%)
Female	25 (62%)
Hand surgery	
All hand surgery performed in our centre	24 (60%)
Surgery elsewhere	16 (40%)
Work status (patients aged >16 y), n (%)	
Student	1 (4%)
Part- or full-time job	10 (42%)
Unemployed	13 (54%)

Quality of life

Sum scores of the quality of life questionnaires are presented in **Table 3**. For the patients aged >16 year, patients (n=11) and caregivers (n=8) scored similar on the SF-36 but patients scored significant higher on the HUI-3, median 0.80 versus 0.52 (p=0.004). Quality of life was significantly lower compared to normal controls, except for the SF-36 mental sum score, which was significant higher. For the results of all domains of the quality of life questionnaires see **Appendix 1, 2 and 3**.

Activity limitation

Outcomes of the activity questionnaires are presented in **Table 4**. In patients aged ≥ 16 year, patients (n=11) scored a significant lower limitation of activity compared to caregivers (n=8); DASH (12.5 versus 50.0, p=0.006), VAS hand function (80 versus 45, p=0.005) and LEFS (75 versus 56, p=0.008). This comparison could not be made for patients aged 6-16 years because all questionnaires were answered by caregivers.

Relations between different questionnaires

In the 6-16 year group the Abilhand-Kids and the LEFS had a moderate to strong correlation with the HUI-3 and the CHQ-PF50 (**Table 4**). For the patients >16 years the DASH and LEFS had a moderate to strong correlation with the HUI-3 and a weak correlation with the SF-36 (**Table 5**).

Table 3 Quality of life questionnaires

	6-16 years		> 16 years	
	Apert Mean (sd), % in normale range[a] n=16	Normative data Mean (sd)	Apert Mean (sd), % in normale range[a] n=24	Normative data Mean (sd)
HUI-3 Multi-attribute score	0.53 (0.3)*, 33%	0.93 (0.1)	0.60 (0.3)	-
SF-36				
Physical	-	-	47.80 (7.2)*, 89%	54.02 (6.9)
Mental	-	-	55.53 *(8.3)[#], 100%	49.78 (9.2)
CHQ-PF50				
Physical	44.9 (15.8)*, 71%	56.4 (5.7)	-	-
Psychosocial	47.8 (5.3)[#], 93%	53.2 (6.4)	-	-
VAS general health	72.3 (27.3)*, 64%	92.7 (9.2)	81.0 (20.5)	-

[a] Percentage of patients with scores > mean -2sd of the normative data

[*] $p<0.001$, [#]$p<0.01$ compared to normative data

Table 4 Questionnaires of upper and lower extremity

	6 - 16 years Mean (sd)	> 16 years Mean (sd)	
	Apert n=16	Apert Mean (sd), % in normale range[a] n=24	Normative data Mean (sd)
Abilhand-Kids	24.9 (11.8)	-	-
DASH	-	29.0 (19.0)*, 68%	10.1 (14.7)
VAS hand function	61.7 (24.7)	68.3 (25.5)	-
VAS hand appearance	64.3 (22.8)	62.8 (27.3)	-
LEFS	60.0 (16.4)	60.9 (19.2)	-

a Percentage of patients with scores > mean -2sd of the normative data
*p<0.01 compared normative data

Table 5 Correlation between QoL and activity limitation*

	DASH	Abilhand-Kids	LEFS
HUI3 multi-attribute	0.84[c]	0.63[b]	0.87[c]
SF-36 physical	0.47[b]	-	0.40[a]
CHQ-PF50 physical	-	0.73[b]	0.76[c]

*Correlation expressed as Spearman's rho (absolute value)
[a] not significant, [b] p<0.05, [c] p<0.001

DISCUSSION

In this study on 40 persons with Apert syndrome we found a significantly lower score compared to normative data on quality of life (HUI-3, SF36, CHQ-PF, VAS) and significantly more on activity limitation (DASH). Despite this, approximately 60% of the participants reported a quality of life and activity limitation within the normal range. More severe activity limitation was associated with lower quality of life.

It is clinically important to know the long-term functioning of persons with Apert syndrome. This information is helpful in parental counselling. Parents should be informed that despite the severe hand and feet anomalies, individual patients

can achieve a good long-term ability and/or quality of life. To our knowledge we are the first to report on long-term functioning of the extremities regarding quality of life and activity limitation in Apert syndrome. Therefore it is not possible to compare our results with those of other investigators.

We found a difference in reporting activity limitation between patients and caregivers. This might be explained by the fact that patients who completed the questionnaires themselves, depending on age, will probably have a higher intelligence. Patients with Apert syndrome can have intelligence within the normal limits, but it can also be severely compromised, about one third has an IQ above 70.[24-26] In patients with myelomeningocele a positive relation between intelligence and hand function was found.[27] If intelligence differed between the two groups, patients with a higher intelligence could have scored a better hand function while the severity of the impairment might be similar to those with a lower intelligence. Another explanation could be the disability paradox, which describes that people with a serious disability experience their disability as less severe compared to most people without a disability.[28] This might have led to an overestimation of the limitation of activity when caregivers completed the questionnaires.

The results of the CHQ-PF50 and the VAS general health were comparable with our previous studies, while the HUI3 was considerably better in this study.[12-13] The results of the HUI3 could be higher due to the disability paradox, because the previous study results are only based on parental reports. No differences were found in the other quality of life questionnaires between patients and their caregivers, while previous studies report a difference between how parents and children report quality of life,[29-30] this difference could go both ways.[30] All mean quality of life scores were considerably lower compared to data from the normal Dutch population, except for the SF-36 mental summary score.[11, 23] This suggests that patients with Apert syndrome do not experience much stress and are happy in general.

Although this is a cross-sectional study, the results imply a relation between activity limitation and quality of life in patients with Apert syndrome. Based on the results in **Table 5** we may conclude that a lower limitation of activity is associated with a higher quality of life and that activity limitations of the upper and lower extremities have a similar relation with quality of life. Furthermore, the CHQ-PF50 seems to have a better responsiveness for upper and lower extremity activity limitation than the SF-36. This difference may be due to the experienced difficulty in answering the questionnaires; several caregivers found that at least some of the activities were not applicable, due to physical or mental impairment of their child.

Study limitations

There are several limitations of this study. Firstly, used questionnaires may not be sensitive to all problems encountered in Apert syndrome. This is strengthened by caregivers who reported difficulties in answering questions not applicable for their child. Secondly, DASH, Abilhand-kids and LEFS mainly measure activity limitation. Objective measurements of severity of impairment and participation are missing. Thirdly, because it is a cross-sectional study; a prospective study is needed to measure the effect of hand surgery on activity limitation and quality of life. Fourthly, we had no objective data of intelligence of these patients. Intelligence will have a large influence on quality of life and participation. These topics should be addressed in future research.

Conclusion

More than 60% of the patients with Apert syndrome report a good quality of life and low limitation of activity. However, individual patients will obtain a very low quality of life and high activity limitation. The presence of a more severe activity limitation should be considered as a risk factor for lower quality of life. Activity limitation of upper and lower extremity have a similar impact on quality of life.

APPENDIX

Appendix 1 HUI3 domains

	6 - 16 years Median (range)	> 16 years Median (range)
Vision	0.95 (0.38 - 1.0)	0.95 (0.0 - 1.0)
Hearing	1.0 (0.86 - 1.0)	1.0 (0.71 - 1.0)
Speech	0.82 (0.41 - 1.0)	0.91 (0.0 - 1.0)
Ambulation	1.0 (0.83 - 1.0)	1.0 (0.36 - 1.0)
Dexterity	0.36 (0.0 - 1.0)	0.67 (0.0 - 1.0)
Emotion	1.0 (0.73-1.0)	1.0 (0.91 - 1.0)
Cognition	0.86 (0.32 - 1.0)	0.86 (0.32 - 1.0)
Pain	1.0 (0.48 - 1.0)	1.0 (0.77 - 1.0)
HUI3 multi-attribute	0.47 (0.09 - 0.91)	0.60 (-0.2 - 1.0)

Appendix 2 CHQ-PF50 domains

	6 - 16 years Median (range)
Physical summary	49.1 (2.3 - 61.3)
Psychosocial summary	48.8 (39.8 - 57.6)
physical functioning	88.9 (33.3 - 100)
Role functioning: emotional/behaviour	72.2 (0 - 100)
Role functioning: physical	91.7 (0 - 100)
Bodily pain	80 (20 -100)
General behaviour	80.8 (30-89.2)
Mental health	70 (30 - 90)
Self-esteem	70.8 (58.3 - 83.3)
General health perceptions	45.4 (13.3 - 91.7)
Parental impact: time	88.9 (0 - 100)
Family activity	87.5 (16.7 - 100)
Family cohesion	85 (57.5 - 100)
Change in health	50 (0 - 100)

Appendix 3 SF-36 domains

	> 16 years Median (range)
Physical component summary	49.7 (26.8 - 55.6)
Mental component summary	58.4 (37.6 - 64.8)
Physical functioning	75 (10 - 100)
Role physical functioning	100 (0 - 100)
Bodily pain	90 (41 - 90)
General health perceptions	70 (40 - 90)
Vitality	75 (45 100)
Social functioning	100 (62.5 - 100)
Role functioning: emotional	100 (0 - 100)
Mental health	84 (40 - 100)

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Part IV
Intracranial pressure
&
Surgical treatment

Chapter 7

Ventricular and brain volume in patients with syndromic or complex craniosynostosis

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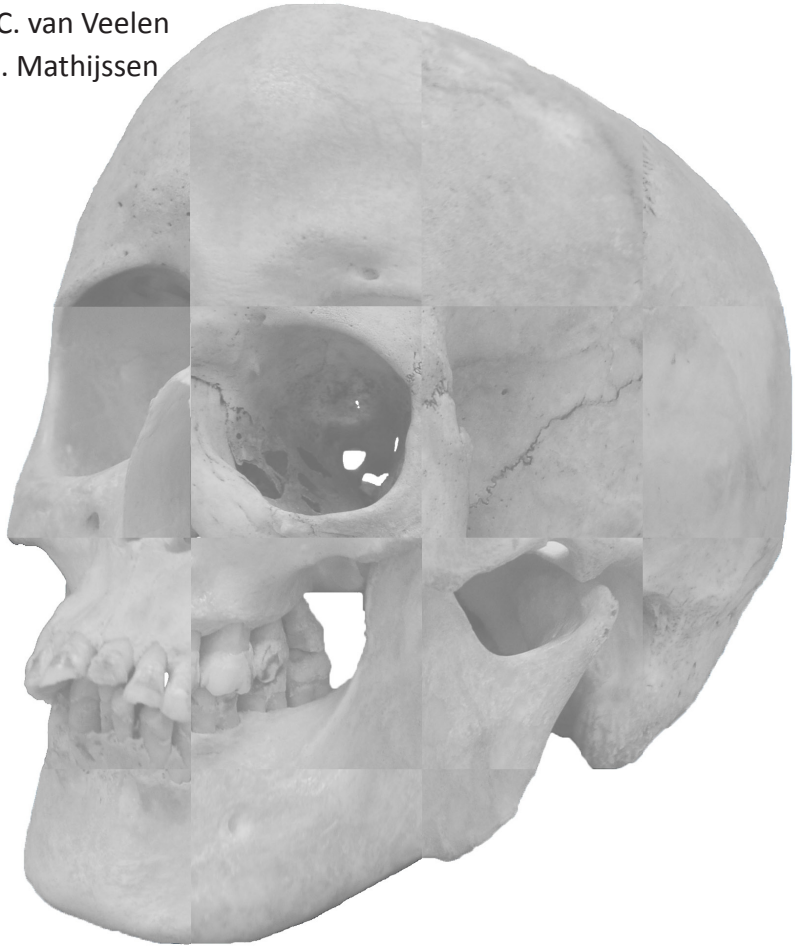

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ABSTRACT

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

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

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

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

INTRODUCTION

Children with craniosynostosis develop an abnormal head shape due to the premature closure of one or more cranial sutures. This congenital malformation occurs in one in 2100 to 2500 births. In up to 20% of these cases it is part of a syndrome, such as Apert, Crouzon, Muenke and Saethre-Chotzen, caused by mutations in the FGFR1, 2 and 3 and TWIST1 gene.[1] Different brain abnormalities are reported in patients with syndromic craniosynostosis including non-progressive ventriculomegaly, callosal agenesis or thinning, agenesis of the septum pellucidum, paucity of the antero-mesial temporal white matter, medial temporal lobe dysgenesis, pyramidal hypoplasia, venous malformations and Chiari I malformations.[2-8] In patients with syndromic craniosynostosis the origin of the abnormalities can either be intrinsic to the genetic defect or develop secondary to the craniosynostosis and associated hydrocephalus and increased intracranial pressure (ICP). A mismatch between intracranial volume versus brain and ventricle volume is thought to be one of the causes of brain abnormalities and elevated ICP. However, in spite of the craniosynostosis the intracranial volumes are reported to be normal in patients with craniosynostosis or even enlarged in Apert and Crouzon syndrome.[9-11] Only one study reports on brain volume in syndromic craniosynostosis. They found that patients with Crouzon syndrome had a similar brain volume compared to normal controls.[12] This contradicts the assumption that a mismatch between intracranial and brain volume is the cause of raised ICP. To improve our understanding of the development of raised ICP, knowledge of brain and ventricular volume in this population is needed.

