EVALUATION OF SURGICAL OUTCOMES IN CRANIOSYNOSTOSIS

Quantitative assessments in metopic and unicoronal synostosis

Giovanni Maltese

GÖTEBORGS UNIVERSITET

Department of Plastic Surgery
Institute of Surgical Sciences at the Sahlgrenska Academy
University of Gothenburg
Gothenburg, Sweden

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e-mail giovanni.maltese@vgregion.se
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To my wife Kristina, and to our
wonderful daughters Clara and Lia Isabella

To the memory of my father Gianni

“Considerate la vostra semenza:
fatti non foste a viver come bruti,
ma per seguir virtute e canoscenza”

“Call to mind from whence ye sprang:
'Ye were not form'd to live the life of brutes,
'But virtue to pursue and knowledge high.”

Dante Alighieri (1265-1321)
La Divina Commedia – Inferno:
C XXVI, v 112-120

He uses statistics as a drunken man uses lampposts — for support rather than illumination
Andrew Lang (1844-1912)

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ABSTRACT

Background: A continuous and objective evaluation of surgical outcomes must be an integrated part of the technical development. The present thesis has the ambition to innovate the evaluation of surgical results allowing systematic and objective assessment of the surgical procedures used for metopic and unicoronal craniosynostosis (UCS).
Material & methods: The effect of springs on hypotelorism was studied by measuring the bony interorbital distance (BIOD) and the axes of the orbits on cephalograms. Thereafter, the pre- and post-operative BIOD in patients operated with spring-assisted surgery (SAS) was compared to that of patients operated using the traditional cranioplasty and to a control group. The effect on forehead symmetry of a fronto-orbital advancement (FOA) and of a more radical forehead substitution with a calvarial bone graft in UCS was measured. To be able to evaluate our results, a computer tool that measured frontal symmetry was developed. Intracranial volume in metopic synostosis, before and after surgery was measured by using a newly developed computer tool that measured volume in CT scans.
Results: 1. Springs had effect on hypotelorism and orbital shape. 2. SAS before 6 months of age normalized BIOD, a result previously not achieved. 3. The computer was simple to use and gave a precise assessment of forehead symmetry. 4. Forehead reconstruction with a calvarial bone graft gives better forehead symmetry than FOA in UCS. 5. Total intracranial volume in metopic synostosis was normal before surgery but significantly lower than in controls at 3 years of age. The ratio frontal-to-total volume before surgery was low in patients with metopic synostosis. The ratio was improved, but not normalized, by surgery.
Conclusion: Systematic evaluation with quantitative measurements of surgical results is important to be able to objectively assess outcomes and to develop and compare surgical techniques.

ABBREVIATIONS

ASC	Absolute symmetry change = $SR_{preop} - SR_{postop}$
BG	Bone grafting group (study II & V)
BIOD	Bony interorbital distance
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FIV	Frontal intracranial volume
FOA	Fronto-orbital advancement
FOA	Fronto-orbital axes (only in paper I)
MA	Mismatch area
MSX2	Muscle segment homeobox 2
OMIM	Online mendelian inheritance in man database
RSC	Relative symmetry change = $\frac{SR_{preop} - SR_{postop}}{SR_{preop}}$
S	Spring group (study II & IV)
SA	skull area outlined by the frontal contour and a line between *end-point* and point *p*
SAS	Spring-assisted surgery
SD	Standard deviation
SR	Symmetry ratio = $\frac{MA}{SA} \cdot 1000$
SSC	Single suture craniosynostosis
TGF-β	Transforming growth factor β
TIV	Total intracranial volume
USC	Unicoronal synostosis
VAS	Visual analogue scale
ZADS	Zide-Alpert deformity scale

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred in the text by their roman numerals (I-V)

I. **Spring-Assisted Correction of Hypotelorism in Metopic Synostosis.**
Giovanni Maltese, Peter Tarnow, Claes Lauritzen.
Plast Reconstr Surg. 2007 Mar;119(3):977-84.

II. **Correction of hypotelorism in isolated metopic synostosis.**
Giovanni Maltese, Peter Tarnow, Robert Tovetjärn, Lars Kölby.
Submitted

III. **A novel quantitative image-based method for evaluating cranial symmetry and its usefulness in patients undergoing surgery for unicoronal synostosis.**
Peter Bernhardt, Annelie Lindström, Giovanni Maltese, Peter Tarnow, Jakob H. Lagerlöf, Lars Kölby.
J Craniofac Surg. 2013 Jan;24(1):166-9.

IV. **New objective measurement of forehead symmetry in unicoronal craniosynostosis – comparison between fronto-orbital advancement and forehead remodeling with a bone graft.**
Giovanni Maltese, Peter Tarnow, Annelie Lindström, Jakob H. Lagerlöf, Peter Bernhardt, Lars Kölby.
Submitted

V. **Intracranial volume before and after surgical treatment for isolated metopic synostosis.**
Giovanni Maltese, Peter Tarnow, Robert Tovetjärn, Lars Kölby.
Submitted

INTRODUCTION

In 1957 a young man consulted Dr. Paul Tessier at the Hôpital Foch in Paris because of his facial deformity. Dr. Tessier´s description of the patient was as having "prodigious exorbitism with a monstrous aspect". That patient suffered from a rare craniofacial syndrome described by the French neurologist Octave Crouzon in 1912 (Figure 1) (Crouzon 1912). Dr. Tessier performed a Le Fort III mid-face advancement via multiple facial incisions, correcting in one stage both the orbital and the maxillary deformity. Sir Harold Gillies had reported in 1950 his experience with such a procedure, but recommended his colleagues «never do it» because of the massive relapse (Jones 1991). In the same period, Dr. Tessier also introduced the trans-cranial approach to the ethmoids for the correction of hypertelorism. This innovative use of a combined intra- and extracranial approach represented the dawn of modern craniofacial surgery. The use of bone grafting, the self-retaining osteotomies and the fixation devices pioneered by Dr. Tessier were something absolutely new, but became standard procedures in surgery for craniosynostosis.

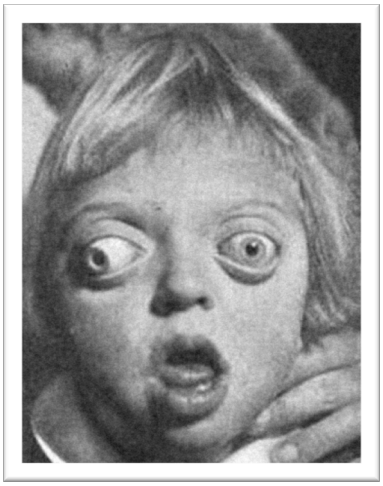

Figure 1 Patient with Crouzon syndrome, original photo from Dr. Crouzon's paper.

4.1 Craniofacial surgery in Göteborg

The chief of the Plastic Surgery Department of Göteborg, Dr. Bengt Johansson, early understood the importance of creating a

dedicated craniofacial center, where different specialists could treat patients affected by these rare conditions. In 1972 he invited Dr. Tessier to Göteborg to perform the first transcranial correction of orbital hyperthelorism together with the Swedish team at Sahlgrenska University Hospital (Lauritzen and Tarnow 2003). The newborn craniofacial unit of Göteborg has since then developed extensively. Gradually, the unit became the principal referral center for craniofacial surgery in Scandinavia. The increasing number of patients allowed the team to gain a considerable experience and to continuously improve its treatment strategies.

Surgical techniques and timing for surgery have been changing over the years. Practically, every procedure used in the early days of the unit has been modified or replaced by new ones. For example, the pi-cranioplasty as described by Jane (Jane, Edgerton et al. 1978) has been supplemented with radial osteotomies of the frontal bone and out-fracturing of the parietal bones to eliminate the residual frontal bossing and to give a natural coronal profile (Figure 2). Similarly, the dynamic cranioplasty for brachycephaly described in 1996 (Lauritzen, Friede et al. 1996) derived from the *floating forehead* technique described by Marchac (Marchac and Renier 1979). The introduction of springs in 1998 represented an important further development for the unit. Spring-assisted surgery (SAS) has, for example, changed the treatment of sagittal synostosis in younger children, replacing more extensive procedures (Guimaraes-Ferreira, Gewalli et al. 2003).

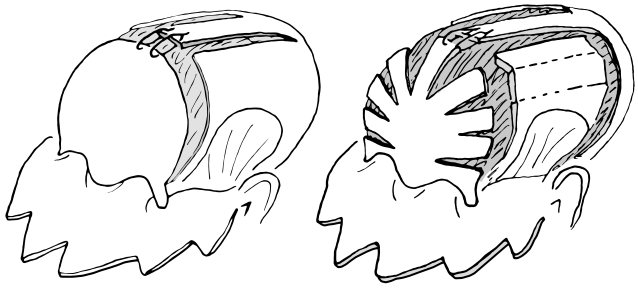

Figure 2 The pi-cranioplasty as described by Jane (left). The modified pi-cranioplasty (right).

A continuous and objective evaluation of surgical outcomes must be an integrated part of the technical development. The present thesis has the ambition to innovate the evaluation of surgical results allowing systematic and objective evaluation of the surgical procedures used for metopic and unicoronal craniosynostosis (UCS).

GROWTH OF THE NORMAL SKULL

5.1 Embryology

Before the closure of the neural folds, between the 24th and the 27th day of intrauterine life, the neural plate shows an enlargement with irregularities at its rostral end, corresponding to the brain. The meninges develop concomitantly. First a thick layer of mesenchyme surrounding the primitive brain is visible (primitive meninx). Already by the 41st day, the primitive meninx can be divided in two different layers: the pachymeninges, or dura mater, and the leptomeninges comprising the arachnoid and the pia mater. At this stage, a skeletogeneous mesenchyme layer is identifiable between the dural limiting layer and the subcutaneous tissue. By the 57th day, cartilage and intramembranous bone are formed within the skeletogeneous layer (Muller and O'Rahilly 2003).

The skull can already at this stage be divided in a neurocranium, i.e. the part surrounding the brain, and a viscerocranium, i.e. the facial skeleton. The neurocranium can be further divided in a chondrocranium and a membranous neurocranium. The chondrocranium corresponds to the cranial base and is formed by endochondral ossification, i.e. via a cartilaginous intermediate template. The membranous neurocranium corresponds to the cranial vault or calvaria and is formed by intramembranous ossification, i.e. via the direct osteogenic differentiation of mesenchymal cell condensations.

The fetal cranial vault consists mainly of five flat bones - two frontal, two parietal and one occipital - with a minor contribution to the lateral walls from the squamous part of the temporal bones and from the greater wings of the sphenoid bone. Development of the skull from a number of separate bones enables growth to take place at the margins

of the bones for as long as the skull is required to expand around the growing brain (Morriss-Kay and Wilkie 2005).

5.2 Normal sutural biology

The cranial *sutures* are articulations in which contiguous margins of bone approximate each other and are united by a thin layer of fibrous tissue (Figure 3) (Cohen 2000).

