On Trigonocephaly

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'The time has come,' the Walrus said,

'To talk of many things:

Of shoes and ships and sealing wax

Of cabbages and kings

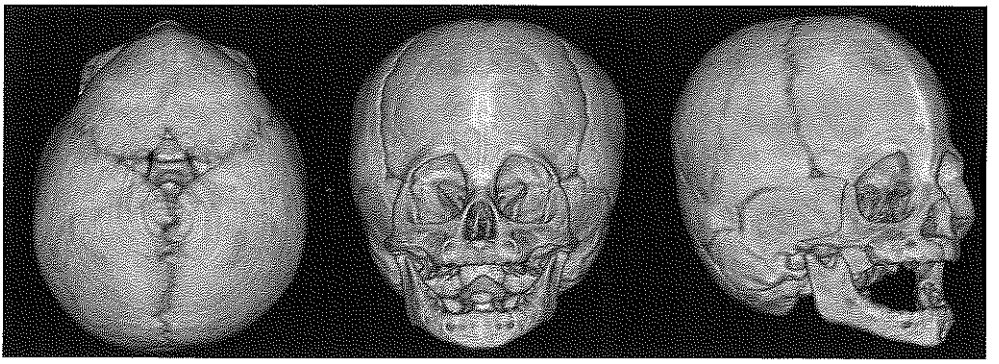
And why the sea is boiling hot

And whether pigs have wings.'

From 'The Walrus and the Carpenter' by Lewis Carroll

(in *Through the Looking-Glass and What Alice Found There*, 1872)

I N D E X



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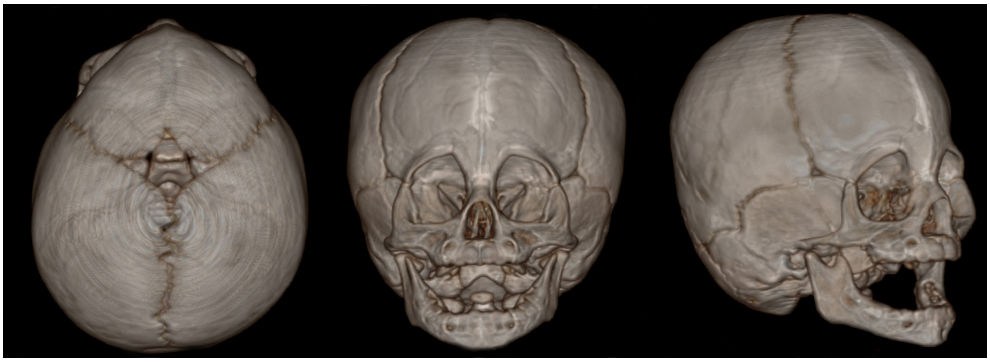
C H A P T E R O N E



Introduction

INTRODUCTION

Craniosynostosis, a congenital condition of premature fusion of the sutures between the bones of the skull, leads to an altered skull shape. One of these shapes is referred to as trigonocephaly, a term derived from the Greek words "trigonon" (= triangle) and "kephale" (= head). This shape is thus characterised by a triangular, or wedge shaped forehead, resulting from a premature fusion and subsequent ossification of the metopic suture (Greek "metopon" = forehead). The term trigonocephaly was first proposed by Welcker in 1862, who used it to describe a child presenting with a wedge shaped skull combined with a cleft lip (fig 1). [1]