MATERIAL AND METHODS

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

ties were 0.99 and 0.97 respectively. Brain volume was compared to that in normal controls at the age of 1, 4, 8 and 12 years, reported in literature.[13-15] Total ventricle volume could not be compared to that of normal controls because of the lack of normative data in the literature. A multivariate analysis was performed to look for potential predictors of brain and ventricular volume; age, gender, syndrome, Chiari I malformation and vault expansion. If patients had more than one MRI, only the first was used in the analysis, and patients with a ventriculoperitoneal shunt were excluded from the analysis. Syndromes were put in the model as dummy variables. The intraclass correlation coefficient was calculated to compare the within-rater and betweenrater reliabilities of the volume measurements. All analyses were done with SPSS 16.0 for Windows. This study was approved by the medical ethical committee of the Erasmus University (MEC2005-273).

RESULTS

Between February 2004 and January 2011, 103 patients were invited to receive an MRI of whom 19 refused to participate. The 84 patient who received an MRI had a mean age of 8.1 years (range 0.3–18.3 years). Of the 84 patients, 13 had Apert syndrome, 31 Crouzon syndrome, 15 Muenke syndrome, 10 Saethre-Chotzen syndrome and 15 complex craniosynostosis. The total group consisted of 44 females and 40 males. A vault expansion was performed in 66 patients prior to the MRI, at a mean age of 1.1 years. A Chiari I malformation was found in 12 (14%) patients, one (8%) patient with Apert syndrome, 10 (32%) with Crouzon syndrome and one (7%) with Muenke syndrome. Three patients had a ventriculoperitoneal shunt and were excluded from the ventricular volume analysis. All three had Crouzon syndrome. The mean brain volumes at 1, 4, 8 and 12 years of patients with craniosynostosis and normal controls are shown in **Table 1**. There was no significant difference between patients and normal controls. Age had a significant influence on brain volume ($p<0.001$) but not on ventricular volume. The brain volume increased significantly in the first 5 years ($p=0.004$) after which it stabilized. Patients with Apert syndrome ($p=0.004$) had a significantly larger ventricular volume compared to all other patients. Patients with a Chiari I malformation ($p<0.001$) had a significantly larger ventricular volume compared to patients without a Chiari I malformation. Unexpectedly, Crouzon syndrome as such was not significantly associated with ventricular volume, although most patients (10 out of 12) with a Chiari I were diagnosed with Crouzon syndrome. Patients with Crouzon syndrome and a Chiari I malformation were significantly older compared to Crouzon patients without a Chiari I malformation, the mean age being 10.1 versus 8.0 years

(p=0.018). Furthermore, they had a larger ventricle volume (p=0.019) and were less likely to have had a vault expansion (p=0.049). The syndrome-specific relation between age and total ventricular and brain volume is shown in **Figures 1** and **2**.

Table 1 Mean brain volume of patients with syndromic craniosynostosis and of normal controls

	Craniosynostosis	Normal controls[13-15]	*p*-value
1 year			
n	4	29	
Age	0.90 (0.43)	1.06 (0.03)	0.048
Brain volume	924.25 (254.62)	855.54 (12.43)	0.118
4 years			
n	8	26	
Age	3.95 (0.60)	3.96 (0.52)	0.960
Brain volume	1280.88 (162.05)	1210.62 (109.20)	0.166
8 years			
n	16	20	
Age	8.41 (0.83)	8.60 (0.70)	0.461
Brain volume	1403.44 (156.87)	1391.42 (23.54)	0.883
12 years			
n	16	20	
Age	11.92 (0.60)	12.10 (0.60)	0.396
Brain volume	1464.50 (148.01)	1439.17 (23.54)	0.455

DISCUSSION

In this study we compared the total brain volume of patients with complex or syndromic craniosynostosis to that of normal controls from the literature. Furthermore, we looked for predictors of brain and ventricular volume. We found that the total brain volume in patients with complex or syndromic craniosynostosis is similar to that in normal controls and that ventricular volume was significantly related to Apert syndrome and the presence of a Chiari I malformation.

The majority of patients with syndromic and complex craniosynostosis have a normal or even enlarged intracranial volume, before as well as after vault expansion.[9-12] The finding that brain volume is normal suggests that the compensatory skull growth is sufficient, to allow normal brain growth. The excess of cerebrospinal fluid we observed may be the driving force behind this compensatory growth of the skull.

Therefore, in these patients, raised ICP is more likely to result from raised CSF pressure than from a mismatch between intracranial and brain volume. In most patients this raised CSF pressure will have a communicating character with papilledema as the only sign.[16]

Chiari I malformation is primarily seen in patients with Crouzon syndrome. In our population 32% of the patients with Crouzon syndrome had a Chiari I malformation, compared to 73% perviously reported by Cinnali et al.[17] This difference can perhaps be explained by the fact that they performed an MRI in case of clinical signs, while we performed MRI as part of a prospective study and in most cases without a clinical indication.

The diagnosis of Crouzon syndrome itself was not associated with an enlarged ventricular volume when it was corrected for Chiari I malformation. This means that Chiari I malformations have a stronger relation with ventricular volume than Crouzon syndrome by itself. With the lack of consecutive data, we are not able to tell whether Chiari I malformation precedes or follows the enlarged ventricular volume. Enlarged ventricular volume could be the consequence of reduced CSF outflow due to Chiari I but could also be the cause of downward pressure on the cerebellum due to raised ICP. Chiari I malformations and raised ICP are both prevalent in Crouzon syndrome.[18]

In Apert syndrome larger ventricles are not related to Chiari I malformation, as only 2 to 8% of the patients with Apert syndrome have a Chiari I malformation.[17] Despite the larger ventricular volume, patients with Apert syndrome have a relatively low prevalence of increased ICP.[19] This could be due to their significantly larger intracranial volume before and after vault expansion.[9-10] In Apert syndrome extra compensatory growth of the skull is facilitated by the enlarged anterior fontanelle that stays open for a relatively long period, preventing the development of increased ICP.

Conclusion

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

Conflict of interest

The authors declare that they have no conflict of interest.

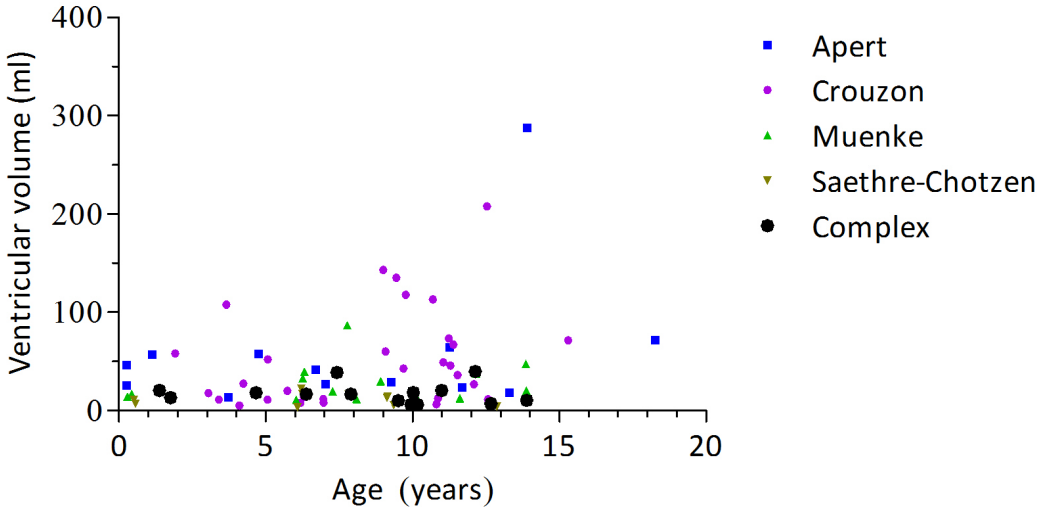

Figure 1 Syndrome-specific relation between age and ventricular volume

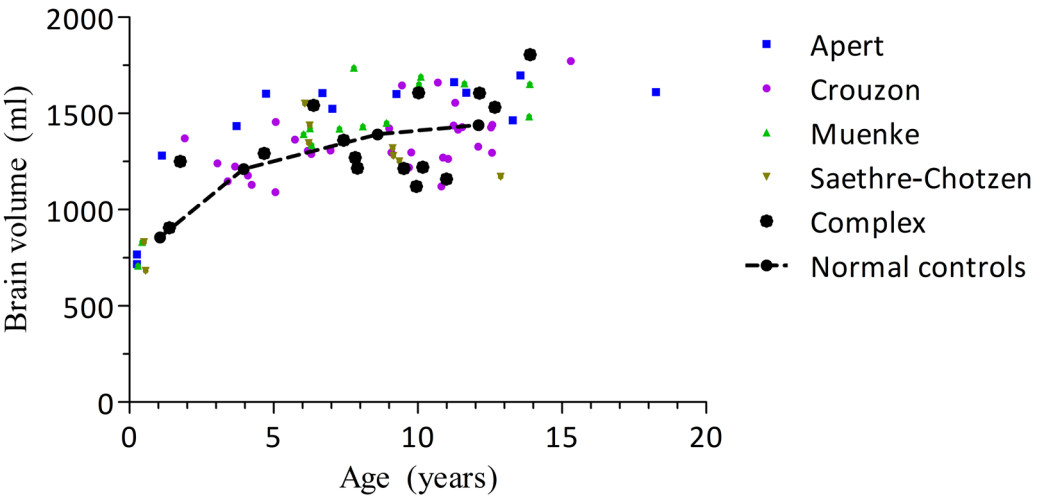

Figure 2 Syndrome-specific relation between age and brain volume

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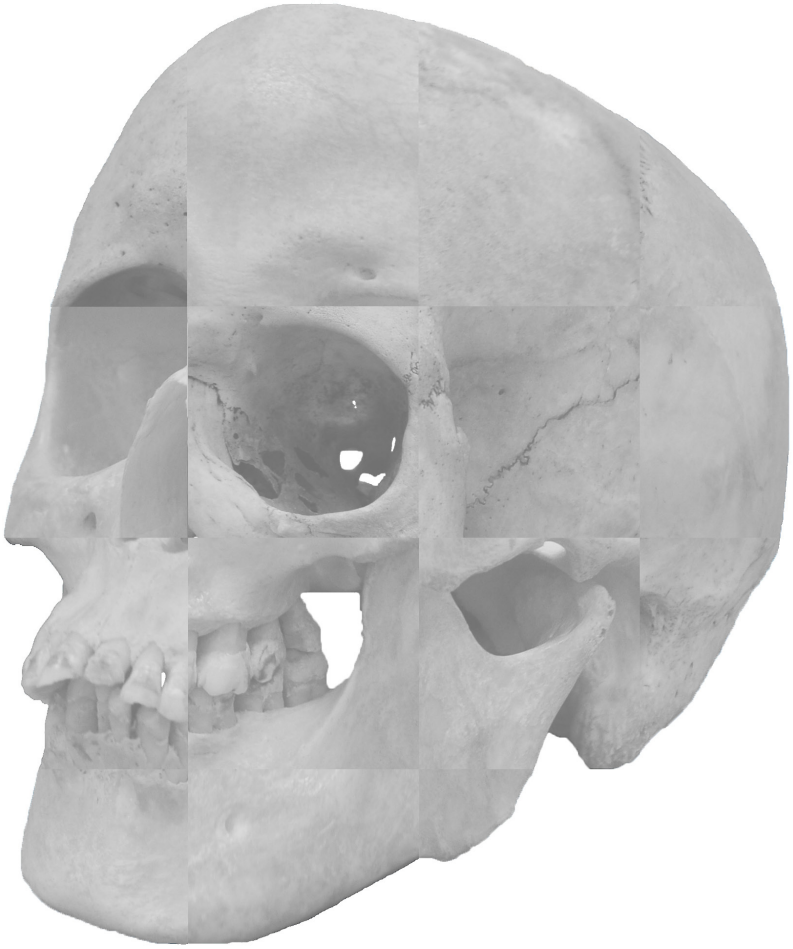
Chapter 9

Spring assisted posterior vault expansion

T. de Jong
M.L.C. van Veelen
I.M.J. Mathijssen



ABSTRACT

Background Patients with Apert and Crouzon syndrome, and craniofrontonasal dysplasia need a vault expansion within the first year of life to treat or prevent the development of raised intracranial pressure. Many craniofacial units perform a conventional posterior vault expansion as initial surgery, an alternative to this technique is the spring-assisted posterior vault expansion.