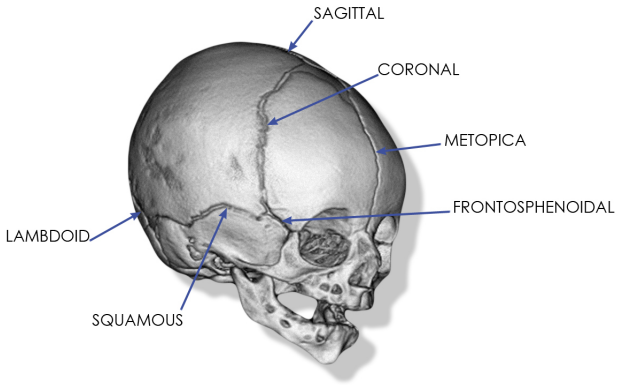

Figure 3 Infant skull with open sutures

It has been shown in a murine model that the frontal bones originate from the neural crest, while the parietal and interparietal bones originate from the mesoderm. Small tongues of neural crest tissue grow between the two parietal bones and also between these and the interparietal bones. Hence the coronal suture represents the boundary between mesoderm and neural crest, while the sagittal and the lambdoid sutures originate from such a boundary and then develop within mesoderm-derived tissue (Figure 4). The posterior frontal suture, analogous to the human metopic suture, is the only calvarial suture that does not initiate at a neural crest-mesoderm interface, being bounded by two neural cell-derived osteogenic fronts (Jiang, Iseki et al. 2002; Morriss-Kay and Wilkie 2005).

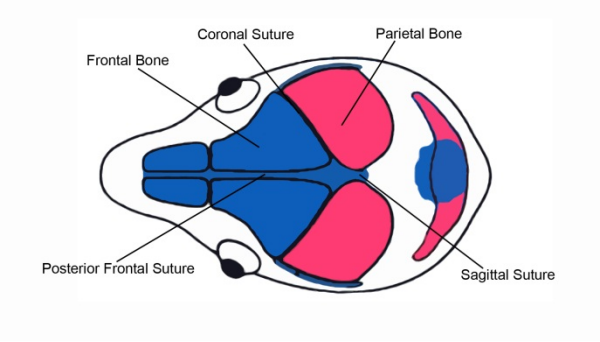

Figure 4 Graphic representation of the neural crest (blue) or mesodermal (red) origin of the cranial vault in a murine model

Normal suture fusion is dependent on a complex signalling cascade. Tissue interactions between dura mater and cranial sutures play a main role in this process. These interactions match the growth of the cranial bone plates to the expansion of the growing brain (Levi, Wan et al. 2012). *In vitro* and *in vivo* murine models show that the subjacent dura mater is directly responsible for the fate of the overlying cranial suture, likely through paracrine mechanisms (Bradley, Levine et al. 1997; Warren, Greenwald et al. 2001; Heller, Gabbay et al. 2007).

5.3 Cranial growth

At birth, suture mobility allows passage through the birth canal. During fetal and post-natal life the cranial sutures represent growth sites where bone is continuously deposited while the opposite bones separate (Enlow 2000). This pattern of growth movement is called *displacement*, and it is accompanied by another pattern of growth called *remodelling* or appositional growth, which is based on bone reabsorption by the osteoclasts at the inner surface of the skull and bone deposition by the osteoblasts on the outer surface. Physiologically, this last mechanism is important for adapting the curvature of the calvarial bone to the changing circumference of the brain and it is active even after fusion of the cranial sutures. Fusion does not normally occur until a later stage in life, with the exception of the metopic suture that physiologically fuses during the first year of life (Vu, Panchal et al. 2001; Weinzweig, Kirschner et al. 2003; Fearon 2012), this being probably a

consequence of its different embryological origin (Morriss-Kay and Wilkie 2005).

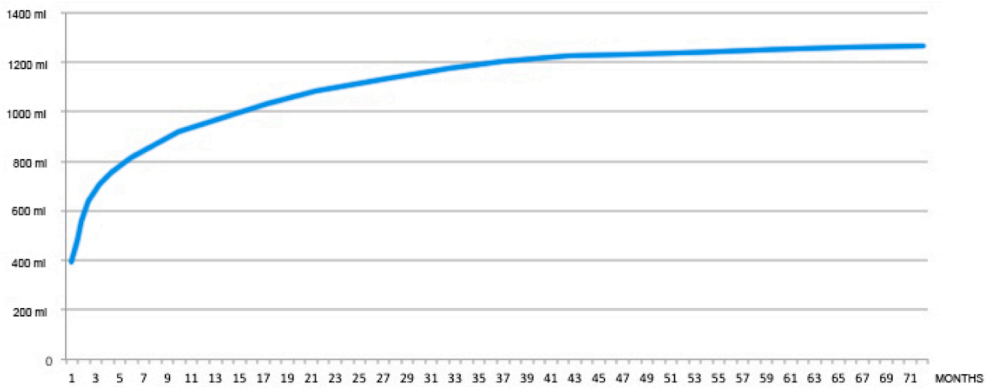

Figure 5 Increase of intracranial volume during the first 6 years of life

The curve of cranial growth after birth is not linear. Growth is most rapid during the first months of life (Figure 5). Intracranial volume doubles during the first 9 months and triples during the first 72 months of life (Kamdar, Gomez et al. 2009). By the age of five years, intracranial volume normally reaches 90% of that observed at 15 years of age (Sgouros, Hockley et al. 1999).

CRANIOSYNOSTOSIS

The term craniosynostosis indicates the premature, pathologic, partial or complete, fusion of one or more of the cranial vault sutures (Levi, Wan et al. 2012).

6.1 Etiopathogenesis

Virchow proposed in 1851 the concept that the calvarial suture itself was the primary locus of the abnormality, i.e. the affected suture had the intrinsic capacity to fuse or stay patent independently of interactions with the underlying dura mater (Virchow 1851). Later, Moss (Moss 1959) hypothesized that an abnormal cranial base would transmit pathological tension to the cranial vault via the dura mater, with the craniosynostosis being the final effect of this mechanism. Modern research has demonstrated the role of the dura mater, which is interacting with the sutures via soluble growth factors in a paracrine fashion (Levine, Bradley et al. 1998). Altered signalling mechanisms due to genetic mutations may therefore be the origin in the pathogenesis of craniosynostosis.

6.2 Genetic considerations

MSX2

A mutation in the gene encoding muscle segment homeobox 2 (MSX2) was the first to be associated to an autosomal dominant craniosynostosis, the Boston-type craniosynostosis (Jabs, Muller et al. 1993). This is a very rare condition, confined to a single large family, characterized by variable craniosynostosis without midfacial hypoplasia or hand and foot anomalies (Warman, Mulliken et al. 1993). MSX2 encodes a homeobox-containing transcription factor that is thought to

preserve the suture space by maintaining preosteoblastic cells of the osteogenic front into an undifferentiated form. Its mutation results in an enhanced degradation, which leads to suture fusion by increasing the pool of osteogenic cells (Yoon, Cho et al. 2008).

FGFR

Mutations of the genes encoding for one of the members of the fibroblast growth factor receptor (FGFR) family have been found in at least 8 different craniofacial dysostoses (the FGFR related craniofacial syndromes). The FGFRs are a family of transmembrane tyrosine kinase receptors that are vital in many areas of skeletal development. They are formed by an extracellular immunoglobulin-like ligand binding domain, a trans-membrane domain and two intracellular sub-domains. The extracellular domain has specific binding properties to the FGF in presence of heparin sulphate proteoglycan. Most of the known mutations involved in cranyosynostosis syndromes are missense mutations that lead to a gain-of-receptor function, i.e. allowing the receptor to be activated independently of its specific ligand or enhancing the receptor/ligand affinity. The exact mechanisms with which mutations in the genes encoding for the FGFR result in a premature suture closure are still unclear. Development of cranial sutures relies on cross-talk between the different FGFRs, resulting in a delicate balance between osteogenic cell proliferation and differentiation. Altered signalling by a mutated FGFR may result in decreased osteoblast differentiation and apoptosis with consequent suture closure (Bonaventure and El Ghouzzi 2003; Chim, Manjila et al. 2011).

TGF-β

Transforming growth factor-β (TGF-β) consists of a super-family of growths factors that have been found to be relevant in cranial suture fusion. In particular, it has been proved in murine models that the altered balance between TGF-β1 and TGF-β3, which mediate dural

stabilizing signals to the suture, and TGF-β2, which promote osteogenesis, may be directly responsible for the premature fusion of cranial sutures (Roth, Gold et al. 1997; Roth, Longaker et al. 1997).

TWIST-1

Saethre-Chotzen is the only known craniofacial syndrome associated with mutation of the gene encoding for the TWIST-1 transcription factor. TWIST-1 controls osteogenic differentiation in mesenchymal cells by modulating FGFR2, leading to activation of signalling pathways involved in osteoblast differentiation. Its genetic mutation results in the expansion of osteogenic cells producing collagen and in premature suture fusion (Miraoui and Marie 2010).

6.3 Types of craniosynostosis

Craniosynostosis can be defined according to several criteria. They can be divided into syndromic and non-syndromic or isolated, depending on the presence of associated defects of the morphogenesis or of a defined genetic mutation.

Isolated synostosis can be classified according to the anatomical location of the synostosis or to the clinical appearance of the skull, which is usually strictly dependent on the location of the fused suture (Table 1).

Single suture synostosis	**Clinical nomenclature**
Sagittal	Scaphocepahly
Metopic	Trigonocephaly
Unicoronal	Anterior synostotic plagiocephaly
Unilambdoid	Posterior synostotic plagiocephaly
Multiple suture synostosis	
Bicoronal	Brachycephaly
Bilambdoid	Posterior brachycephaly
Combined synostosis	Variable

Table 1 Craniosynostosis and the associated clinical nomenclature

Craniosynsotosis can also be divided in primary and secondary. In secondary synostosis, a pathological condition responsible for the synostosis can be identified.
Craniosynostosis can be *simple*, i.e. when only one suture is synostotic, or *complex* or *multiple*, i.e. when two or more sutures are synostosed. In current medical literature the term single suture craniosynostosis (SSC) is usually preferred to the term simple synostosis and it will be the one used in this thesis.

6.4 Epidemiology

Most cases of SSC are sporadic, with a varying frequency of positive familial history depending on the suture involved. Craniosynostosis are relatively rare conditions, occurring approximately in one in 2000 - 2500 live births. Sagittal synostosis is the most common form of SSC with an incidence of 1 in 5.000 live births (45% of all SSC), followed by unilateral coronal synostosis (1 in 11.000 live births) and metopic synostosis (1 in 15.000 live births). Lambdoid synostosis is a more rare condition with an incidence of 1 in 200.000 live births (2-3% of all SSC) (Cohen 2000; Lee, Hutson et al. 2012). Recent studies from several craniofacial centers have reported a significantly higher frequency of metopic synostosis and a change in the spectrum of distribution of the craniosynostosis sub-types (Cohen 2000; Selber, Reid et al. 2008; van der Meulen, van der Hulst et al. 2009). Metopic synostosis nowadays accounts for about 25% of all cases, being the second most common SSC. The estimated rate of nonsyndromic uni- and bicoronal synostosis has been more ambiguous, varying from 17% to 24%. This is probably a consequence of the increasing use of genetic investigations that allows for a more precise classification of these cases. The same consideration might be valid for all non-syndromic multisutural synostosis, with rates that varies from 7% to 13% in the latest studies (Di Rocco, Arnaud et al. 2009; Kolar 2011; Lee, Hutson et al. 2012).

6.5 Morphogenesis

Skull growth occurs perpendicularly to the cranial sutures. Premature fusion prevents separation of the opposing bones and causes restriction of the growth vector perpendicular to the affected suture. This is accompanied by compensatory growth both in the other patent sutures and by remodelling (Morriss-Kay and Wilkie 2005). This mechanism leads to typical cranial shapes that are characteristic for each cranial suture synostosis (Figure 6).

A first description of cranial deformation secondary to craniosynostosis was proposed by Virchow (Virchow 1851), who postulated that cranial growth is restricted in the plane perpendicular to the affected suture and is enhanced in a plane parallel to it (Virchow's law). Delashaw et al. (Delashaw, Persing et al. 1991) described 4 principles of compensatory growth that better explain the clinical morphological findings in isolated suture craniosynostosis:

1. cranial vault bones that are prematurely fused act as a single bone plate with decreased growth potential
2. asymmetrical bone deposition occurs at perimeter sutures with increased bone deposition directed away from the bone plate
3. sutures adjacent to the synostotic suture compensate in growth more than sutures not adjacent
4. non-perimeter sutures representing the continuation of a synostotic suture undergo enhanced symmetric bone deposition

Sagittal synostosis

Secondary to the synostosis of the sagittal suture, the skull grows in the anteroposterior direction while growth is inhibited transversally. This head shape has been termed *scaphocephaly*. A frontal bossing and a pointed occipital area are usually present at a variable degree. Some degree of hypertelorism has also been reported (Guimaraes-Ferreira, Gewalli et al. 2006).

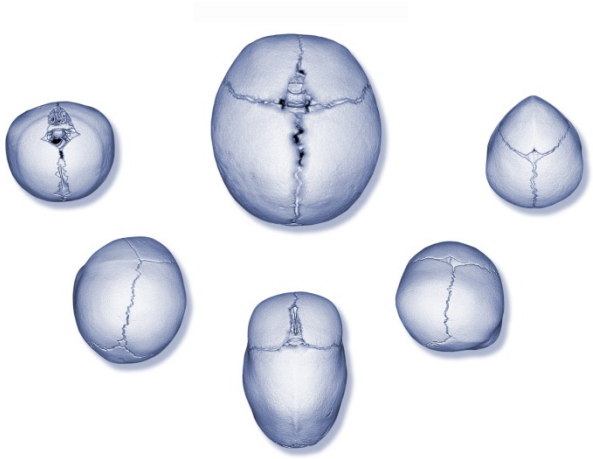

Figure 6 Three-dimensional CT reconstructions of a normal skull (center), and the most common form of SSC below. From left to right: bicoronal, left-sided UCS, sagittal, right sided lambdoid and metopic synostosis.

Metopic synostosis

Metopic synostosis is associated with a triangular shape of the head when seen from the bird's view, hence the term trigonocephaly. A midline forehead ridge is typically present, together with a bilaterally recessed supraorbital bandeau and a compensatory increase of the parietal width. Hypotelorism is present at variable degree and accompanied by a typical deformation of the orbital shape (the so-called egg-shaped or teardrop orbits).

Unicoronal synostosis

Infants affected by UCS typically present with forehead asymmetry. The forehead is flat on the affected side while contralaterally a compensatory bossing is present. Furthermore these patients present upwards displacement of the ipsilateral orbital roof with a recessed supraorbital rim and depressed contralateral supraorbital rim. The root of the nose is deviated towards the affected side and, in more extreme cases, malar hypoplasia with rotation of the midface and chin towards the affected side is also present (Marsh, Gado et al. 1986; Bruneteau and Mulliken 1992).

Bicoronal synostosis

In bicoronal synostosis, the antero-posterior diameter of the skull is reduced (brachicephaly comes from the greek βραχύς, short). The occiput is flat, the biparietal diameter is wide and the height is elevated (Persing 2008).

Lambdoid synostosis

Unilateral lambdoid synostosis is associated with flattening of the parietooccipital area and a prominence of the mastoid on the affected side. Contralaterally, a parietooccipital bulge is present (Huang, Gruss et al. 1996). This condition is usually called posterior synostotic plagiocephaly. The bilateral lambdoid synostosis it characterized by symmetrical occipital flattening.

6.6 The craniofacial syndromes

A continuously growing number of syndromes involving craniosynostosis are delineated. At present, by entering the word *craniosynostosis* on the search engine of the Online Mendelian Inheritance in Man (OMIM) database of the Johns Hopkins University, 159 entries are encountered. Among the most commonly recognized craniofacial dysostosis are Crouzon, Apert, Pfeiffer, Saethre-Chotzen, Jackson-Weiss, and Muenke syndrome. Most cases of syndromic craniosynostosis occur sporadically and exhibit autosomal dominant pattern of inheritance. In craniofacial syndromes, the cranial vault usually presents with bicoronal synostosis, isolated or in combination to other cranial suture synostosis. The cranial base and the upper *viscerocranium* are variably involved, with consequent midface hypoplasia. Each of these syndromes is associated with a specific set of accompanying anomalies and with precise genetic mutations as illustrated in Table 2

Syndrome	Type of associated craniosynostosis	Main associated clinical features	Mutated gene
Crouzon	Bicoronal	Midface hypoplasia	FGFR2
Crouzon AN	Bicoronal	Midface hypoplasia, Acantosis nigricans	FGFR3
Pfeiffer	Bicoronal	Midface hypoplasia, 3 clinical subtypes	FGFR1/ FGFR2
Jackson-Weiss	Bicoronal	Broad and medially deviated great toes	FGFR1/ FGFR2
Muenke	Uni- or bicoronal	Hearing impairment	FGFR3
Apert	Bicoronal	Midface hypoplasia, syndactyly of hands and feet	FGFR2
Saethre-Chotzen	Bicoronal	Eylid ptosis, low hairline	TWIST1/FGFR2

Table 2 Most common syndromic forms of craniosynostosis and the mutated gene

6.7 Functional aspects

The cranial volume doubles during the first nine months of life to cope with the rapid brain growth. Cranial sutures play a crucial role in this process. In presence of craniosynostosis, brain growth may be restricted since cranial expansion is potentially altered, but compensatory mechanisms such as enhanced growth at the other patent sutures and remodelling reduce the problem (Delashaw, Persing et al. 1991; Morriss-Kay and Wilkie 2005). A significant disparity between brain growth and cranial capacity may thus lead to elevated intracranial pressure. Although this is more likely to happen in the presence of multiple suture craniosynostosis (Renier, Sainte-Rose et al. 1982), high intracranial pressure in SSC has been described. In the syndromic cases, intracranial venous congestion, hydrocephalus and upper airway obstruction might also contribute to raised intracranial pressure (Tamburrini, Caldarelli et al. 2005).

In most cases, the rise in intracranial pressure is not a constant, but rather an intermittent event, for example during sleep. Usually clinical symptoms are subtle or absent in SSC (Renier, Sainte-Rose et al. 1982; Thompson, Malcolm et al. 1995; Tamburrini, Caldarelli et al. 2005). On the contrary, high intracranial pressure is a common finding in multiple suture synostosis (Camfield 2000). Typical symptoms include headache, emesis, visual disturbance and decreased mental status.

6.8 Neurodevelopment

SSC have been classically considered as morphologic disorders rarely associated with functional morbidity (Anderson and Geiger 1965; Shillito and Matson 1968). A study from 1993 showed that in presence of non-syndromic synostosis 93% of the patients had IQ-scores ranging from borderline retardation to very superior, following the distribution of the normal population. Neither the severity of the deformation nor the presence of corrective surgery seemed related to the mental outcomes (Kapp-Simon, Figueroa et al. 1993). However, in 1998 the same authors reported that mental development in children affected by SSC ranged within normal limits in infancy, but the rate of mental disorder increased significantly with age, and almost half of these children had some form of learning difficulties at school age (Kapp-Simon 1998). A higher rate of cognitive and behavioral abnormalities more easily detectable at school age was also reported in a study focusing on a population of children affected by metopic synostosis. The authors found a five to six folds increase of ADHD compared to the normal population, with almost 50% of the children in the study being affected (Sidoti, Marsh et al. 1996). Other studies have presented similar figures (Becker, Petersen et al. 2005; Kapp-Simon, Speltz et al. 2007; Speltz, Kapp-Simon et al. 2007; Da Costa, Anderson et al. 2012; Starr, Collett et al. 2012).

Three hypotheses attempt to explain the association between craniosynostosis and neurodevelopmental impairment. A first hypothesis suggests that prolonged elevation of intracranial pressure caused by the synostosis, and the subsequent hypovascularity, could lead to hypoplasia of the brain tissue (Arnaud, Renier et al. 1995; Cohen and Persing 1998). A second hypothesis is based on magnetic resonance images showing brain deformations secondary to the craniosynostosis. Aldridge in 2002 reported dysmorphic cortical and sub-cortical features in patients with sagittal and metopic synostosis (Aldridge, Marsh et al. 2002). This hypothesis was recently further developed suggesting that the growth of cortical and subcortical tissues would be locally affected by the restriction imposed by the synostosis and hence redirected towards unaffected areas (Speltz, Kapp-Simon et al. 2004). A third hypothesis postulates that both the craniosynostosis and the possible brain anomalies could be the expression of underlying neuropathology, likely originating early in the embryologic development (Kjaer 1995).

However it remains unclear if the premature fusion of a cranial suture is a cause, or rather a correlate, of the associated neurodevelopmental impairment. Most importantly, there is lack of evidence that the severity of the malformation, or corrective surgery, influence the risk for neuro-developmental problems (Kapp-Simon, Speltz et al. 2007).

TREATMENT

7.1 A brief historical perspective

The first scientific reports of surgical treatment of craniosynostosis came at the end of the 19th century. Dr. Odilon Lannelongue, Professor at the Faculté de Médecine de Paris and Dr. L. C. Lane, Professor of surgery at the Cooper Medical College of San Francisco reported, almost at the same time, their experiences with suturectomy in children affected by craniosynostosis (Lannelongue 1890; Lane 1892). The goal of their operations was to improve microcephaly, an idea based on the assumption that the surgical release of the synostosis would allow a more physiological skull growth.

These first surgical attempts to correct cranial deformities were subject to hard criticism by Abraham Jacobi, the father of American Pediatrics, who stated «No ocean of soap and water will clean those hands. No power of corrosive sublimate will disinfect the souls» (Jacobi 1894) .

Despite this scepticism, craniotomies were still performed, advocating the importance of preventing functional sequelae (Faber 1924). Ingraham popularized the use of bilateral parasagittal craniectomies for release of sagittal synostosis (Ingraham, Alexander et al. 1948). The fast re-ossification rate encouraged the scientific community of the time to explore more effective methods. Various interposition materials or chemical compounds in the craniectomy lines were used in the attempt to prevent the early refusion of the craniotomy (Simmons and Peyton 1947; Ingraham, Alexander et al. 1948; Anderson and Johnson 1956). Jane proposed a more complex osteotomy design, resembling the shape of the greek letter pi (π), to correct scaphocephaly (Jane, Edgerton et al. 1978). Modifications of that pi-cranioplasty are still used today in many craniofacial centers including our own.