Objective To demonstrate the efficacy of spring-assisted posterior vault expansion and to compare this technique with the conventional method in children with multisuture craniosynostosis.

Methods A retrospective study was conducted among all consecutive patients who received a posterior vault expansion between 2006 and 2012. Patients treated with springs were compared with patients treated with the conventional technique for blood loss, duration of surgery, postoperative hospital admittance, increase in skull circumference and anterior-posterior length, and complications.

Results Of the 31 included patients, 15 were treated with springs and 16 with the conventional technique. Patients treated with springs had a significantly larger increase in skull circumference and anterior-posterior length, and less blood loss (difference not significant) compared with the conventional group. Complications in the conventional group were: minor dural tear in 3 patients, problematic wound healing in 1 patient, and insufficient expansion in 1 patient. Spring-related complications included skin perforation in 2 patients, a minor dural tear in 2 patients, and leakage of cerebrospinal fluid after an unnoticed dural tear during spring placement in 1 patient.

Conclusion Spring-assisted posterior vault expansion has many advantages over the conventional technique and is therefore the preferred technique in our center.

INTRODUCTION

Patients with multisuture craniosynostosis need a vault expansion within the first year of life to treat or prevent the development of raised intracranial pressure (ICP). In many craniofacial units a posterior vault expansion is done as initial surgery in patients with Apert and Crouzon syndrome, and craniofrontonasal dysplasia. It is thought that posterior vault expansion offers a greater volume increase compared to frontal vault expansion, preserves the facial profile in case of midface hypoplasia, and leaves the frontal part of the skeleton untouched which may reduce the complications of a monobloc or facial bipartition performed at a later age.[1] The conventional technique for posterior vault expansion needs a large dural dissection compared to the spring technique to release the dura from the bone flap; this involves a higher risk for significant blood loss. Furthermore, the amount of push back of the occiput is restricted by the tightness of the skin. These problems have been solved with the introduction of distraction osteogenesis assisted vault expansion.[2-5] The current technique with internal distractors that protrude through skin incisions has some disadvantages such as pin infection and mechanical problems.[6] Spring-assisted posterior vault expansion is a possible alterative. Spring-assisted expansion was introduced by Lauritzen et al.[7] and has since been used for various indications and types of craniosynostosis.[8-10]

The aim of this study was to demonstrate the efficacy of spring-assisted posterior vault expansion and to compare this technique with the conventional method in children with multisuture craniosynostosis.

PATIENTS AND METHODS

A retrospective study was done on all consecutive patients who received a posterior vault expansion between February 2006 and December 2011. Demographic data of all patients were collected, including syndrome diagnosis, gender, and age at surgery. Perioperative data included estimated blood loss, duration of surgery, postoperative hospital admittance, gain in skull circumference (expressed in standard deviation; SD), gain in anterior-posterior (AP) length, maximal spring expansion, presence of ossification defects, and the presence of papilledema. Standard deviations of skull circumference were used to correct for rapid skull growth during infancy. The SD was calculated with Growth Analyser 3.0. The AP length was measured by taking the longest distance from forehead to occiput on lateral skull X-rays. Gain in AP length was calculated from the difference between pre and post length. At the end of the expansion the excursion of the most cranial spring was measured,

as this spring reaches most excursion. The presence of ossification defects one year after expansion was studied on lateral skull X-rays. Complications occurring within the first 30 days after surgery were included. Data of patients who received the conventional technique were compared with those who received spring-assisted vault expansion.

The spring technique was introduced in our center in 2009 and has been used since in almost all cases. According to our protocol, an occipital expansion is first choice for patients with Apert, Crouzon/Pfeiffer, craniofrontonasal dysplasia (CFND), or multisuture synostosis involving the lambdoid sutures. Because Crouzon and Pfeiffer syndrome often cannot be distinguished from each other, even from a genetic point of view,[11] they were considered to be a homogenous group.
If the patient is referred early, this primary occipital vault expansion is planned around the age of 6 months. For patients who require a second skull expansion because of elevated ICP, an occipital expansion is chosen if the presenting shape of the skull allows it. If patients have severe obstructive sleep apnea or severe exorbitism, we choose to perform a monobloc with distraction primarily. Another contraindication for posterior vault expansion is occipital anomalous venous drainage.[12-13] Division of these veins can lead to severe blood loss and a rise in ICP as the venous outflow is restricted.[13]

Statistical analysis
Differences between groups were compared with the Mann-Whitney U test. Differences in gain of AP length of the skull were analyzed with a linear regression model to correct for age at time of vault expansion. Percentage of blood loss was calculated by dividing the estimated blood loss by the circulating blood volume. Circulating blood volume was calculated using the formula 84 cc/kg for those aged 1-6 months, 75.4 cc/kg for those aged 6-24 months, 75.7 cc/kg for those aged 2-5 years, and 74.9 cc/kg for those aged 5-12 years.14
Analyses were performed with SPSS 16.0 for Windows. A two-sided p-value of 0.05 was considered to be significant.

Technical notes
Imaging through 3D CT-angiography is done before surgery to plan craniotomies and evaluate the presence of anomalous occipital venous collaterals.[13]

Spring technique

During surgery, patients are placed in prone position. After coronal incision and dissection, the occipital skin flap is pushed caudally. The neurosurgeon performs the osteotomy. For safety reasons, the most caudal horizontal osteotomy is positioned just above the transverse sinus and the torcula (**Figure 1**). In the center of the horizontal osteotomy a bone strip of 1 cm is left intact, to act as a hinge and prevent an inward collapse of the bone flap or the development of a large occipital ridge. If this bone strip is too thick to allow hinging, the outer cortex is drilled away. The bone flap is left attached to the dura at the site of the lambdoid sutures. In the youngest patients with thin bone in most cases four springs can be placed, whereas in the older patients six springs can be placed if considered necessary. The youngest child in whom we used springs was 5 months of age. Even when the bone was very thin or had several defects, a spot was always found to place the springs; no dural dissection was performed in these cases. Once the springs are inserted, the degree of widening of the osteotomy lines is judged (**Figure 2**). Particularly in secondary surgery the resistance can to be too strong to allow for adequate distraction. In those cases a limited detachment of the bone flap from the dura is created. We used 10.3 g springs (Active Spring Co. Ltd, UK), which produces a force of 3.11 Nmm/degree. After surgery, all patients are transferred to the ICU and return to the ward the following day. Springs were left in place for an average of 76 days. Springs were removed by opening the old scar. After removing the covering soft tissue, the springs were cut halfway which allows to take the springs out with a rotating movement, given the curve at the end of the springs.

Conventional technique

For the conventional technique the same positioning of the patient, incision and osteotomy lines are used. An extra osteotomy line is added to create a bandeau of the most anterior part of the bone flap. The bandeau is placed horizontally, just above the occipital osteotomy. The bone flap is used to close the remaining defect, with the aim to gain as much volume as possible, with the tightness of the skin to allow closure being the limiting factor. The bandeau and the bone flap are fixed with resorbable plates and screws. After surgery, all patients are transferred to the ICU and return to the ward the following day. Postoperative skull x-rays of both techniques are shown in .

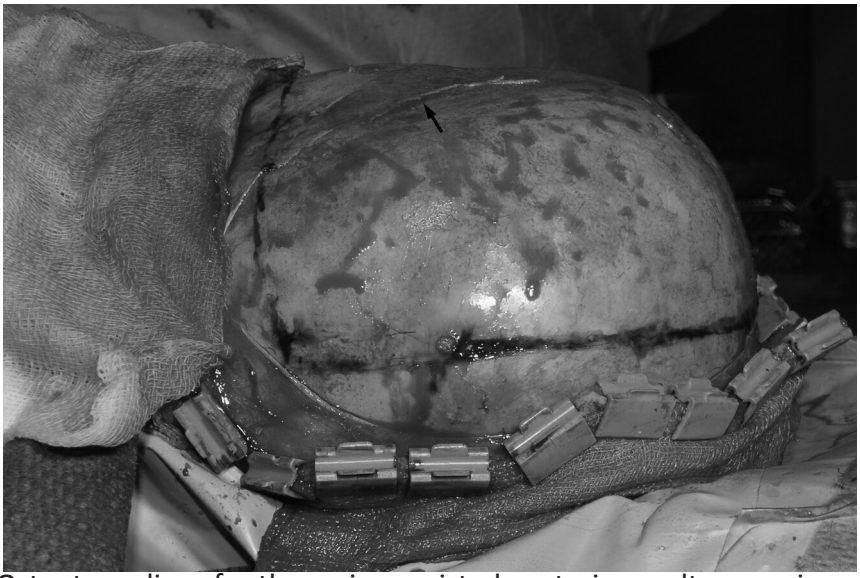


Figure 1 Osteotomy lines for the spring-assisted posterior vault expansion
Arrow: right lambdoid suture.

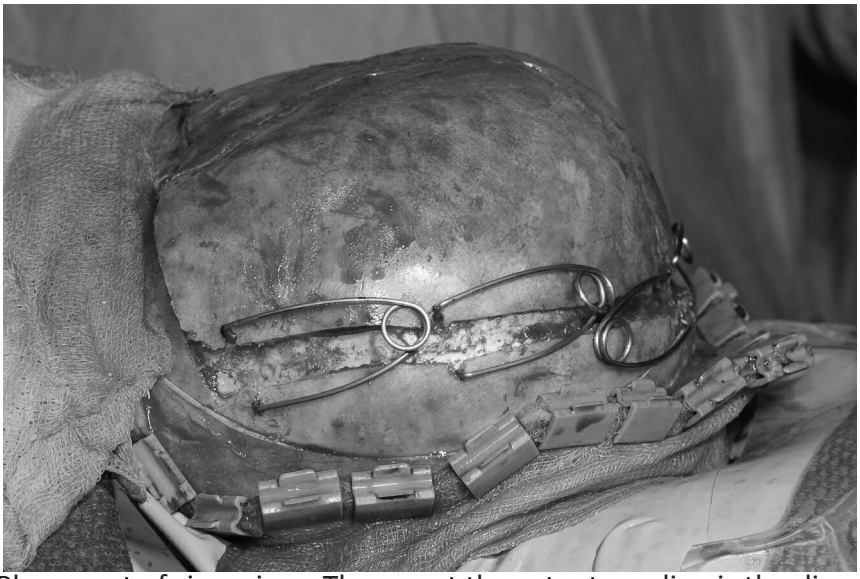


Figure 2 Placement of six springs. The gap at the osteotomy line is the direct effect of the springs.

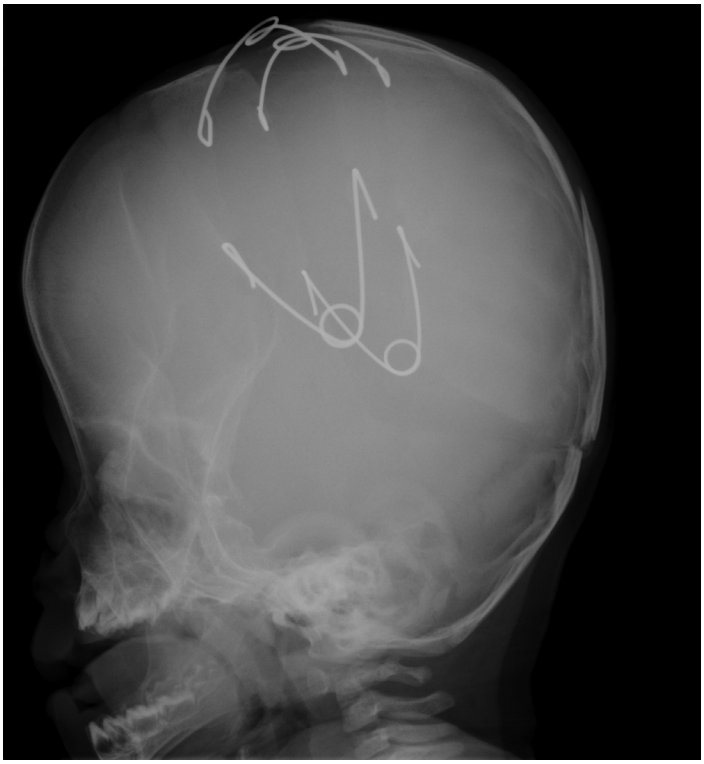


Figure 3 Lateral skull x-ray after spring placement

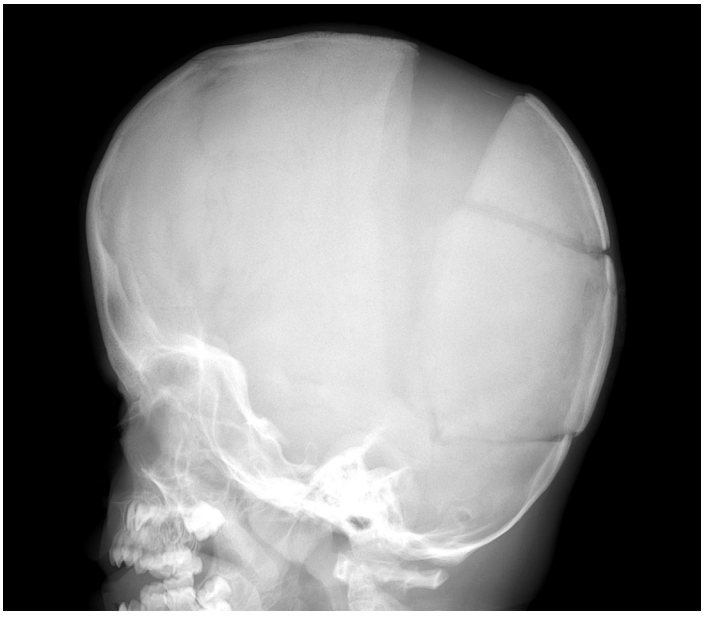


Figure 4 Lateral skull x-ray after the conventional technique. The bone flap is fixed with resorbable plates and screws.

RESULTS

In the defined period 31 patients received a posterior vault expansion, 15 with springs and 16 with the conventional technique. There were 7 males in the spring group and 8 in the conventional group. Diagnosis in the spring group included Apert (n=5), Crouzon (n=2), Saethre-Chotzen (n=2) and Kabuki syndrome (n=1), EFNB1-craniofrontonasal dysplasia (n=3), and complex craniosynostosis (n=2). Diagnosis in the conventional group included Apert (n=3) and Crouzon syndrome (n=6), EFNB1-craniofrontonasal dysplasia (n=1) and complex craniosynostosis (n=6). Posterior vault expansion was the first procedure in 9 patients treated with springs and in 13 treated with the conventional technique. In both groups, the mean age at time of surgery in primary cases was 1.2 years. In secondary cases, it was 3.1 years in the conventional group and 3.8 years in the spring group.

Perioperative data are presented in **Table 1**. There was no significant difference in blood loss, surgical time, or duration of postoperative hospital admittance between groups. Increase in the SD of skull circumference was significantly larger in the spring group (p=0.029), as was the increase in AP length of the skull (p=0.028). The time interval between the AP measurement prior to and after surgery was 6.1 months for the spring group and 8.5 for the conventional group (p=0.17).

At the time of removal the springs positioned the most cranially, spread for an average of 41 (range 22-62) mm. Postoperative ossification defects were seen in 4 patients treated with a conventional expansion and in 3 patients treated with springs. The group with ossification defects had a mean age at expansion of 3.4 years compared to 1.4 years in the group without defects (p=0.006). One patient treated with springs needed plate fixation after removal of the springs, because there was insufficient ossification for stability. Papilledema was present prior to posterior vault expansion in 7 (47%) patients of the spring group and in 7 (44%) of the conventional group; this resolved in all cases treated with springs. In the conventional group papilledema persisted in one patient and one patient developed papilledema two years after vault expansion.

Spring-related complications included skin perforation in 2 patients, a minor dural tear in 2 patients, and an unnoticed dural tear during spring placement in 1 patient. As the springs expanded the leakage of cerebrospinal fluid became noticeable, after which the springs were removed earlier than scheduled and a conventional expansion was performed. In 1 patient a spring perforated the skin and needed to be removed, while the other three springs were left in place; this was a complicated case as he was already operated on twice in another center and in both

instances an extensive number of metal plates and screws were used. However, this complication did not affect the obtained expansion of his skull. Complications seen in the conventional group included a minor dural tear in 3 patients, problematic wound healing in 1 patient, and insufficient expansion in 1 patient. The patient with insufficient expansion received a spring-assisted posterior vault expansion 20 months after the conventional occipital expansion due to persisting papilledema.

Table 1 Data on perioperative posterior vault expansions

	Conventional n=16	Springs n=15	
		Placement	Removal
Mean age at surgery, years	1.6	2.2	2.4
Blood loss, %	44	29	13
Duration of surgery, minutes	164	142	59
postoperative admittance, days	4.1	3.6	1.2
Increase in skull circumference, sd	0.9	-	1.9
Increase in anterior-posterior length, cm	1.7	-	2.3

DISCUSSION

Compared to the conventional technique, spring-assisted posterior vault expansions are associated with a larger increase in skull circumference and AP length. Blood loss was lower in the spring compared with the conventional group, but the difference was not significant. Most complications seen in both groups were minor. In the spring group 1 patient needed additional surgery for removal of one of the four springs after skin perforation, and springs had to be removed early in 1 patient when cerebrospinal fluid leakage was noticed during expansion. In patients treated with the conventional technique this dural tear would probably have been noticed during surgery, whereas with springs the bone flap is left in place and may hide dural tears. Therefore, in patients treated with springs, meticulous inspection of the dura is indicated before closure to prevent traction on the dura tear.

Although there was no significant difference in blood loss between the groups, we consider the conventional technique to involve a higher risk of significant blood loss. The reason that we did not find this difference is probably due to our preference to put the lowest osteotomy just above the transverse sinus, to minimize the risks for blood loss.

Patients with Apert, Crouzon, CFND and multisuture craniosynosis are at risk of developing several episodes of raised ICP and most patients need a midface advancement or facial bipartition to treat midface hypoplasia and/or hypertelorism.[15] A primary posterior vault expansion will give a large increase in intracranial volume while leaving the anterior skull untouched. This enables us to perform the midface advancement or facial bipartition at a later age, with a reduced risk of complications from difficult dissection in a previously operated area.

To treat raised ICP in craniosynostosis a vault expansion is the primary choice of treatment in most instances. Depending on the cause, treatment of OSA and hydrocephalus must also be considered when present. During vault expansion the intracranial volume increases, correcting the cranio-cerebral disproportion. This might be present even in patients with an enlarged intracranial volume due to enlarged ventricular volume.[16] Because springs result in a significantly larger increase of skull circumference and AP length, we assume that springs are associated with a larger increase in intracranial volume. In turn, a larger increase in intracranial volume will most likely be more effective in treating elevated ICP and preventing future episodes.

The AP measurement was not expressed in standard deviations and the increase we found in AP length will be partially attributed to the growth during the measurement interval. However, the spring group had a shorter measurement interval (6.1 versus 8.5 months) with a larger increase of AP length, and therefore we may conclude that with springs a larger expansion is achieved compared to the conventional technique. A similar magnitude of expansion can be obtained through distraction osteogenesis with internal distractors.[4] Both devices have the same disadvantage, that they have to be removed in a second procedure. Patients with internal distractors also need capable and involved parents to daily turn the screws. Furthermore, internal distractors are associated with complications such as breakage, loosening of the footplate, and trauma to the distractor[4, 17] and need solid bone for screw fixation. Our experience with internal distractors is limited to 1 case who developed long-lasting wound-healing problems during and after distraction. An advantage of internal distractors is that they allow a more gradual distraction of 0.5-1 mm a day, resulting in an osteogenetic effect. Springs give the largest distrac-

tion force in the beginning, after which the force decreases with expansion of the springs. Theoretically, this may cause incomplete ossification, although a higher age appeared to be a more important factor for an ossification defect. At the young age when most patients require an occipital expansions the ossification rate is so high that the true advantage of gradual distraction is not of major importance. In our experience internal distractors should be reserved for older patients who are more depended on distraction osteogenesis to allow bone formation, who are more compliant in dealing with an external device and in whom bone thickness allows fixation of a distractor. In the future, additional adjustments of the springs will be made on an individualized custom-made basis, and possibly made of resorbable material to preclude the second procedure.[18]

Conclusion

This study compared the efficacy of spring-assisted posterior vault expansion with a conventional method in children with multisuture craniosynostosis. Spring-assisted posterior vault expansion is associated with a larger increase in skull circumference and AP length of the skull. Springs can applied in the very young, making springs a useful alternative for vault expansions performed with the conventional technique or with internal distractors.

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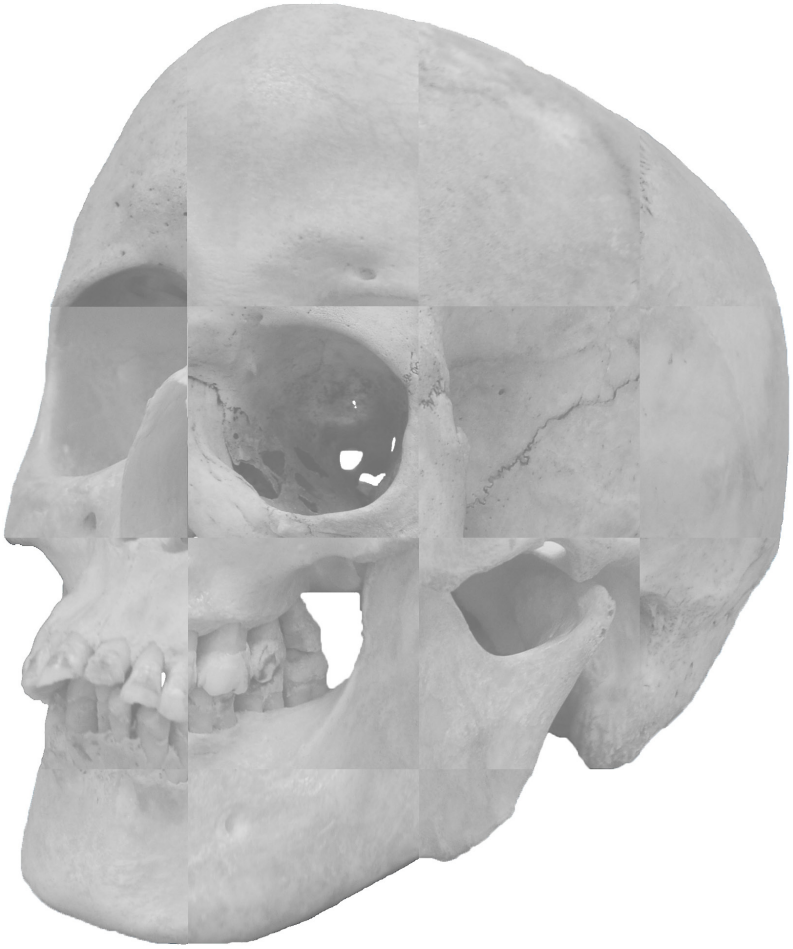
Part V

Discussion & summary

Chapter 9

General discussion

T. de Jong



DISCUSSION

This thesis addresses several outcomes of care for patients with syndromic and complex craniosynostosis. In this chapter first the main findings of this thesis will be discussed followed by the interpretation of the results, clinical implications and recommendations for future research. The main strength of this thesis is the relatively large cohort available in the Dutch craniofacial center, Rotterdam.