Andersson in the early sixties presented an extensive approach with remodelling of the frontal region to correct trigonocepaly (Anderson, Gwinn et al. 1962).

In the late sixties, more radical reconstructions were developed. Dr. Tessier´s work (Tessier 1967; Tessier, Guiot et al. 1967; Tessier, Guiot et al. 1969) dramatically changed the approach to craniosynostosis and to their related facial anomalies. The first description of the "floating forehead" cranioplasty for brachycephaly by Marchac and Renier (Marchac and Renier 1979), in which the frontal bone flap was let free to adapt to the underlying brain and dura advancement, further developed the principle of dynamic cranioplasties (Lauritzen, Friede et al. 1996; Gewalli, da Silva Guimaraes-Ferreira et al. 2001) introduced by Jane. The advantages of this approach were to produce both immediate and progressive cranial reshaping and to virtually eliminate any extradural dead space after the cranioplasty.

Further innovations were represented by the application of distraction osteogenesis principles and the introduction of SAS. Codivilla (Codivilla 1905) and Ilizarov (Ilizarov 1980) pioneered and popularized distraction osteogenesis as a safe and effective method for lengthening of long bones. The first experimental mandibular distraction osteogenesis in a canine model was reported by Snyder (Snyder, Levine et al. 1973). McCarthy (McCarthy, Schreiber et al. 1992) and Molina (Molina and Ortiz Monasterio 1995) reported the first cases of distraction osteogenesis of the human mandible in the western world. Evolutions of these techniques today are part of the craniofacial surgeon´s armamentarium in the treatment of mandibular, midfacial and cranial defects (Chin and Toth 1997; Yu, Fearon et al. 2004; Fearon 2008; Derderian and Bartlett 2012; Derderian, Bastidas et al. 2012).

Skull expansion through a spring placed across a suturectomy line in rabbits was reported by Persing in 1986 (Persing, Babler et al. 1986). Lauritzen in 1998 reported the first cases of SAS on children affected by craniosynostosis (Lauritzen, Sugawara et al. 1998). The result encouraged the use of springs in many different conditions.

Nowadays, application of springs after suturectomy is a widely used method to treat sagittal synostosis (Guimaraes-Ferreira, Gewalli et al. 2003; David, Plikaitis et al. 2010; Taylor and Maugans 2011; van Veelen and Mathijssen 2012). SAS had the advantage of avoiding extensive bone remodelling and the creation of dead space between the dura mater and the inner surface of the skull bones. SAS has been proven to be effective also in the treatment of bicoronal synostosis (Tovetjarn, Maltese et al. 2012), in multiple suture synostosis (Tuncbilek, Kaykcoglu et al. 2012), in posterior skull expansion (Arnaud, Marchac et al. 2012) and in the treatment of secondary sagittal synostosis (Davis and Lauritzen 2008).

7.2 Treatment of the three most common single suture craniosynostosis in Göteborg

Sagittal synostosis is the SSC most commonly seen and treated at the Craniofacial unit of Göteborg.

Patients with sagittal synostosis were previously operated with a modified pi-cranioplasty. The promising results of springs encouraged the use of the same principles to treat scaphocephaly. Today, patients who present before 6 months of age are operated using SAS while patients older than 6 months are treated using the pi-cranioplasty.

The effectiveness of SAS has been compared to the modified pi-cranioplasty both in terms of morphological outcomes and with regards to procedure safety (Guimaraes-Ferreira, Gewalli et al. 2003). It has been concluded even in the long term that both techniques achieve a good postoperative correction, with the cranial index being slightly closer to normal after pi-cranioplasty than after SAS. SAS is a significantly less invasive procedure in terms of operative time, need of blood substitution and postoperative hospital stay (Windh, Davis et al. 2008).

Metopic synostosis is the second most common SSC treated at our unit. The surgical technique for treatment of this malformation consisted of a fronto-obital remodelling combined with a bone graft inserted in the middle of the supra-orbital complex to correct the hypotelorism (Lauritzen 1995). The postoperative outcomes have been evaluated by cephalometric analysis and subjective criteria in a group of 15 patients (Kocabalkan, Owman-Moll et al. 2000). The technique could achieve a good improvement in terms of forehead contour and bitemporal width, but more than half of the patients still had some degree of hypotelorism. When springs were introduced and regularly used for sagittal synostosis at our unit, it was thought that SAS could be used also to correct trigonocephaly. In the first three patients, a simple suturectomy followed by the insertion of a spring in the glabellar region was used. In the following 14 patients, barrel-stave osteotomies of the frontal bone were also performed to improve the frontal contour. Still unsatisfactory results in terms of frontal contour led to the currently used technique, i.e. a more complex fronto-orbital remodelling combined with a spring aimed solely at correcting the hypotelorism. The traditional cranioplasty with bone grafting is still used for patients older than six months.

The third most common SSC in our practice is UCS. This was treated using a fronto-orbital advancement (FOA) procedure until 1997. The high re-operation rate for correction of residual forehead asymmetry led to implementation of a new technique, in which the forehead and the supra-orbital bandeau were substituted with a calvarial bone graft.

EVALUATION OF SURGICAL RESULTS

An appropriate and objective evaluation of surgical outcomes is necessary to assess the ability of a procedure to correct the morphological features of craniosynostosis and to support the choice of a specific technique.

In craniofacial surgery, numerous methods to evaluate postoperative outcomes have been described. These methods can be divided in methods based on subjective evaluation and methods based on objective evaluation.

Methods based on subjective evaluations are popular in craniofacial surgery. One of the first such methods reported was the Zide-Alpert deformity scale (ZADS) (McCarthy, Epstein et al. 1984). This method was based on the quantitative evaluation, by a panel of observers, of craniofacial disfigurement on a five-point scale (from 1 = normal to 5 = gross deformity). Other methods, particularly those used in cleft surgery, are instead based on the judgment of postoperative appearance on a Visual Analogue Scale (VAS) by a panel (Al-Omari, Millett et al. 2005). The Whitaker scoring method to evaluate postoperative results is a commonly used system (Whitaker, Bartlett et al. 1987; Selber, Brooks et al. 2008). It is based on the need for secondary surgery, assigning the patients to one of four different categories: category I, no revision; category II, soft-tissue or lesser bone-contouring revisions are desirable; category III, major alternative osteotomies or bone grafting procedures are needed; category IV, patients who required craniofacial procedures duplicating or exceeding in extent the original surgery.
These methods have the advantages of focusing on important aspects such as the patients overall appearance or the need for further reoperations, but more objective indicators are needed for assessment

of the impact of surgical treatment. Additionally, subjective evaluations suffer from observer bias. For example, the panels can be variously composed: the treating surgeons, health care professionals and laymen. The rater's characteristics may influence the way facial appearance is judged. The surgeon evaluating the need for additional surgery might be inclined to under- or over-estimate residual deformity depending on personal attitude. Modifications of subjective methods, based on the division of the face in sub-units and the submission of a list of specific questions to the raters and reduction of the scoring to a binary system (yes/no), have shown a good level of "objectivity" (Versnel, Mulder et al. 2007). Still, totally objective studies might be a difficult goal to achieve with analysis predisposed to subjective bias (Anand, Campion et al. 2013).

Direct anthropometry is virtually an ideal method to evaluate pre- and postoperative facial deformity. Direct anthropometric measurements, e.g. calculation of the cranial index, have been the most commonly employed methods to quantitatively assess results. Anthropometry has the advantage of avoiding the use of ionizing radiation. Furthermore, a large database of normal values for comparative analysis is available (Farkas 1994). The principal drawback with direct anthropometry is that it requires a very experienced examiner to accurately locate the anatomical landmarks. Furthermore, it requires a compliant subject, so it might be difficult to perform on small children (Oh, Wong et al. 2008).

Indirect anthropometry based on three-dimensional photography is a promising tool to evaluate body deformity and postoperative results (Oh, Wong et al. 2008; Heike, Cunningham et al. 2009; Wilbrand, Szczukowski et al. 2012). It has been successfully employed in breast surgery (Losken, Fishman et al. 2005; Losken, Seify et al. 2005) and many reports on its use in evaluating craniofacial deformity have been presented (Oh, Wong et al. 2008; Heike, Cunningham et al. 2009; Wilbrand, Szczukowski et al. 2012). Compared

to direct anthropometry, digital three-dimensional photogrammetry has the advantage of an extremely rapid acquisition time. Since the measurements are performed after the data acquisition, this method do not require the patients to keep still for prolonged periods, which is particularly advantageous when working with small children. In addition, the images are available for repeated measurements.
Other non-ionizing image-based methods, like laser scanning, providing a detailed visual evaluation of the superficial morphological features, give very interesting results (Plank, Giavedoni et al. 2006; Djordjevic, Toma et al. 2011). Such techniques evaluate the aesthetic aspect of soft tissue instead of focusing exclusively on the bone tissue. With laser-based as well as with photography-based imaging systems, landmark localization might be difficult as in the case of landmarks covered by hair or defined in reference to the underlying bone. A specific problem with laser-based systems is capture speed; even the newest systems cannot effectively perform in less than a second, which can be too long for small children (Weinberg and Kolar 2005). In addition these methods have the disadvantage of requiring expensive equipments and software. Most importantly, they have been available for a relatively short amount of time, so neither are large databases available, nor is a retrospective study possible.

Cephalograms were among the first techniques developed to study craniofacial growth and to evaluate surgical outcomes (Broadbent 1931; Brodie 1941). While avoiding exposure to ionizing radiation is preferable in young children, the precision, availability, and temporal comparability of current CT-based measurement techniques are superior to alternative methods. CT images offer a detailed description of cranial morphology and thickness. CT images are not only an important tool for evaluation of preoperative deformity and postoperative outcome, but also allow planning of surgical treatment. Measurement of anatomical landmarks using CT scans has been widely validated (Waitzman, Posnick et al. 1992; Richtsmeier, Paik et al. 1995)

and large databases exist providing normative data (Abbott, Netherway et al. 2000; Kamdar, Gomez et al. 2009; Marcus, Domeshek et al. 2009; Tilotta, Richard et al. 2009).

In our practice, the routine use of CT scanning for preoperative and follow-up evaluation has replaced cephalometry, which was regularly used until 2004.

This thesis is based on measurements performed on radiographic images (cephalograms and computed tomography). In the first two studies a distance, i.e. a one-dimensional physical quantity was measured and compared. In the third and fourth studies, the symmetry of an area, i.e. a two dimensional quantity, representing the symmetry of the two forehead halves, was calculated. In the fifth study, a volume, i.e. a three-dimensional quantity was measured.

AIMS OF THE THESIS

The aim of the present thesis was essentially to innovate the evaluation of surgical outcomes after correction of metopic and UCS and to compare the new techniques to the old ones. Specifically, the aim of each study was

- to describe, in detail, the spring-assisted correction of hypotelorism in metopic synostosis and its effects on bony interorbital distance and on the orbital shape (study I)
- to compare postoperative bony interorbital distance of patients affected by metopic synostosis and treated with SAS to that of patients treated with traditional cranioplasty and to an adequate control group (study II)
- to develop an image-based method to evaluate frontal symmetry in patients affected by UCS in a simple and reproducible way (study III)
- to use the newly developed method in Study III to objectively evaluate pre- and postoperative frontal symmetry in patients affected by UCS treated with a full forehead replacement or with a fronto-orbital advancement procedure (study IV)
- to use a newly developed image-based computer tool to measure intracranial volume changes of patients affected by metopic synostosis treated with SAS or with traditional cranioplasty and to compare the two groups to a control group (study V).