MAIN FINDINGS

- With our treatment protocol the lifetime prevalence of raised intracranial pressure (ICP) is 53% in Crouzon, 33% in Apert, 21% in Saethre-Chotzen and 5% in Muenke syndrome, despite routine early vault expansion. The onset of raised ICP is in almost all cases before the age of 6 year.
- The main cause of hearing loss in Muenke syndrome is sensorineural hearing loss that is particularly larger at the lower frequencies. This type of sensorineural hearing loss is not seen in other craniosynostosis syndromes.
- Patients with syndromic craniosynostosis have a normal total brain volume compared to normal controls.
- The main reported causes of a lower quality of life include: problems with vision, hearing and speech in all syndromes, with cognition in Apert, Crouzon and Muenke syndrome and with dexterity in Apert syndrome.
- The Health Utility Index (HUI)-3 has a medium to strong correlation with objective measurements of vision, hearing and intelligence. However, in individual patients there can be a big discrepancy between the objective measurement of vision, hearing and intelligence and that reported by the parents.
- Patients with Apert syndrome can achieve a good quality of life and low activity limitation regarding upper and lower extremity. However, quality of life and activity limitation have a broad range about one third of the patients will obtain a very low quality of life and/or high activity limitation.
- Muenke syndrome can be associated with hypoplasia of the frontal sinus, dysplastic elbow joints with restricted elbow motion, mild cutaneous syndactyly and ptosis of the upper eyelids. Particularly this last finding makes a clinical distinction from Saethre-Chotzen syndrome difficult and therefore genetic analysis is required.

- Good long-term intelligence and visual acuity can be achieved with the current treatment protocol of performing a vault expansion prior to the age of 1. However, a significant larger proportion of patients in all syndromes has an IQ lower than -2sd compared to the normal population (46% Apert, 16% Crouzon, 12% Saethre-Chotzen, 2.3% norm).
- Spring assisted posterior vault expansion results in a larger increase in skull circumference and anterior-posterior length compared to the conventional technique and is thus associated with a larger increase in intracranial volume.

INTERPRETATION OF RESULTS

Intracranial pressure

Close follow-up for the development of raised ICP is indicated in syndromic craniosynostosis because it is related to vision loss and thought to negatively influence intelligence on the long-term.[1-4] In **chapter 2** we report on the lifetime prevalence of raised ICP. In our center the diagnosis of raised ICP is primarily based on presence of papilledema at fundoscopy. The interpretation of a fundoscopy is observer-dependent and the sensitivity is reported to be low (22%) in patients under the age of 8 years.[5] However, this is the only publication on the sensitivity and specificity of papilledema in young children. More research on this topic is indicated, as fundoscopy is a frequently used screening method for raised ICP. The low sensitivity of fundoscopy suggests that the prevalence we found could be an underestimation. We found raised ICP in 53% of the patients with Crouzon, 33% with Apert, 21% with Saethre-Chotzen and in 5% with Muenke syndrome. A previous study from Paris reports frequencies of raised ICP of 62.5% in Crouzon syndrome, 45% in Apert syndrome, and 29% in the other syndromes based on intracranial measurements.[6] If we compare our prevalence of papilledema to the reported frequency of raised ICP based on intracranial measurements by Paris, we may conclude that we theoretically miss approximately 10% of the patients with raised ICP. This indicates that the sensitivity of fundoscopy in our unit is higher than the previous reported 22% in patients under the age of 8 years.[5] This higher sensitivity is probably due to the fact that all our patients are screened by a small group of experienced pediatric ophthalmologists. The sensitivity will however never be 100%. Therefore the chance for false-negative results remains. On the other hand, when compared to the gold standerd intracranial pressure measurements, fundoscopy is non-invasive, can frequently be repeated,

does not need 24 hours admittance to the hospital, is inexpensive and is not associated with severe complications such as haemorrhage and infection.

To prevent missing the diagnosis of raised ICP additional screening methods should be considered. Potential useful methods are ultrasonographic measurements of the diameter of the optic nerve sheet (ONS),[7] visual evoked potentials (VEP's)[8] and optical coherence tomography (OCT) of the optic disc.[9] Ultrasonography of the ONS diameter gives a real time indication of the ICP,[7] because at daytime ICP is normal in most cases the measured ONS ultrasonography is negative.[10] However, during nocturnal episodes of raised ICP the diameter of the ONS increases making ultrasonography of the ONS only useful when measurements can be performed during sleep, preferably during REM sleep when ICP peaks. An advantage of ultrasonography of the ONS is that there is no need for patient cooperation since measurements are taken during sleep. This makes this method useful for all ages.

Optical coherence tomography is able to reveal a higher number of optic abnormalities compared to fundoscopy in patients with idiopathic intracranial hypertension.[9] It is a quick procedure making it potentially useful as a screening method for patients with craniosynostosis, especially as it provides quantitative data. A downside of this method is the need for patients to cooperate. This will be difficult in at least some of the patients, especially the younger ones who are most at risk of developing raised ICP. In our experience OCT gives reliable results in most children from the age of 3 years. Furthermore, results of OCT in patients with craniosynostosis or healthy children are not yet available and comparison to intracranial pressure measurements are missing in the current literature.

In the craniofacial unit at Great Ormond street (London) VEP's are used to detect raised ICP.[8, 11-12] Serial recordings are required to diagnose central vision dysfunction, because the VEP's can initially be within the normal clinical range. Gradual loss in amplitudes of the VEP are used to recognize the presence of raised ICP. This technique can be used in all ages, but is influenced by cooperation and arousal of the patient.[13] A disadvantage of this technique is the need for frequent and time consuming recordings which is a burden to both the patient and parents and to the ophthalmologic department. Although the sensitivity of serial VEP may be higher than fundoscopy, still cases with raised ICP can be missed due to false-negative results.

Invasive intracranial pressure measurements should be considered when there is a high clinical suspicion (decline in growth of the skull circumference, copper beaten pattern) for raised ICP in the absence of papilledema, in the decision making for a second vault expansion in the presence of intermitting or a trace of

papilledema and whenever papilledema does not disappear within 3 to 6 months after vault expansion.

Patients with syndromic craniosynostosis often develop a second episode of raised ICP, whether they have received a routine skull expansion within their first year of life (Paris and Rotterdam protocol) or only at presentation of signs of elevated ICP (London protocol). The cumulative incidence of this episode is highest in Crouzon syndrome and is seen around the age of 3 years. The cause of this episode remains unknown at this moment but must be related to a mismatch between intracranial volume relatively to the intracranial volume of brain, cerebrospinal fluid (CSF), and blood.

Most patients with Apert and Crouzon syndrome do have a larger intracranial volume compared to normal controls, prior and post vault expansion. In most cases this can be explained by the enlarged ventricle volume seen in patients with Apert syndrome and Crouzon syndrome with Chiari I malformation There are however some patients that have a smaller or near normal intracranial volume; particularly patients with Crouzon syndrome can develop pansynostosis during their first years of life, resulting in a deviation of the skull circumference curve. These patients might be the ones who are particularly at risk of developing a second episode of raised ICP. This hypothesis is supported by the results of Renier et al. who found that a smaller intracranial volume is related to a higher risk of developing raised ICP[15] and the fact that brain volumes are comparable to that of normal controls (**chapter 7**). Testing the hypothesis that a relatively too small intracranial volume is the cause of the second episode of raised ICP requires a longitudinal study with repeated measurements of the various components of intracranial volume and occurrence of raised ICP.

Other potential causes are an increase of CSF and/or blood volume. Although we did not find an increase of ventricular volume with age in **chapter 7**, this was a cross-sectional study and longitudinal results have to confirm our data. Ventricular volume increase could be related to restricted outflow or limited absorption of CSF. Whether ventricular volume increases and if this is related to restricted outflow should be studied with serial MRI studies, including a phase-contrast serie which can show CSF flow and the level op obstruction.[18] Obstruction of outflow could be caused by a narrow foramen magnum and/or herniation of the cerebral tonsils.[16-17] In case of a too small foramen magnum or a Chiari I malformation CSF flow is expected to be obstructed at the craniovertebral junction.[18-19] Another potential side of obstruction is the cerebral aquaduct. However, obstruction of CSF is not the only cause of enlarged ventricular volume as third ventriculostomy does

not treat this in all cases.[20] Other causes of an enlarged ventricular volume could be overproduction of CSF or an abnormal development of the ventricles. Raised ICP could also be caused by an increase of intracranial blood volume that could potentially be caused by nightly obstructive sleep apnea (OSA) or by a too small jugular foramen.[10, 21-22] Intermitting episodes of OSA cause hypercapnia, hypoxemia and a negative intrathoracic pressure. Hypercapnia causes an intracerebral vasodilatation, while hypoxemia and a negative intrathoracic pressure result in pulmonary hypertension wich obstructs the intracranial venous outflow. These mechanisms could cause an increase in intracranial blood volume leading to episodes of raised ICP. Furthermore, the obstructive moment will end with a moment of arousel which increases the heart rate, blood pressure and cardiac output, this could also cause a raise in ICP. Obstructive sleep apnea is found in around 30% of the patients with Crouzon and Apert syndrome in a retrospective study (**chapter 2**). From prospective data we now know that the prevalence is much higher, around 68% (Driessen et al. Unpublished data) and that severity of obstructive sleep apnea in syndromic craniosynostosis decreases or stabilizes with age and does not peak around the age of 3 years.[23] It is therefore unlikely that OSA is the main cause for the second episode of raised ICP since this episode is usually seen around the age of 3 years. A small jugular foramen could cause a raise in ICP by obstructing venous outflow resulting in an increase of intracranial blood volume. However, the relation between a small jugular foramen and raised ICP as reported by Rich et al.[22] could not be reproduced in our population (Florisson et al. personal communication). This makes a too small jugular foramen an less likely cause for raised ICP in patients with syndromic craniosynostosis.

To determine whether insufficient intracranial volume and/or an increasing ventricular volume are related to the second episode of raised ICP, a longitudinal study is indicated. This study should include a CT-scan pre and post vault expansion to measure intracranial volume and routine MRI with a phase-contrast serie to study CSF flow and brain and ventricular volume.

Quality of life

There are many potentially functional and psychological problems that can influence the quality of life of patients with syndromic craniosynostosis and their parents. However there is only one previous publications on this topic.[24] To address this important topic we used different questionnaires to asses quality of life in this thesis. In **chapter 5** we studied health related quality of life of patients with syndromic and

complex craniosynostosis based on the HUI-3. In **chapter 6** we used several questionnaires to assess quality of life and disability of the upper and lower extremity in patients with Apert syndrome.

The only previous reported study on quality of life in patients with syndromic craniosynostosis was also performed in Rotterdam and includes partially the same patients.[24] Bannink et al. reported a lower quality of life compared to that of normal controls. Furthermore, they found a significantly lower quality of life of the parents on psychosocial domains of the Short Form (SF)-36.