MATERIAL & METHODS

10.1 Patients & Controls

Study I is a retrospective study on the first 23 consecutive patients operated for metopic synostosis using SAS (1999-2004). At the time, CT examinations were not regularly performed, and patients were evaluated with cephalograms, which were taken routinely before surgery, at 1 month and at 6 months follow-up as well as at three years follow-up. BIOD from an already published report were used as normative data, while measurements of the fronto-orbital axes in a group of 10 children born with cleft lip and/or palate were used as controls.

In study II & V, patients operated for isolated metopic synostosis and examined by computed tomography at Sahlgrenska University Hospital between 2002 and 2009 were identified using The Göteborg Craniofacial Registry. Seventy-one patients were included in study II: 24 in the bone grafting group (BG) and 47 in the spring group (S). In study V, 60 patients were included (23 in the BG group and 37 in the S group). The higher number of patients in study II is due to the fact that it was undertaken after study V. Furthermore, some CT examinations were unsuitable for calculating the intracranial volume because they were cut before the vertex, but could still be used to determine the BIOD. In both studies, patients with complete preoperative and follow-up (at 3 years of age) CT examinations were used for the comparison between preoperative and follow-up values while patients with only preoperative or follow-up CT examinations were included in the comparison between patients and the control groups.

Two gender- and age-matched controls per case, both preoperatively and at follow-up, were identified from children who had

undergone CT examinations for neurological or post-traumatic evaluation. Children presenting conditions that could alter the cranial shape or volume, for example hydrocephalus or large intracranial masses, were excluded. This resulted in a total of 236 controls for study I and 198 controls for study V.

In study III, 15 patients operated on for UCS and with complete preoperative and follow-up examinations (7 CTs and 8 cephalometries) were used to test the computer program. They were chosen independently of the operation method used.

In study IV, 88 consecutive patients operated for UCS between 1979 and 2008 were included. Of these, 46 were operated with fronto-orbital advancement (FOA, group 1) and 42 were operated with forehead replacement with a calvarial bone graft (group 2). Complete radiographic examinations had been performed on a total of 66 patients (54 documented by cephalograms and 12 by CT scans; 33 FOA and 33 frontal replacement with a bone graft). CT scans were available only for patients in group 2 (from 2004).

10.2 Operative procedures

In study I, three different operative methods had been used (Figure 7). In the first three patients, a simple suturectomy was performed from the anterior fontanel down through the nasofrontal suture. In the subsequent 14 patients, together with the craniotomy a series of barrel-stave of osteotomies was performed bilaterally in the frontal bone to improve the forehead convexity. Finally, in the last 6 patients, the superior part of the frontal bone was removed while the supraorbital bandeau was divided sagittally and advanced laterally through a temporal tongue-in-groove. The frontal bone was thereafter split sagittally and repositioned leaving a central bony defect. In each case, a steel spring was inserted in the glabellar region through two burr-holes at 5 mm from the midline.

Figure 7 The three different operation methods described in study I. From left to right: Suturectomy, suturectomy and barrel-stave osteotomies, fronto-orbital remodelling. In each case, a spring was inserted in the glabellar region.

In study II and V, the spring technique (S group) corresponds to the last technique described in study I. The cranioplasty with the bone grafting is described as follows: the superior two thirds of the frontal bone were removed after dissection of the dura mater through burr holes. The supraorbital bandeau was removed at the level of the nasofrontal suture and divided along the fused metopic suture in two halves. An osteotomy was performed sagittally through the nasofrontal

suture for about 5-10 mm in order to partially separate the nasal and ethmoidal bones. A calvarial bone graft 15 mm wide was interposed between the two halves of the supraorbital bandeau and the whole complex was repositioned and rigidly fixated. The calvarial bone graft was v-shaped in its caudal aspect, and the v was inserted between the cranial aspect of the nasal bone in order to maintain the gap. A few barrel-stave osteotomies were carried out on the parietal bones perpendicularly to the coronary sutures, followed by out-fracturing of the staves. Finally, the remaining frontal bone fragments were rigidly fixated (Figure 8).

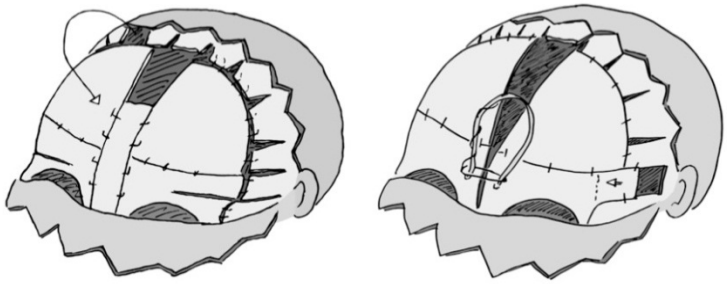

Figure 8 The surgical techniques described in study II and V. Left: fronto-orbital remodelling and bone grafting. Right: fronto-orbital remodelling and spring insertion.

The operative procedures utilized in study IV were:

Fronto-orbital advancement

A fronto-orbital bandeau was advanced on the affected side with a tongue-in-groove osteotomy in the temporal area, while it was pivoted on the contralateral side. The superior part of the frontal bone was rotated 180°, repositioned and fixated.

Calvarial bone graft

In the search for a suitable bone graft to serve as a new forehead, the whole cranial vault was inspected with a lead template curved according to the desired shape. The bone graft was designed so that it allowed a

raise of the supraorbital rim on the non-affected side (Figure 9). The frontal bone and the supraorbital bar were removed *en bloc* and switched with the bone graft. The orbital rim and roof on the non-affected side were osteotomized, lifted and adapted to the new supraorbital bar. The orbital rim on the affected side was moved anteriorly by osteotomy and green-stick fracturing. Osteotomies and green-stick fracturing of the most superior part of the frontal bone on the affected side were sometimes performed to allow better fixation to the bone graft (Figure 9).

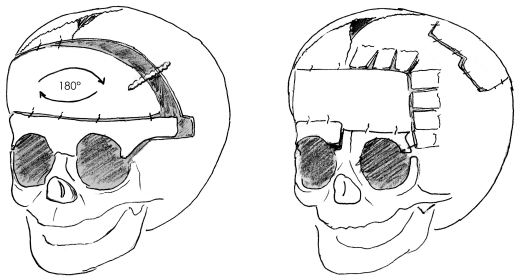

Figure 9 The surgical techniques described in study IV. Left: fronto-orbital advancement. Right: substitution of the frontal region en bloc with a calvarial bone graft and elevation of the superior orbital rim.

10.3 Measurements and Computer programs

In study I, the BIOD was measured as the distance between the left and the right cephalometric landmark *orbitale medius* (orm), i.e. the point on the medial orbital margin closest to the midline in cephalometry images (Friede, Alberius et al. 1990). Trigonocephaly is typically associated with a particular orbital shape. Anderson in 1962 described the radiographic shape of the orbits in trigonocephaly as "being oval or egg-shaped with the longer axis extending upwards and medially from the inferolateral orbital margins" (Anderson, Gwinn et al. 1962). It was noted that after SAS orbital shape normalized. To be able

to express the effect of springs on orbital shape, a novel parameter was introduced, the frontoorbital axis angle. The fronto-orbital axis was defined as the long axis passing through the highest point of the superior rim and the lowest point of the inferior orbital rim. The frontoorbital axes angle was defined as the angle of intersection between the right and left frontoorbital axes, and it was assigned as positive if crossing below the orbits and negative if above (Figure 10).

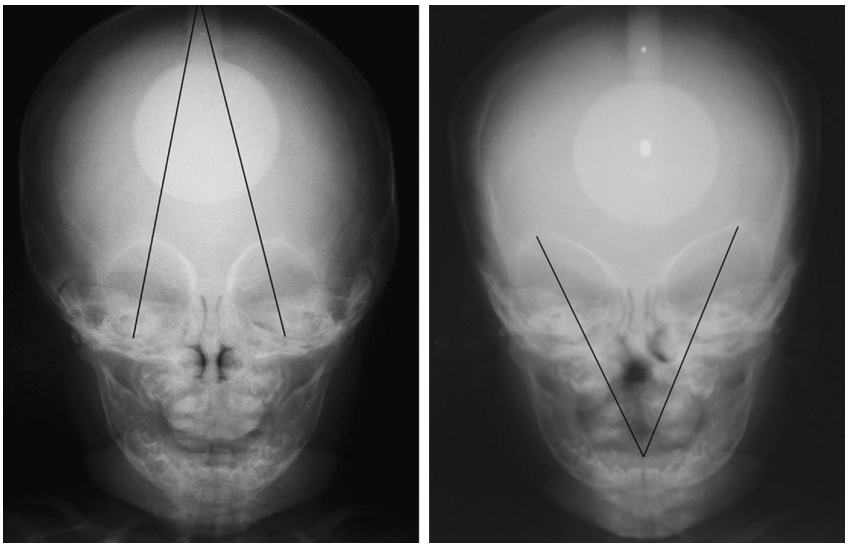

Figure 10 Fronto-orbital axes in a child with metopic synostosis (left) and control (right). In normal children the axes are crossing below the orbital area, whereas in children with metopic synostosis the axes cross superiorly to the orbits.

In study II, the BIOD was measured on CT scans as described by Waitzman (Waitzman, Posnick et al. 1992). The program used to perform the measurements was Centricity Enterprise Web © 2010 GE Healthcare IT, Little Chalfont, UK. The axial slice that exhibited the greatest ocular globe diameter was selected for the measurements, and the anterior bony interorbital distance was measured using the digital ruler available in the program (Figure 11). The measurements were repeated three times and the mean was used for statistical analysis.

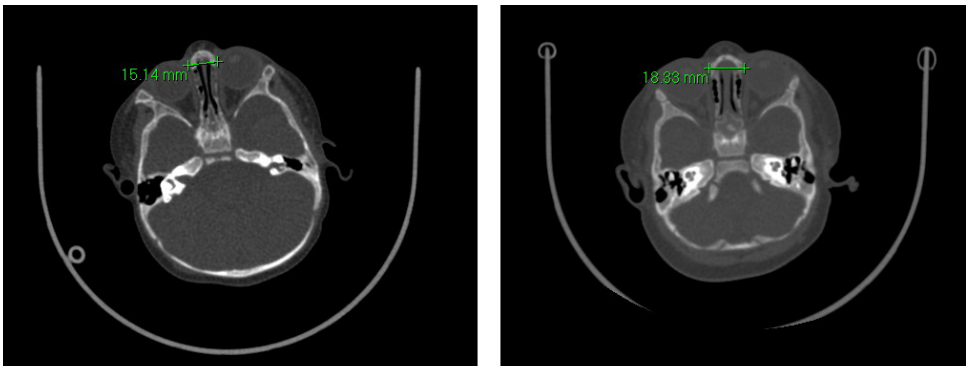

Figure 11 The bony interorbital distance calculated in an axial CT slice. Left: child with metopic synostosis. Right: control.