The main causes of a lower quality of life that we found included problems with vision, hearing and speech in all syndromes, cognition in Apert, Crouzon and Muenke syndrome and dexterity in Apert syndrome. Vision will get sufficient attention during follow-up in most patients because they are routinely referred to a paediatric ophthalmologist for fundoscopy.[25] The need for regular visits to a paediatric ophthalmologist should be emphasized to all parents, to diagnose raised ICP and strabismus.[26] Especially raised ICP can have a devastating effect on the vision of both eyes when left untreated.[1, 27] Hearing and speech may get less attention. Based on our results we advice screening for hearing loss early in life in all patients. In patients with Muenke syndrome SNHL is the main cause of hearing loss therefore screening should especially be focused on this type of hearing loss. Regular follow-up for recurrent otitis media and conductive hearing loss should be done for patients with Apert and Crouzon syndrome (**chapter 4**). In **chapter 5** speech was one of the main problems reported by parents. However, literature on this topic is limited. One study on Apert syndrome reports factors for speech problems including oral abnormalities, recurrent episodes of hearing loss (due to middle ear infections) and a lower cognition.[28] Non-syndromic craniosynostosis is also associated with speech and language abnormalities in 23-37% of the cases.[29-30] Reported risk factors for speech abnormalities in non-syndromic craniosynostosis are synostosis of the coronal sutures, lower cognition and family history of speech and language impairment.[29-30] Recurrent episodes of hearing loss were not found to be related to speech and language impairment.[30] However, from larger studies on patients with cleft lip and palate we know that hearing loss is associated with speech and language impairments.[31-32] From these results we might deduce that to improve speech we have to treat oral abnormalities and hearing loss, and screening for speech abnormalities by a speech therapist should at least be done in patients with oral abnormalities, recurrent episodes of hearing loss, a lower cognition and a family history of speech and language impairment.

In patients with Apert syndrome quality of life is negatively associated with

activity limitation, predicting 20-55% of the experienced quality of life (**chapter 6**). In the other forms of syndromic craniosynostosis none or only minor abnormalities of the extremities are found[33-36] and will therefore only have a small influence on quality of life.

Besides health related problems there are several psychological factors related to quality of life in with congenital facial disfigurements. Known psychological problems in patients with congenital disfigurements are low satisfaction with appearance, fear of negative appearance evaluation and low self-esteem.[37-38] These problems could also be present in patients with syndromic craniosynostosis. A known period with high psychological stress is the period around craniofacial surgery. This period will have a large impact on patients and their parent. Patients experience stress mainly due to change in facial appearance, ICU stay, feeding difficulties and removal of external distractors (Bredero et al. submitted). Parents can experience stress because they have to make a decision for their child whether to be operated or not, change in appearance and feeding problems (Bredero et al. submitted). Therefore we advice to inform all parents about psychosocial problems, especially around the period of craniofacial surgery and offer them psychological support whenever needed. Future research should focus on how to prepare families for craniofacial surgery in such a way that stress is reduced. Furthermore, change in satisfaction with appearance before and after craniofacial surgery and its influence on social functioning should be prospectively tested. This information will help in guiding the parents and patients in making the decision to undergo craniofacial surgery.

A limitation of our study is the use of proxy reports. This was done because of the high prevalence of cognitive impairment, especially in Apert and Muenke syndrome (**chapter 8**). On an individual level parental proxy reports may give a distorted view. Ardon et al. found that despite the fact that mean outcomes do not differ significantly, on an individual level large disagreement can be found between patients and parents, that can go in both directions.[39] Child's pain and parental well being are reported to influence parental proxy reporting.[40] Researchers should be aware of these confounders whenever children are unable to complete quality of life questionnaire themselves.

For clinical evaluation standardized outcome measures should be used to make comparison between different centers easier.[41-43] Preferably these outcomes are objectively measured and can be quantified to aid in comparison between different treatment options and protocols. A suggestion for standardized outcome measures are given in **Table 1**.

Table 1 Suggestions for standardized outcome measures to use in clinical evaluation

	parameter	method
Functional	ICP	*Screening*: Fundoscopy (at routine visits), growth chart of skull circumference (at routine visits), *Diagnosis*: intracranial measurement (when in doubt), MRI (excluding hydrocephalus)
	Obstructive slee apnea	*Screening*: Brouilette score (OSA-18) Diagnosis: PSG (first visit/pos. Brouilette)
	Sleeping	Nocturnal EEG (clinical complaints)
	Vision Function of lacrimal apparatus	Visual acuity (at routine visits), Eye examination by ophthalmologist (clinical complaints)
	Hearing	Audiometry (early in life all/ clinical suspicion)
	Oral health (problems with teeth, occlusion) Speech intelligibility	Oral examination by dentist (after start primary dentition at routine visits) Screening: MOS (screening) Diagnosis: evaluation by speech therapist
	nutritional status, growth	Growth chart of wheight, length and skull circumference (at routine visits), Weight (weekly during distraction)
	Disability of the extremities	DASH, LEFS (at routine visits in Apert and Crouzon/ Pfeiffer)
Aesthetic	Objective measurement	Versnel score (clinical evaluation)
	Satisfaction with (facial) appearance	VAS, Body Cathexis Scale (clinical evaluation)
Psychosocial	Cognition	Bayley scales of infant development (<6y, pre and post vault expansion), WISC (at least once >6y)
	Behavioural problems	CBCL, SDQ (clinical complaints)
	Psychosocial functioning	CHQ, SF-36 (clinical evaluation)
Quality of life	Overall quality of life	CHQ (patients <18 y), SF-36 (patients ≥18 y and parents) (clinical evalution)

MRI: magnetic resonance imaging, OSA-18: OSA disease-specific questionnaire, PSG: Polysomnography, EEG: Electroencephalography, MOS: Mean Opinion Scale DASH: Disability of Arm Shoulder and Hand, LEFS: Lower Extremity Functioning Scale, VAS: Visual Analogue Scale, YQOL-FD: Youth Quality Of Life – Facial Differences. WISC: Wechsler Intelligence Scale for Children, CBCL: Child Behaviour Checklist, SDQ: Strengths and Difficulties Questionnaires, CHQ: Child Health Questionnaire, HUI: Health Utility Index, SF-36: Short Form-36

Surgical treatment

There are many surgical treatment options and protocols for patients with craniosynostosis. However, long-term functional outcomes are missing in the literature. The aim of **chapter 7** was to report on long-term intellectual and visual outcome of patients treated according to the treatment protocol of the craniofacial units in Paris and Rotterdam. Most patients treated with this protocol achieved good long-term intelligence and visual acuity. However, a significant larger proportion in all syndromes has an IQ lower than -2sd compared to the normal population. The average IQ of patient who could be tested was 75 in Apert, 98 in Crouzon, 102 in Saethre-Chotzen, 77 in Muenke syndrome and 95 in complex craniosynostosis. The average visual acuity was 0.80 in Apert, 0.82 in Crouzon, 0.93 in Saethre-Chotzen, 0.94 in Muenke syndrome and 0.98 in complex craniosynostosis (**chapter 7** & unpublished data). This is in accordance with what parents reported in **chapter 5**.

Only a small number of papers studied intelligence in syndromic craniosynostosis.[44-50] In patients with Apert and Crouzon syndrome similar IQ's were found.[44, 48-49] Higher IQ's were reported in patients with Muenke syndrome and plagiocephaly,[50] no studies were found reporting on average IQ's in Saethre-Chotzen syndrome. However, in patients with Saethre-Chotzen syndrome development delay is reported in approximately 10% and higher frequencies of development delay are reported in patients with TWIST deletions.[51-52] Based on the literature and our results we may conclude that syndrome diagnosis is the main predictor of IQ. It remains the question if age at time of vault expansion influences long-term intellectual outcome. Studies on this topic present contradictory results; some state that surgery should be performed before the age of one year to get the best possible intelligence,[6, 44] while others can not find such a relation.[45, 48-49]

Visual impairment, defined as a visual acuity of ≤0.5 in the best corrected eye, was found in 8% of the patients with Apert, Crouzon and Saethre-Chotzen (**chapter 7**). This is lower compared to the literature were visual impairment is reported in 17%-35% of the patients with these syndromes.[53-56] This difference might be explained by the close follow-up we perform in our craniofacial unit in the first 6 years in combination with ophthalmological examinations. The main reported reasons for visual loss are ametropia and amblyopia. Risk factors for amblyopia seen in syndromic craniosynostosis are strabismus, ametropia, astigmatism and ptosis. Optic nerve atrophy, also thought to be a cause of vision loss in syndromic craniosynostosis, is reported in 5%-16% of the patients with Apert and Crouzon syndrome[54, 56-57] and in 0%-10% of the patients with Saethre-Chotzen and Muenke syndrome.[33, 58] We found a similar frequency of optic nerve atrophy in **chapter 7**. All the previous stud-

ies on visual outcome show that vision loss in syndromic craniosynostosis is multifactorial. Therefore vision loss is probably more dependent on the ophthalmological follow-up and treatment than on timing of vault expansion. The long-term results of different treatment protocols are needed to allow comparison and aid in the discussion of timing of vault expansion. If similar long-term results can be achieved with the London protocol, the current dogma to perform vault expansion before the age of 1 year should be reconsidered. As long as this has not been demonstrated, it seems sensible to adhere to the current Rotterdam/Paris protocol.

During the last 15 years an increasing number of craniofacial units are using posterior vault expansions as primary surgery in syndromic craniosynostosis with midface hypoplasia.[59-62] The main advantage of a posterior vault expansion is the larger increase in intracranial volume compared to a frontal-orbital advancement.[63-64] Furthermore, it leaves the face untouched, making it easier to perform a monobloc or facial bipartition at a later age. The gain in volume can be further increased by the use of springs (**chapter 8**). However, posterior vault expansions can be associated with severe complications when anomalous occipital venous drainage is present.[65] A large part of the venous drainage can be cut during dissection resulting in an untreatable rise of intracranial pressure.[66]

Future research should focus on the development of raised ICP and Chiari I malformations after a posterior vault expansion. If a limitation in growth of intracranial volume is a cause of the second episode of raised ICP, patients who received a primary posterior vault expansions might have a lower incidence of raised ICP. Furthermore, the development of Chiari I malformations might be prevented or treated by the increased volume of the posterior fossa.[67] When posterior vault expansions can prevent or limit the development of raised ICP and/or Chiari I malformations in at least some of the patients, it will justify the use of this method as primary surgery. The additional value of distractors and springs should also be proven, to justify the use of these devices as they need a second surgery for removal.

CLINICAL IMPLICATIONS

- Screening for raised ICP should be done pre- and post-surgery in all patients. Thereafter it should at least be done annually until the age of 6 years in Apert, Crouzon, Saethre-Chotzen and Muenke syndrome. Fundoscopy is at this moment the preferred screening method.

- Screening for hearing loss should be done early in life in all patients with syndromic craniosynostosis. In patients with Muenke syndrome screening should especially be focused on sensorineural hearing loss . Regular follow-up for recurrent otitis media and conductive hearing loss should be done for patients with Apert and Crouzon syndrome.
- Speech should be checked by a speech therapist in all children with oral abnormalities, recurrent episodes of hearing loss, a family history of speech and language impairment and a lower cognition. In patients with a very low intelligence this might not be feasible.
- All parents should be informed about psychosocial problems that they and their child can expect, especially around the period of craniofacial surgery of their child. Psychological support should be offered whenever needed.
- Screening for enlarged ventricular volume and the presence of a Chiari I mal formation with the help of MRI is indicated in all patients with Apert and Crouzon syndrome at first presentation, at the age of 3-4 years and when signs of raised ICP are present.
- Until long-term results of other treatment protocols are presented the current protocol which implies vault expansion before the age of one and close follow-up should be followed.
- Spring assisted posterior vault expansion is a useful technique to get a larger gain in intracranial volume compared to the conventional technique.

FUTURE PERSPECTIVES

- A high percentage of patients with syndromic craniosynostosis develop a second episode of raised ICP around the age of 3 years. Understanding the origin of this episode will guide future treatment and may prevent this episode. Especially patients with Crouzon syndrome should be considered for such a longitudinal study, as they have the highest prevalence of raised ICP.
- Several non-invasive methods are currently available to screen for raised ICP including fundoscopy, OCT, VEP and ONS ultrasonography. At this moment there are no or only limited data on the sensitivity and specificity of these methods. These data are necessary to select the best method and help with interpreting the test results.