In study III, a novel computer based method was created in MATLAB version 7.11.0.584 (2010b)(MathWorks inc., MA, USA). The program compared the shape of the two halves of the forehead from a center-point O, i.e. the point where the bony nasal septum projects on the forehead, to the open coronal suture on the unaffected side (End-point) and a corresponding point on the affected side (p), at the same distance from O as the end-point. The program calculated the difference between the sides by finding the minimal mismatch area (*MA*) when the two curves representing the edges of the halves of the forehead were superimposed. The *MA* was related to the skull area *SA* (outlined by the contour of the forehead and a line between the open coronary suture and the corresponding point on the affected side) to create a measure independent of growth from time of surgery to time of follow-up (Figure

12). The symmetry ratio (SR) was defined as $SR = \frac{MA}{SA} \cdot 1000$. The Absolute symmetry change (ASC) was defined as the difference between the preoperative SR and the postoperative SR ($SR_{preop} - SR_{postop}$). The relative symmetry change (RSC) was defined as $\frac{SR_{preop} - SR_{postop}}{SR_{preop}}$. As RSC approached the value of 1, it indicated a very successful operation. RSC = 1 meant perfect symmetry. A negative RSC indicated that the forehead was more asymmetrical after surgery.

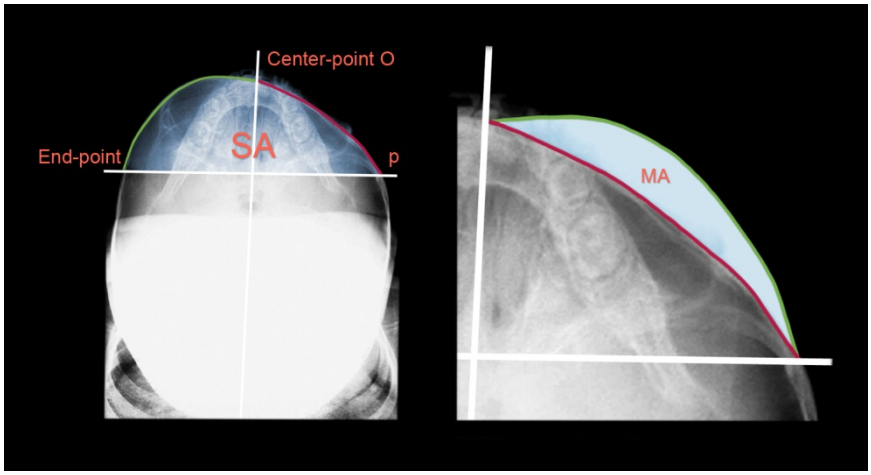

Figure 12 Cephalometry of a child with left-sided UCS. Left: The center-point O, the end-point and the point p are shown. The SA area is colored in blue. Right. The two curves are superimposed and the MA area is colored in white

The program was tested on a cylindrical phantom and on a symmetrical elliptical phantom to validate its ability to evaluate symmetry. Thereafter it was tested on 15 clinical images (8 cephalometries and 7 CT).

In study IV, The MATLAB tool previously described was used to measure the *SR* and the relative symmetry change on patients operated for isolated UCS between 1979 and 2008. A comparison was made between the two different operation methods.

In study V, a previously described MATLAB tool was used to measure the total intracranial volume (TIV) and the frontal intracranial volume (FIV), i.e. the intracranial volume in front of the coronal sutures, as well as the FIV/TIV ratio, in patients operated for metopic synostosis (Figure 13).

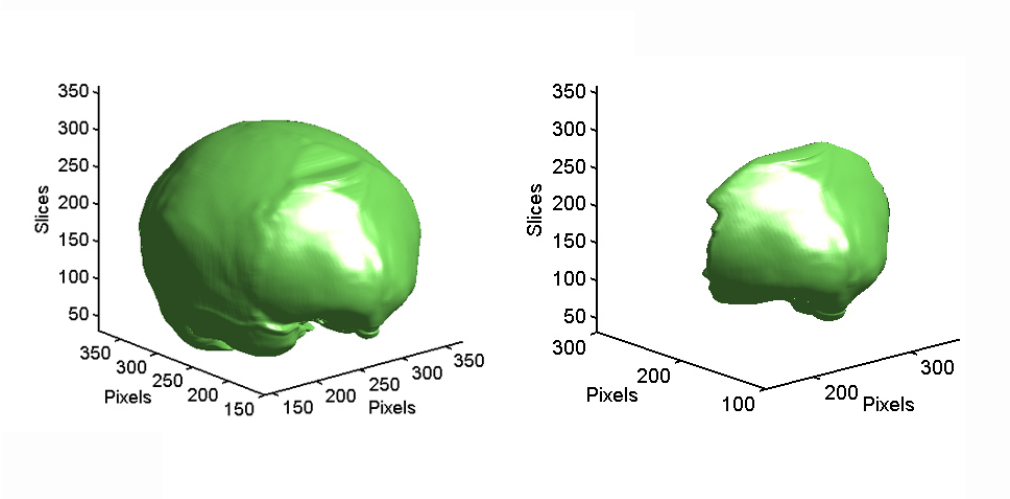

Figure 13 Left: 3D reconstruction of the total intracranial volume. Right: 3D reconstruction of the frontal intracranial volume, i.e. the portion of intracranial volume anterior to the coronal suture.

The program performed semiautomatic segmentation of axial CT slices and used functions such as region growing, watershed and thresholding to allow exclusion of bone tissue and extra-cranial soft tissues. Intracranial volume was then calculated by the Cavalieri's principle, i.e. as the sum of each slice area multiplied by slice thickness, from vertex to foramen magnum (Wikberg, Bernhardt et al. 2012).

10.4 Statistical methods

In study I, Student's independent samples *t*-test was used to compare the pre- and postoperative BIOD and the fronto-orbital axes angle in the metopic synostosis group to that of the controls.

In study II and V, Student's paired sample *t*-test was used to compare preoperative and follow-up values in each group of patients. Student's independent samples *t*-test was used to compare preoperative and follow-up values between the metopic synostosis groups and the control groups. Student's independent samples *t*-test was also used to compare the values at follow-up between the BG group and the S group. The relationship between age at surgery and values at follow-up within each group was investigated using Pearson product-moment correlation coefficient.

In study III, for each image the relative standard deviations and the mean SR, RSC and ASR were calculated.

In study IV, Student's paired sample *t*-test was used to compare the mean pre- and postoperative values from patients treated with either technique. Student's independent samples *t*-test was used to compare the mean *RSC* of patients treated with the FOA to that of patients treated with forehead remodelling.

Pearsons chi-square test was used to compare reoperation rates. P-values < 0.05 were considered significant in all studies.

Statistical analysis was performed using SPSS version 19.0.0 (IBM© SPSS® Statistics, SPSS Inc. Chicago, IL.)

RESULTS

Springs have the ability to change the orbital shape in metopic synostosis (study I)

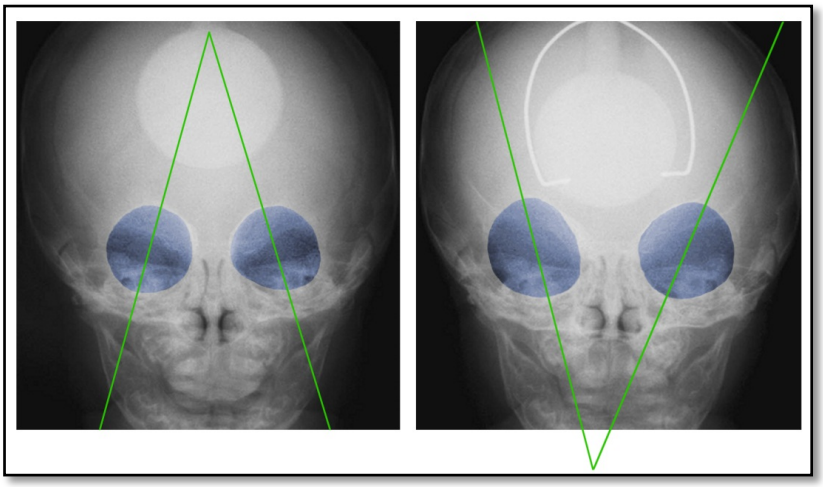

Figure 14 Frontoorbital axes in a patient with metopic synostosis before and during treatment with SAS

The mean preoperative frontoorbital axis angle was -4 ± 14 (mean ± SD) degrees, while it was + 48 ± 8 degrees on the control group ($p < 0.001$). Postoperatively, the mean frontoorbital axes angle increased to + 28 ±11 degrees ($p < 0.001$) (Figure 14). The results of the statistical analysis were not previously published.

Springs correct hypotelorism in metopic synostosis (study I & II)

The mean preoperative BIOD measured on posteroanterior cephalograms was significantly smaller than controls (Table 3) ($p < 0.001$), while at 5 months follow-up there was no significant difference ($p >> 0.2$).

	Age range months BIOD, mean ± SD mm	Age range months BIOD, mean ± SD mm	Age range months BIOD, mean ± SD mm
Metopic	3 – 8 10.6 ± 1.4	4 – 9 15.7 ± 3.8	6 – 13 16.2 ± 3.8
Control	0 – 4 14.9 ± 1.4	5 – 8 16.0 ± 2.1	9 – 12 16.6 ± 2.2

Table 3 Upper row: mean bony interorbital distance in children affected by metopic synostosis before treatment (left), 1.5 months after surgery (center) and 5 months after surgery (right). Lower row: BIOD in controls within the nearest age range

Preoperatively, children with metopic synostosis have significantly smaller BIOD than controls (study II).

Both the BG group and the S group had a significantly smaller preoperative anterior bony interorbital distance when compared to their respective control group (Table 4) ($p < 0.001$ in both cases).

PREOPERATIVE	N	Age at CT, months	Age at op, months	Pre op biod, mm
BG	19	9.0 ± 2.9	9.8 ± 2.5	14.7 ± 1.0
Controls	38	8.8 ± 2.9	-	18.8 ± 1.4
p-value				< 0.001
S	30	4.2 ± 0.8	4.3 ± 0.9	13.8 ± 1.6
Controls	60	3.7 ± 1.1	-	18.6 ± 1.4
p-value				< 0.001

Table 4 Summary of the preoperative data in Study II (mean ± SD)

At follow-up BIOD was significantly improved in both groups, but only children operated with SAS reached normal values (study II).

The mean BIOD in the S group did not significantly differ from the control group ($p = 0.3$), while the mean postoperative BIOD in the

BG group was significantly smaller when compared both to the respective control group and to the S group (Table 5) ($p < 0.001$ in both cases).

FOLLOW-UP	N	Age at CT, months	Post op BIOD, mm
BG	23	36.5 ± 1.2	17.6 ± 1.8
Controls	46	36.6 ± 2.5	20.0 ± 1.1
p-value			< 0.001
S	46	37.1 ± 1.6	19.7 ± 2.9
Controls	92	37.4 ± 3.5	20.2 ±1.3
p-value			= 0.3

Table 5 Summary of the postoperative data in Study II (mean ± SD)

The BIOD at follow-up is not influenced by the age at which surgery is performed (study II).