- Most studies on hearing loss are cross-sectional. Therefore knowledge about how hearing loss evolves over time is missing. Especially in patients with Muenke syndrome, who can have severe SNHL, this information is crucial for patient follow-up and counselling. If the hearing loss does not worsen over time a single screening for SNHL at an early age will be enough in Muenke syndrome.
- Furthermore, results of brainstem evoked response audiometry and auditory event related potential will give information about central sound processing. This might give a better understanding of the brain functioning in the very young patients.
- Studying the relation between elevated ICP, Chiari I malformation and enlarged ventricle volume to determine which finding precedes the other.
- Since 2006 several questionnaires have been used in our population.[24, 37-38, 68-70] The next step would be to select the questions and questionnaires that are best at measuring health status and change in health status change. From the most informative questions a new questionnaire could be developed specifically for craniosynostosis that covers all affected domains. After validation this questionnaire should be used in all future research to enhance comparability between different studies.
- Abnormal speech was found to have a large impact on quality of life. However, at this moment information about the main problems causing abnormal speech are missing. This knowledge is needed for adequate screening and treatment. To improve our understanding of speech problems in this population all parents and patients should be asked about speech problems and referred to a speech therapist when present. The speech therapist should report on the cause and the effect of treatment when given.
- Although a relatively large proportion of patients with Apert syndrome are disabled due to problems with hips and knees, there are no studies, except ours, on functioning of the lower extremity in Apert syndrome. More knowledge about pathology and functioning of hips, knees and feet would enable better screening and treatment improving quality of life.
- To get international consensus on which treatment protocol results in the best intellectual and functional outcome a RCT is probably needed. As this study design is not very feasible, at least long-term data on intelligence and visual acuity are needed from other treatment protocols. Given the rarity of syndromic craniosynostosis, multi-center studies and international cooperation will have a large added value.

- Long-term results need to prove the usefulness of springs in preventing and treating a second episode of raised ICP and Chiari I malformations.
- The largest disadvantage of spring assisted posterior vault expansion is the need for a second procedure to remove the devices. Resorbable springs with the same mechanical property would prevent the need for a second surgery.

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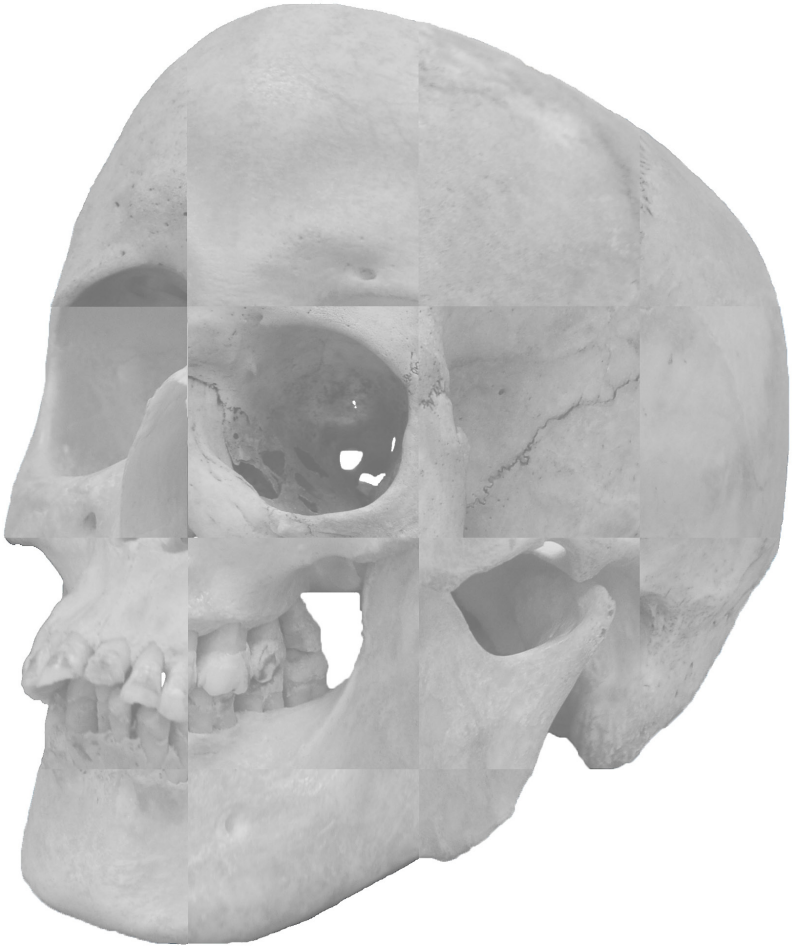
Chapter 10

Summary

Nederlandse samenvatting



SUMMARY

The aim of this thesis was to give a better understanding of syndromic craniosynostosis regarding ICP, OSA, hearing loss and quality of life, describe the relation between genotype and phenotype, and report different outcomes of various treatment options.

Chapter 1: Craniosynostosis is a condition in which one or more sutures of the skull prematurely fuse. When craniosynostosis is associated with other congenital malformations and/or is caused by a mutation or deletion we speak of syndromic craniosynostosis. The most prevalent syndromes are Crouzon, Muenke, Saethre-Chotzen and Apert. If no genetic cause can be found and two or more sutures are closed we speak of complex craniosynostosis. The aetiology, most prevalent problems, and the surgical treatment modalities are discussed in this chapter.

Chapter 2 is a retrospective study describing functional problems of 167 patients diagnosed with Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome, aged 1-25 years. The main results of **chapter 2** and **chapter 4** are presented in **Table 1**. The prevalence of raised ICP remains high in the first years after vault expansion, with a peak around the age of 3 years. Based on these data, guidelines for follow-up of patients per syndrome are suggested.

Table 1 main results of chapter 2 and 4

	Raised ICP	OSA*	Refractive error	Strabismus	Hearing loss
Apert	33%	31%	76%	93%	44%
Crouzon/Pfeiffer	53%	27%	39%	63%	29%
Muenke	5%	5%	49%	39%	29%
Saethre-Chotzen	21%	5%	52%	37%	62%

* Prospective numbers are higher due to the absence of routine PSG before 2006

The aim of **chapter 3** was to report on long-term visual and intellectual outcome of the treatment protocol used in Rotterdam and Paris. We report on a group of 147 patients with Apert, Crouzon and Saethre-Chotzen syndrome. All patients received early surgery and received an IQ test at the age of 6 years or older. Data of visual acuity was reported on in a subgroup of 39 patients from the Rotterdam cohort. There was a good long-term intellectual outcome in patients with Crouzon and Saethre-Chotzen. Patients with Apert syndrome had a significantly lower IQ compared to both other syndromes ($p<0.001$). However, in all three syndromes a significantly

larger proportion had an IQ lower than -2 sd compared to the normal population (46% Apert, 16% Crouzon, 12% Saethre-Chotzen, 2.3% norm). On average, a good vision was found in all syndromes. Nevertheless, the visual acuity of the best corrected eye was ≤ 0.5 in 8% of the patients. With our current policy to perform early vault expansions a good long-term intelligence and visual acuity could be achieved. However, despite early vault expansion a number of cases will still have a low IQ.

Syndrome-specific type, severity, and prevalence of hearing loss is presented in **chapter 4**. Hearing loss is conductive in most patients with Apert, Crouzon, and Saethre-Chotzen syndromes and is predominantly sensorineural in patients with Muenke syndrome. Sensorineural hearing loss at lower frequencies is only seen in patients with Muenke syndrome. Based on these findings we recommend routine visits to the general practitioner or otolaryngologist, depending on national standards of care, to screen for otitis media with effusion throughout life. In addition, we recommend early screening for sensorineural hearing loss among children and young adults with these syndromes.

Chapter 5 presents Health-related quality of life measured with proxy reports of the Health Utility Index mark 3 (HUI-3) and the Visual Analogue Scale (VAS). All data were compared to a normative Dutch population. Vision, hearing and intelligence were objectively measured and correlated to the corresponding HUI-3 attribute. The HUI-3 multi-attribute and the VAS were significant lower compared to the normative Dutch population. A high prevalence of vision and speech problems were reported in all syndrome groups. Cognitive problems were mainly reported in patients with Apert, Crouzon and Muenke syndrome. Ambulation and dexterity problems were reported in Apert, Crouzon, Saethre-Chotzen and complex craniosynostosis. Only patients with Apert syndrome scored significantly worse on pain. The HUI-3 attributes vision, hearing and intelligence had a medium to strong correlation with the objectively measured visual acuity, hearing and intelligence.

Chapter 6 describes quality of life and activity limitation of upper and lower extremity in patients with Apert syndrome aged ≥ 6 years. Questionnaires were answered by patients, patients with the help of a caregiver or by caregivers only. More than 60% of the patients with Apert syndrome have a quality of life and activity limitation within the normal limits. However, the outcomes of all questionnaires had a broad range and about one third of the patients obtained a very low quality of life and/or high activity limitation. Activity limitation was negatively correlated with quality of life. Caregivers scored significant higher on activity limitation compared to patients themselves. This difference was not found in the quality of life questionnaires.

In **Chapter 7** we report on volumes of the total brain and ventricular system. Total brain volume in syndromic craniosynostosis equals that of normal controls, in the age range of 1 to 12 years. Brain growth occurred particularly in the first 5 years of age, after which it stabilized. Within the studied population, ventricular volume was significantly larger in Apert syndrome compared to all other syndromes and in patients with a Chiari I malformation. Chiari I malformations are mostly found in patients with Crouzon syndrome. Therefore we advice screening of all patients with Apert and Crouzon syndrome for the development of enlarged ventricle volume and the presence of a Chiari I malformation.

In many craniofacial units a posterior vault expansion is done as initial surgery in Apert and Crouzon syndrome, and craniofrontonasal dysplasia It is thought to offer a greater volume increase compared to frontal vault expansions and leaves the frontal part of the skeleton untouched which may reduce the complications of a monobloc or facial bipartition performed at a later age. Spring assisted posterior vault expansion could be a possible improvement for the conventional technique. In **chapter 8** we report on spring assisted posterior vault expansion and compare this technique with the conventional technique in children with multisuture craniosynostosis. We included 31 patients, 15 treated with springs and 16 with the conventional technique. Spring assisted posterior vault expansions were associated with a larger increase in skull circumference and anterior-posterior length. This with only minor complications. Blood loss and operation time were not significant different. We conclude that springs assisted posterior vault expansions are associated with a larger increase in intracranial volume and a useful alternative for conventional occipital expansion.

NEDERLANDSE SAMENVATTING

Het doel van dit onderzoek was om een beter beeld te geven van syndromale craniosynostose ten aanzien van hersendruk, OSAS, gehoorverlies en kwaliteit van leven, om de relatie tussen genotype en fenotype te beschrijven en het presenteren van lange termijn resultaten van de chirurgische behandeling.

Hoofdstuk 1: Craniosynostose is een aandoening waarbij één of meerdere schedelnaden prematuur sluiten. Als craniosynostose geassocieerd is met andere aangeboren afwijkingen en/of een genetische oorzaak heeft spreken we van syndromale craniosynostose. De meest voorkomende syndromen zijn Crouzon, Muenke, Saethre-Chotzen en Apert. Als er geen genetische oorzaak gevonden wordt en twee of meer schedelnaden zijn prematuur gesloten spreken we van complexe craniosynostose. Patiënten met craniosynostose hebben een schedel vergrotende operatie nodig om verhoogde hersendruk te voorkomen of behandelen. Dit wordt meestal voor het eerste levensjaar gedaan. Hiernaast kunnen ze een groot aantal andere klinische problemen hebben. Hierbij valt te denken aan slaap apneu syndroom, gehoor en visus daling, handafwijkingen en problemen met de ontwikkeling.

Hoofdstuk 2 is een retrospectieve studie die de functionele problemen van 167 patiënten met syndromale craniosynostose beschrijft, in de leeftijd van 1 tot 25 jaar. De bevindingen van hoofdstuk 2 en 4 zijn samengevat in Tabel 1. De prevalentie van verhoogde hersendruk blijft hoog ook na schedelexpansie. Dit is voornamelijk te zien rond de leeftijd van 3 jaar. Aan de hand van deze gegevens wordt er een syndroom specifieke richtlijn gepresenteerd.