The Pearson product-moment correlation coefficient did not show a significant correlation between the variables age at surgery and postoperative BIOD within either group ($p = 0.1$ for the BG group and 0.3 for the S group).

Three patients were excluded from study II because they were operated at three years of age. Their preoperative BIOD were 16.6 mm (36 months of age), 17.1 mm (36 months of age) and 17.4 mm (34 months of age).

The presented computer tool is able to measure forehead symmetry in UCS with good precision (study III).

For every run on the cylindrical or on the elliptical phantom the program calculated the SR as 0, i.e. evaluated the images as perfectly symmetrical. In measurements performed in cephalometric images the

relative standard deviation was generally higher than in measurements performed in CT images (Tables 6 and 7). The relative SD also increases when SR decreased, either as a results of a relatively little improvement of surgery or as a consequence of a small pre-operative asymmetry (Figure 15).

	RSC	SD (%)	ASC	SD (%)
1	0.56	2.41	18.03	2.68
2	0.90	0.37	53.81	1.51
3	0.99	0.38	57.84	1.06
4	0.75	1.34	32.51	1.84
5	0.98	0.26	48.59	0.33
6	0.93	0.36	63.40	0.64
7	0.75	1.48	16.29	2.72

Table 6 Relative Symmetry Change, RSC, and Absolute Symmetry Change, ASC, values for CT images

	RSC	SD (%)	ASC	SD (%)
8	0.82	3.83	36.11	10.48
9	0.85	3.74	39.22	9.00
10	0.90	4.63	25.37	9.99
11	-0.36	24.24	-10.54	20.74
12	0.94	1.38	73.94	5.32
13	0.79	3.85	34.54	7.00
14	0.95	2.15	54.01	7.33
15	0.84	5.39	22.65	14.42

Table 7 Relative symmetry change, RSC, and Absolute symmetry change, ASC, values for cephalometry

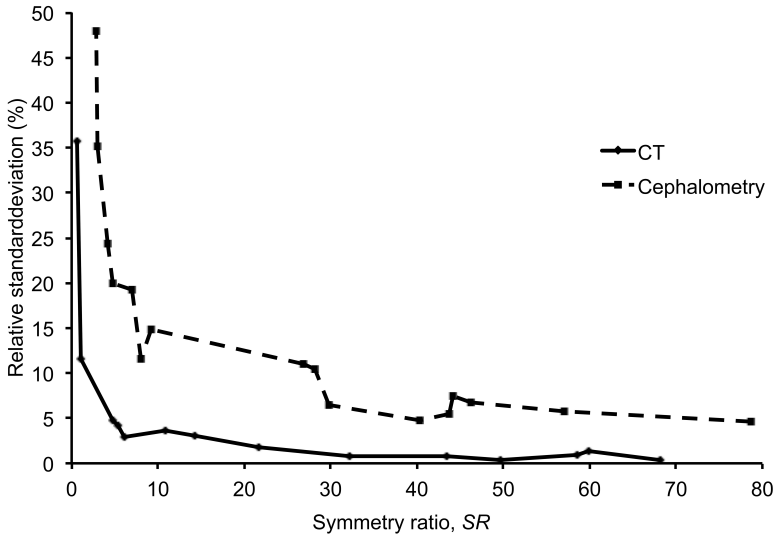

Figure 15 The relative standard deviation was higher for measurements done in cephalometry images than in CT images. The relative standard deviation increased when SR decreased.

RSC is a more objective estimator of the postoperative improvement.

A more successful operation was represented by a value close to one in *RSC* and a high value in *ASC*. The *ASC* (= SR_{preop} - SR_{postop}) is strictly dependent on the degree of preoperative symmetry, while RSC (= $\frac{SRpre-op - SRpost-op}{SRpre-op}$) is more independent and hence a more objective estimator of the postoperative improvement.

The substitution of the frontal region in UCS results in a better postoperative forehead symmetry than a fronto-orbital advancement procedure (study IV).

Both the fronto-orbital advancement and the forehead remodelling significantly reduced the *SR* (p < 0.001 in both cases).

Forehead remodelling improved *RSC* significantly more than FOA (Table 8) (mean *RSC* = 0.80 *vs.* 0.64, $p = 0.02$).

	Group 1	Group 2
n	33	33
Mean SR_{Preop} (± SD)	57.8 (± 21.6)	52.7 (±18.5)
Mean SR_{Postop}(± SD)	15.9 (± 12.2)	9.4 (± 6.8)
Mean RSC (± SD)	0.64 (± 0.37)	0.8 (± 0.14)

Table 8 The preoperative SR values were identical in the two groups of patients. Forehead remodelling (group 2) improved the symmetry significantly more than FOA (group 1)

Intracranial volume in children with metopic synostosis is equivalent to intracranial volume in normal children, but it is differently distributed (study V)

	n	*Age at CT*, months	*Age at op*, months	*TIV*, L	*FIV*, L	*Ratio FIV/TIV*
BG	16	8.7 ± 3.3	9.0 ± 2.9	0.995 ± 0.137	0.103 ± 0.019	0.104 ± 0.013
Controls	32	8.8 ± 3.1	-	1.015 ± 0.175	0.144 ± 0.032	0.142 ± 0.021
***p*-value**				0.7	< 0.001	< 0.001
S	26	4.0 ± 0.8	4.2 ± 0.8	0.789 ± 0.070	0.076 ± 0.013	0.097 ± 0.012
Controls	52	3.7 ± 1.0	-	0.790 ± 0.120	0.115 ± 0.024	0.146 ± 0.019
***p*-value**				1.0	< 0.001	< 0.001

Table 9 Summary of preoperative data (mean ± SD)

Preoperatively, the mean TIV for children with metopic synostosis was not significantly different to that of the control groups ($p = 0.7$ with 95 percent CI -0.18 – 0.09 L for the BT group; $p = 1.0$, 95

percent CI -0.04 – 0.04 L for the S group), while the FIV and the ratio FIV/TIV were significantly less than in the controls ($p < 0.001$ for both groups) (Table 9).

Postoperatively, the distribution of intracranial volume is more similar to that of normal children (study V).

	n	Age at CT, months	TIV, L	FIV, L	Ratio FIV/TIV
BG	22	36.3 ± 1.2	1.270 ± 0.101	0.141 ± 0.023	0.111 ± 0.018
Controls	44	36.1 ± 2.7	1.356 ± 0.103	0.184 ± 0.032	0.135 ± 0.017
p-value			0.002	< 0.001	< 0.001
S	35	37.1 ± 1.6	1.263 ± 0.123	0.141 ± 0.034	0.111 ± 0.020
Controls	70	38.0 ± 2.7	1.346 ± 0.115	0.182 ± 0.032	0.135 ± 0.016
p-value			0.001	< 0.001	< 0.001

Table 10. Summary of data from the 3-year follow-up (mean ± SD)

Paired-samples *t*-test showed that TIV and FIV were significantly greater at follow-up in both groups ($p < 0.001$ in all cases). The FIV/TIV ratio was improved in both groups (p = 0.058 for the BG group, p < 0.001 for the S group). At follow-up, both groups had significantly lower FIV and FIV/TIV ratio than their respective controls (Table 10) ($p < 0.001$ in both cases).

Postoperatively, the TIV in children operated for metopic synostosis is lower than that in normal children (study V).

At follow-up, both groups showed a TIV that was significantly lower than in the respective controls (BT group: $p = 0.002$; S group: $p = 0.001$)

The two techniques do not differ in changing the distribution of intracranial volume (study V).

At 3-year follow-up, there was no significant difference in TIV, or in the FIV/TIV ratio, between the BT group and the S group ($p > 0.5$ in all cases).

The age at which surgery is performed does not influence the outcome (study V).

The Pearson test did not show any significant correlation between age at surgery and ratio at follow-up ($p = 0.7$ for the BT group and $p = 0.9$ for the S group).

DISCUSSION

Over the years, the techniques used to treat craniosynostosis at our unit have been changed. In this process, an objective evaluation is important to compare the surgical results.

The first part of this thesis focuses on the correction of hypotelorism in metopic synostosis, which is still a controversial issue among craniofacial surgeons. Some authors state that directly addressing the hypotelorism may be unnecessary since the fronto-orbital reshaping alone would release the growth restriction and hence promote indirect, secondary correction, especially if surgery is undertaken at an early age (Fearon, Kolar et al. 1996; Hinojosa, Esparza et al. 2002; Di Rocco, Frassanito et al. 2012). Previous reports are often flawed by low numbers, inadequate methodology or small control populations. Posnick presented a series of 10 patients operated with fronto-orbital reshaping and bone grafting (Posnick, Lin et al. 1994). Interorbital distances were assessed on CT scans and compared to normative data, resulting in a significant average improvement, but not a complete correction. Fearon et al. presented a series of 16 patients operated for metopic synostosis in which no attempt to directly correct hypotelorism was made. Their results were based on objective anthropometric measurements (intercanthal width) and on CT measurements (interorbital width). A significant improvement of hypotelorism was reported in all cases, however width was below normative data (Fearon, Kolar et al. 1996). Hinojosa reported a series of 28 patients of which only 18 were evaluated as having hypotelorism. Of these, 7 were operated without directly addressing the hypotelorism while for the remaining 11 direct surgical correction of hypotelorism was performed with a sagittal osteotomy through the naso-frontal junction and the interposition of a bone graft. An improvement of

interorbital distance measured on CT scan was reported in all patients, but none from the group where hypotelorism was not directly corrected reached normal values. Hilling et al. presented a series of 45 patients operated for metopic synostosis, in which the correction of hypotelorism was attempted only in those patients with a more severe form. The outcomes were judged on clinical photographies by a panel, and an incomplete correction of hypotelorism was reported. Van der Meulen reported the analysis of the cephalograms of a series of 92 operated patients in which the hypotelorism was not directly corrected. A tendency towards some degree of postoperative auto-correction of the hypotelorism was suggested (van der Meulen, Nazir et al. 2008). Di Rocco described a personal technique where hypotelorism was corrected indirectly, i.e. by sagittal osteotomy from the midline of the supraorbital bar through the nasofrontal junction (Di Rocco, Frassanito et al. 2012), however, an evaluation of the postoperative results was not presented.

A supra-orbital bar remodelling and a sagittal osteotomy through the naso-frontal junction with the interposition of a bone graft to widen the supraorbital bandeau and support the lateral displacement was the approach used to treat metopic synostosis at our unit as well as in several other centers. The technique showed to correct hypotelorism only to some extent (Kocabalkan, Owman-Moll et al. 2000). Springs started to be used to correct hypotelorism in metopic synostosis in 1998. The first consecutive 23 patients are described in study I. The first three patients were treated by suturectomy and spring insertion alone. Thereafter, a more extensive forehead remodelling was implemented, in combination with a spring aiming at correction of the hypotelorism. In study I, the BIOD was measured in postero-anterior cephalograms as the distance *Orm-Orm.* Our results showed a significant postoperative improvement of the hypotelorism. Also, the fronto-orbital axes angle was introduced as a new parameter. The frontoorbital axes angle was positive in normal infants and negative in trigonocephalic children (i.e.

crossing superiorly to the orbits). After treatment, the frontoorbital axes angle had increased to positive values, and the orbits had a more natural shape. In study II, BIOD in patients affected by metopic synostosis and operated with the spring technique (S group) were compared to the BIOD of patients operated with the fronto-orbital remodelling and bone grafting (BG group), and to that of an adequate control group. In this study, the BIOD was measured on axial CT examinations. The results showed that, at follow-up, BIOD of patients operated with springs did not differ significantly from the control group. BIOD was on the other hand not completely corrected in the group of patients that underwent supraorbital advancement and bone grafting. Compared to previous studies this study hade a large population, an objective measurement was performed and it had a gender and age matched control population. Hence, direct comparison of the mean values could be done without any extensive statistical manipulation.