Tabel 1 Resultaten hoofdstuk 2 en 4

	Verhoogde hersendruk	OSA*	Refractieve afwijkingen	Strabismus	Gehoor verlies
Apert	33%	31%	76%	93%	44%
Crouzon/Pfeiffer	53%	27%	39%	63%	29%
Muenke	5%	5%	49%	39%	29%
Saethre-Chotzen	21%	5%	52%	37%	62%

* Prospectieve cijfers zijn hoger door afwezigheid van routinematige screening voor 2006

De meeste craniofaciale chirurgen adviseren een eerste schedelexpansie voor het eerste levensjaar. Er zijn echter geen lange termijn resultaten aangaande de intelligentie en de visus van dit behandelprotocol. In **hoofdstuk 3** presenteren wij de

lange termijn resultaten van een studie in samenwerking met het craniofaciale centrum in Parijs. In deze studie hebben we 147 patiënten geincludeerd met Apert, Crouzon en Saethre-Chotzen die een vroege schedelexpansie hebben gehad en een IQ test op de leeftijd van 6 jaar of later. Hiernaast wordt van 39 patiënten uit Rotterdam de visus beschreven. Een goede lange termijn intelligentie werd geobserveerd in patiënten met Crouzon en Saethre-Chotzen. Patienten met het Apert syndroom hadden een significant lagere intelligentie vergeleken met de andere twee syndromen. In alle drie de syndroom groepen zitten significant meer patiënten met een IQ lager dan -2 standaard deviaties vergeleken met de normale populatie (46% Apert, 16% Crouzon, 12% Saethre-Chotzen, 2.3% norm). In 8% van de patiënten was de visus 0.5 of lager gemeten met de Snellen kaart. Wij concluderen dat met het huidige beleid van vroege schedelexpansie een goede lange termijn intelligentie en visus behaald kan worden. Echter, ondanks een vroege schedelexpansie zullen er patiënten zijn met een laag IQ.

Type, ernst en prevalentie van gehoorverlies per syndroom worden beschreven in **hoofdstuk 4**. Patiënten met Apert, Crouzon en Saethre-Chotzen hebben met name een gehoorverlies met een geleidingscomponent. Terwijl patiënten met het Muenke
syndroom met name een perceptief gehoorverlies hebben dat erger is in de lage frequenties. Dit gehoorverlies wordt alleen gezien bij patiënten met het Muenke syndroom. Aan de hand van deze bevindingen adviseren wij levenslange regelmatige controle van het gehoor door de huisarts of KNO-arts, om te screenen op middenoorontstekingen met effusie. Verder adviseren wij te screenen op een perceptief gehoorverlies bij kinderen met syndromale craniosynostose.

Hoofdstuk 5 beschrijft de kwaliteit van leven gemeten met de Health Utility Index mark 3 (HUI-3) en een Visual Analogue Scale (VAS). Alle patiënten werden vergeleken met Nederlandse normaal data. Visus, gehoor en intelligentie werden objectief gemeten en vergeleken met het corresponderende deel van de HUI-3. De HUI-3 en de VAS waren significant lager ten opzichte van de gemiddelde Nederlandse populatie. Een groot deel van de ouders meldt dat hun kind problemen met de visus en/of spraak heeft. Een lagere intelligentie werd met name in patiënten met het Apert, Crouzon en Muenke syndroom gemeld. Moeite met lopen en handfunctie werd met name gezien in Apert, Crouzon, Saethre-Chotzen en complexe craniosynostose. Alleen in patiënten met het Apert syndroom werd significant meer pijn gescoord. De HUI-3 onderdelen visus, gehoor en intelligentie hadden een gemiddeld tot sterke relatie met de objectief gemeten visus, gehoor en intelligentie.

Aan de hand van verschillende vragenlijsten is de kwaliteit van leven en

beperkingen van de onderste en bovenste extremiteit bestudeerd in patiënten met het syndroom van Apert (**hoofdstuk 6**). De vragenlijsten werden beantwoord door de patiënt, de patiënt met behulp van een ouder/verzorger of alleen door een ouder verzorger. Ongeveer 60% van de patiënten met het syndroom van Apert heeft een beperking en kwaliteit van leven binnen de norm. De behaalde resultaten hebben echter een brede spreiding en rond een derde deel van de patiënten heeft een zeer lage kwaliteit van leven en ernstige beperkingen. De ernst van de beperking van de extremiteiten was negatief gecorreleerd aan kwaliteit van leven. Ouders/verzorgers scoorde gemiddeld lager op vragenlijsten over de beperking dan patiënten die de vragenlijst zelf beantwoorden. In de kwaliteit van leven vragenlijsten werd dit verschil niet gevonden.

In **hoofdstuk 7** presenteren we volume metingen van de hersenen en het ventrikel systeem. In de leeftijd van 1 tot 12 jaar is het hersenvolume gelijk aan dat van de norm populatie. De groei van de hersenen vindt met name plaats tijdens de eerste 5 jaar, waarna het stabiliseert. In de studiepopulatie werd een relatie gevonden tussen het volume van het ventrikelsysteem en het hebben van het Apert syndroom of een Chiari I malformatie. Chiari I malformaties worden met name gezien in patiënten met het Crouzon syndroom. Daarom adviseren wij om in patiënten met het Apert en Crouzon syndroom te screenen op vergrote ventrikels en de aanwezigheid van Chiari I malformaties.

Achterhoofdexpansies worden veelvuldig gebruikt als eerste schedelexpansie bij patiënten met Apert en Crouzon syndroom en craniofrontonasale dysplasie. Deze techniek geeft een grotere toename in volume en laat het aangezicht onaangeraakt wat bij een latere mono-block of facial bipartition de kans op complicaties mogelijk verminderd. Het gebruik van metalen veren om het achterhoofd naar achter te duwen zou deze techniek nog verder kunnen verbeteren. In **hoofdstuk 8** beschrijven we de achterhoofdexpansie met behulp van veren en vergelijken deze techniek met de conventionele techniek. Er zijn 31 kinderen geincludeerd waarvan er 15 met veren zijn behandeld en 16 met de conventionele techniek. Kinderen die met veren waren behandeld hadden een grotere toename van schedelomtrek en voorachterwaartse lengte van het hoofd. Bloedverlies en operatieduur waren niet significant verschillend. Er werden alleen milde complicaties gezien. Wij concluderen dat een schedelexpansie met veren geassocieerd is met een grotere toename van het intracraniële volume en een goed alternatief vormt voor de conventionele techniek.

Part VI
Appendices

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CURRICULUM VITAE

Tim de Jong was born on 22 January 1982 in Brisbane, Australia. He finished the HAVO in 2000 at the OSG, Schagen. During high school he had no clue what he wanted to become. After a career test he decided to entered the study physical therapy at the Thim van der Laan, Utrecht. Het obtained his BSc physical therapy in 2005. During this study the idea grew of studying medicine, why not?! Therefore he obtained the VWO certificates biology, chemistry, mathematics and physics. In 2005 he entered medical school at the Erasmus University, Rotterdam through 'decentrale selectie'. During his study he obtained a MSc in Clinical Research at the Netherlands Institute of Health Sciences (NIHES). In January 2012 he finished medical school on Friday the thirteenth. In his second year of medical school he started doing research on syndromic craniosynostosis at the department of plastic surgery under supervision of prof. dr. Irene Mathijssen, which resulted in this thesis.

PUBLICATIONS

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T. de Jong, M.L.C. van Veelen, I.M.J Mathijssen *Spring-assisted posterior vault expansion in multisuture craniosynostosis*. Submitten

T. de Jong, F. Di Rocco, M. Maliepaard, A. Diaz, I. Bleyen, M.L.C. van Veelen, D. Renier, I.M.J. Mathijssen, E. Arnaud. *Long-term intellectual and visual outcome in patients with syndromic craniosynostosis.* Submitted

M.L.C. Van Veelen, O. Eelkman-Rooda, **T. de Jong**, R. Dammers, L.N.A. Van Adrichem, I.M.J. Mathijssen. *Results of early surgery for sagittal suture synostosis: evolution of a technique.* Submitten

PhD Portfolio Summary

Name PhD student:	Promotors:
Tim de Jong	prof. dr. S.E.R. Hovius,
Erasmus MC Department:	prof. dr. I.M.J. Mathijssen
Plastic and Reconstructive Surgery	
Research School:	
Nihes	

1. PhD training

	Year	Workload
General academic skills		
Biomedical English Writing and Communication		
- Wetenschappelijk schrijven	2008	4 hours
- Critical Reading of the Epidemiologic Literature*	2009	8 hours
- English medical writing	2009	24 hours
Research skills		
Statistics		
- Introduction to Data-analysis	2008	0.7 ECTS
- Regression Analysis	2008	1.9 ECTS
- Survival Analysis	2008	1.9 ECTS
- Modern Statistical methods	2008	4.3 ECTS
- Principles of epidemiologic data analysis	2010	0.9 ECTS
- Advanced analysis of prognostic studies	2010	0.9 ECTS

Methodology		
- Principles of Research in Medicine and Epidemiology	2007	0.7 ECTS
- Introduction to Methods for Decision making in Medicine	2007	0.7 ECTS
- Methods of Clinical Research	2007	0.7 ECTS
- Case-control Studies	2007	0.7 ECTS
- Clinical Trials	2007	0.7 ECTS
- Pharmaco-epidemiology	2007	4.3 ECTS
- Study Design	2007	0.9 ECTS
- Introduction to Clinical Research	2008	0.9 ECTS
- Intervention Research and Clinical Trials	2008	0.9 ECTS
- Diagnostic Research	2008	0.9 ECTS
- Advanced Topics in Decision-making in Medicine	2008	0.9 ECTS
-Prognostic Research	2008	0.7 ECTS
- Topics in Meta-analysis	2009	0.9 ECTS
- Observational Epidemiology*	2009	1.9 ECTS
- Epidemiology in Evidence Based Policy*	2009	0.9 ECTS
- Clinical trial management*	2009	0.9 ECTS
- Pharmaco-epidemiology and drug safety	2010	1.9 ECTS
- Advance topics in clinical trials	2010	0.9 ECTS
*Bloomberg school of public health, Johns Hopkins, Baltimore, USA		
In-depth courses		
- Structure and organization of the nervous system	2008	3 ECTS
- Microsurgery training	2011-2012	85 hours

Presentations		
- ICP, OSAS and development in children with syndromic craniosynostosis. Voorjaarsvergadring NVPC, Utrecht	2008	40 hours
- Invloed van leeftijd tijdens schedelexpansie op de mentale ontwikkeling bij kinderen met complexe en syndromale craniosynostosis. Voorjaarsvergadring NVPC, Utrecht	2009	40 hours
- Audiologisch profiel van kinderen met syndromale craniosynostosis. Najaarsvergadering NVSCA, Tilburg	2009	40 hours
- Quality of life and mental outcome in patients with syndromal and complex craniosynostosis. Refereeravond afdeling Plastische chirurgie, Rotterdam	2010	40 hours
- Gezondheids gerelateerde kwaliteit van leven in kinderen met syndromale en complexe craniosynostosie. Najaarsvergadering NVSCA, Den Haag	2010	40 hours
- Timing of surgery and mental outcome in children with complex and syndromic craniosynostosis. ISCFS XIV biennual international congress, Livingstone, Zambia	2011	40 hours
- Ventricular and brain volume and their predictors in patients with syndromic and complex craniosynostosis. ISCFS XIV biennual international congress, Livingstone, Zambia	2011	40 hours
- Invloed van leeftijd tijdens schedelexpansie op de mentale ontwikkeling in patiënten met syndromale en complexe craniosynostose. Najaarsvergadering NVSCA, Amsterdam	2011	40 hours
International conferences		
- International Society of Craniofacial Surgery, Oxford, United Kingdom	2009	24 hours
-International Society of Craniofacial Surgery, Livingstone, Zambia	2011	24 hours

Seminars and workshops		
- Wondcongres	2007	8 hours
- NVPC, voorjaar vergadering	2008	8 hours
- NVPC, najaar vergadering	2008	8 hours
- NVSCA, najaar vergadering	2008	8 hours
- Wondcongres	2008	8 hours
- NVPC, voorjaar vergadering	2009	8 hours
- NVSCA, najaar vergadering	2009	8 hours
- NVPC, voorjaar vergadering	2010	8 hours
- Postacademisch Onderwijs Sophia, expertise in aangeboren en cognitieve erfelijke aandoeningen	2010	8 hours
Didactic skills		
- Basisdidactiek	2012	8 hours
Other		
- Organisation Esser course: Around The Wrist Symposium, Rotterdam	2011	80 hours