The BIOD in the S group showed a much higher postoperative variability, as expressed by the larger standard deviation. This is not an unexpected finding with spring-assisted surgery. Springs are powerful tools, strongly dependent on factors such as the spring force, the quality of the bone, the implantation site and the surgeon. It was surprising not to find any correlation between the age at which surgery was performed and the BIOD at follow-up, as we would have expected. This might be a consequence of the small age-span at which surgery was performed.

Since the two surgical techniques were used in groups with different ages they cannot be directly compared, as would have been possible if patients had been randomly assigned to one of the two groups. Our results simply show that spring-assisted surgery performed before six months of age, although with some variability, corrects hypotelorism to normal values, while the cranioplasty with bone grafting performed at an older age result in undercorrected BIOD. These results do not contradict that self-correction can play a role as suggested by several authors (Fearon, Kolar et al. 1996; van der Meulen, Nazir et

al. 2008; Di Rocco, Frassanito et al. 2012). However until now no other group has presented normalization of BIOD and one possible explanation to the complete correction with SAS could be the effects that springs have on patent cranial sutures. In study I it was speculated that after release of the metopic suture, the continuous spreading force of the spring applied over the glabellar region could indirectly promote ethmoid sutural expansion. A successive study showed that springs have the ability to transmit expansile force across the fronto-ethmoid suture, thus performing a form of sutural distraction rather than producing a plastic deformation of the bony structures (Davis and Lauritzen 2009).

It can be concluded that hypotelorism due to metopic synostosis is well corrected with spring-assisted surgery performed before 6 months of age. Whether this is due to the young age at which surgery is performed or to the springs themselves remains to be determined. Further research is necessary to expand our knowledge on spring-assisted surgery, in particular on which steps of the surgery or which associated conditions generates the observed variability, in order to systematically achieve the best results.

The second part of this thesis was centred on the evaluation of the symmetry of the frontal contour as a new method to evaluate postoperative outcomes after correction of UCS. There are no clear criteria on how to evaluate outcomes in UCS independent of the evaluator. The Whitaker classification, together with similar methods based on the evaluation of clinical photography by a panel, is widely used in long-term retrospective analyses (Hilling, Mathijssen et al. 2006; Selber, Brooks et al. 2008; Mesa, Fang et al. 2011; Seruya, Oh et al. 2011). The method has limitations such as providing qualitative data and being subjected to observer bias. More objective methods have been presented. Anthropometry has been used to evaluate pre- and postoperative status and to compare techniques (Meara, Burvin et al. 2003). Oh reported a series of 15 patients older than 10 years operated

for UCS, which were evaluated by indirect anthropometry on three-dimensional digital images (Oh, Wong et al. 2008). The method has shown many advantages compared to other quantitative methods, but the study was limited to the evaluation of the postoperative status. Measurements on three-dimensional CT have been used to document deformity in UCS, providing objective data for evaluation (Kane, Kim et al. 2000; Becker, Fundakowski et al. 2006). The aim of our evaluation was to compare patients operated with different techniques and in different periods. Patients operated with the fronto-orbital advancement had all been examined by cepahlograms. Of the 42 patients that underwent the frontal reconstruction with bone grafting, 30 were evaluated with cephalograms and 12 with CT scans. Therefore, we created a program to provide a quantitative evaluation of forehead symmetry from both CT and cephalograms. The reliability of the program was tested on images of symmetrical phantoms and on 15 patients before and after treatment and evaluated either by cephalograms or CT. In measurements done in cephalograms the relative standard deviation was generally higher than in measurements done in CT images. This is due to the poor contrast in some of the cephalograms, which caused some problems in automatically detecting the outermost edge of the cranium so that segmentation had to be done manually. Still, for the expected range of SR the relative standard deviation remained low even for cephalograms, thus allowing measurement of the symmetry independently of whether patients had been examined by cephalograms or CT scans.
The relative standard deviation increased when the *SR* decreased, i.e. with very good symmetry, and when the low definition makes the placement of the *O* and the *end-point* more difficult.

The paper describes two measures aimed to evaluate the success of operation for deformed skulls: the Absolute Symmetry Change (*ASC*) and Relative Symmetry Change (RSC). The two measures do not evaluate an operation to be successful equally. *RSC* is preferable for

evaluation of clinical outcome, since it is normalized with the *SR* before operation and has thereby an upper limit of success, i.e. *RSC* equal to 1 means a perfect operation. An *RSC* of 0 means no difference and a negative *RSC* means that the forehead is more asymmetric after surgery.

In study IV, the program was used to evaluate the symmetry of the forehead in the two groups of patients operated with different surgical techniques.

Our measurements show that forehead asymmetry was significantly reduced by both the techniques, but that forehead replacement with a calvarial bone graft resulted in significantly better symmetry.

Whether the unilateral FOA or the bilateral FOA would be the best technique to correct forehead deformity in UCS has been a matter of discussion (Sgouros, Goldin et al. 1996; Hansen, Padwa et al. 1997). The present study shows that forehead advancement does not take into account the different shape and convexity of the two halves of the forehead and supraorbital bar. Residual frontal asymmetry is often the single most obvious deformity after surgical correction (Meara, Burvin et al. 2003).

Reoperation rate was significantly higher in patients operated with FOA than in patients operated with forehead reconstruction. The result of the present study supports the idea that the lower reoperation rate in patients operated with forehead remodelling is due to the better symmetry achieved with this method.

We conclude that a free bone graft harvested from the calvaria and used as a new forehead/supraorbital bar complex gives better forehead symmetry and lowers the reoperation rate as compared to FOA and is therefore a better method for treatment of UCS. The new tool introduced for measurement of forehead symmetry makes objective evaluation of the result of surgery for unicoronal synostosis possible.

In the literature, there is contrasting evidence as to whether the intracranial volume in patients with isolated metopic synostosis is different from that in the normal population (Gault, Renier et al. 1990; Posnick, Armstrong et al. 1995; Sgouros, Hockley et al. 1999; Anderson, Netherway et al. 2004; Sgouros 2005) Previous studies have suggested that children with metopic synostosis have intracranial volumes larger than - or within the range of - the normal population.(Posnick, Armstrong et al. 1995; Sgouros, Hockley et al. 1999) Many of these previous studies have suffered from problems of small numbers of cases and inadequate controls. More recent reports, with higher number of patients and better methodological consistency, have found evidence that (at least in the male population) intracranial volume in trigonocephalic children is significantly reduced.(Anderson, Netherway et al. 2004) Still, an extensive statistical effort was needed to support the result.

Our results indicate that children with metopic synostosis have normal intracranial volumes—at least up to the ninth month of life. This may be a direct consequence of the biparietal widening. This compensatory deformation associated with the narrow shape of the forehead makes the total intracranial volume equivalent to that in normal children, but the distribution of this volume is abnormal. Our study shows that in metopic synostosis, the proportion of intracranial volume anterior to the coronal sutures is about 30% lower than normal. This is not a surprising finding, since a reduction in the intercoronal diameter compared to the interparietal diameter in these children has been documented previously.(Posnick, Lin et al. 1994; Bottero, Lajeunie et al. 1998; Shimoji, Shimabukuro et al. 2002; Ruiz-Correa, Starr et al. 2008)

Our results also show that the remodelling of the forehead redistributed intracranial volume, reflected by a significant improvement in the FIV/TIV ratio. At follow-up, however, this ratio did

not reach normal values. Whether this is due to surgical under-correction or to some form of postoperative "relapse" needs to be investigated further. A series of immediate postoperative CT scans would be informative for this evaluation. The results also showed that the two methods used did not differ much in their ability to correct volume distribution. This is not surprising, since the two cranioplasties are fairly similar and the use of a bone graft or a spring is mainly aimed at correction of the hypotelorism.

We conclude that, at least up to 9 months of age, the TIV in children with metopic synostosis is similar to that in the normal population, while the FIV/TIV ratio is significantly reduced. Both surgical techniques changed the distribution of intracranial volume toward that of the normal population, but at three years of age, children operated for metopic synostosis had significantly lower intracranial volumes compared to normal children.

In paper V, TIV and FIV were obtained using precisely the same methods in cases and controls. The patient material was large and uniform, and our control population consisted of sufficient numbers of gender- and age-matched individuals. For the first time in any study, we have measured the TIV and the fraction of the intracranial volume, in front of the coronal sutures, that is the primary target for the surgical procedure.

In the five papers presented, the evaluation of surgical outcomes was based on radiographic imaging. The risks associated with medical radiation represent an obvious drawback. Exposure to ionizing radiation is of even greater concern in children, due to greater organ sensivity, to their smaller body dimensions and to the greater number of remaining years of life during which pathology can develop. However, it has been demonstrated that low-dose protocol imaging, such as the one routinely used for our patients (100 kV, 30 mA), results in an absorbed

dose per scan that is comparable to 1 to 2 months of background radiation. Low dose protocols have demonstrated acceptable accuracy. Even with nearly 90% reduction of mAs, osseous details such as suture patency can be accurately assessed. In this aspect, the risk to benefit ratio support the routine use of CT scanning in craniofacial surgery (Domeshek, Mukundan et al. 2009). Furthermore, until a satisfactory non-ionizing image-based method is established, it will be difficult to meaningfully compare the outcomes of the many techniques currently available for the treatment of SSC.

CONCLUSIONS

In summary, this thesis has presented evidence to support the following conclusions

1. A new operative method to correct hypotelorism in metopic synostosis with the use of springs is described. Springs have shown the ability to correct hypotelorism and to change the orbital shape in metopic synostosis.

2. BIOD in patients affected by metopic synostosis and operated with SAS before six months of age is normalized, while it is undercorrected in patients operated with fronto-orbital remodelling and bone grafting.

3. A program to evaluate forehead symmetry in patients with UCS before and after treatment has been developed for both CT and cephalometry images. The method is simple to use and independent of head rotation at the time of image acquisition. Results are more reliable with CT images than cephalograms.

4. In children affected by UCS, the substitution of the forehead and supraorbital bar with a calvarial bone graft gives better forehead symmetry and lower reoperation rate than FOA and is therefore a better method for treatment of UCS.

5. At least up to 9 months of age, the TIV in children with metopic synostosis is similar to that in the normal population, while the FIC/TIV ratio is significantly reduced. Both surgical techniques change the distribution of intracranial volume toward that of the normal population, but at three years of age, children operated for metopic synostosis have significantly lower intracranial volumes than normal children.

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