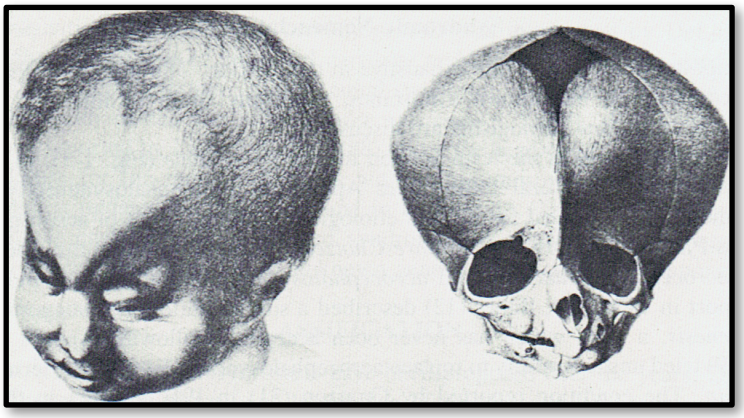


fig 1. First description of trigonocephaly by Weckler in 1862

This metopic suture separates the two frontal bones at birth and is the first skull suture to close physiologically, starting as early as 3 months and generally being completely fused at the age of 8 months.[2, 3] A premature fusion however, results not only in an obvious ridge over the midline of the forehead due to ossification of the suture, but also in a lateral growth restriction of the frontal bones. According to the theory of Virchow, this wedge shape is even further enhanced by the increased compensatory growth of the remaining skull sutures while the skull keeps expanding.[4]

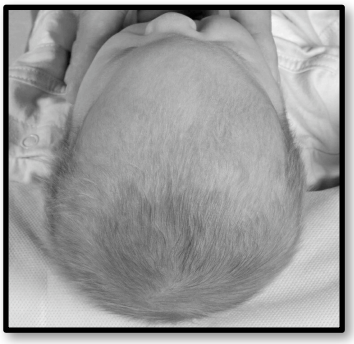


Fig 2. Top view of child with metopic synostosis

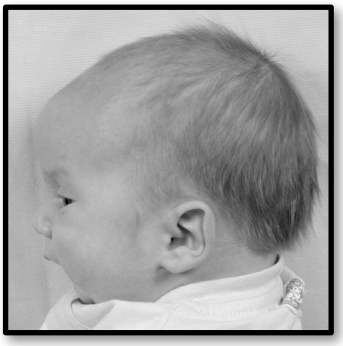


Fig 3. Lateral view of the same child

The end product is a skull with a triangular forehead, a bony midline ridge and a shortening of the anterior cranial fossa. (fig 2-4). Often there is some degree of soft tissue excess along the same line. In 55% of cases the anterior fontanel is closed prematurely.[5] Deficient lateral orbital rims add to the supraorbital retrusion and the bitemporal indentations. In severe cases the lateral canthal angles are elevated. At the level of the medial orbital walls there is hypotelorism combined with ethmoidal hypoplasia. Epicanthal folds are often present. The orbits are teardrop shaped and angulated towards the midline of the forehead (fig 4 & 5). Vertical growth restriction as expressed in reduced auricular head height is one of the most significant components of the midline growth anomalies. The cephalic index (maximal skull width / maximal skull length) remains within normal limits, even though there is bitemporal shortening and biparietal widening.[6-16]

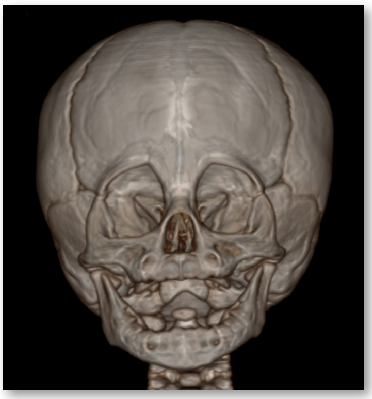


Fig 4. 3D-CT scan of child with metopic synostosis

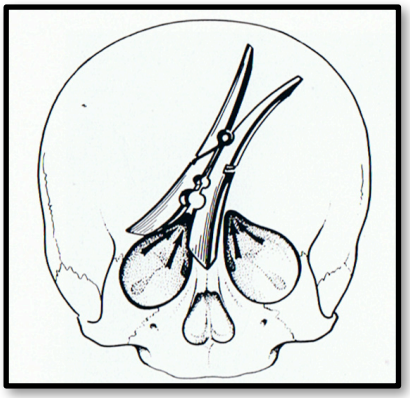


Fig 5. Principle of orbital changes due to metopic fusion

HISTORY OF SKULL MALFORMATIONS

People unfortunate enough to be born with an oddly shaped skull were, over the centuries, often rejected as being cursed and a work of the devil.[11] This attitude towards congenital craniofacial malformations still persists in large parts of the world today, even though often the intellectual development is normal. Judgement of ones character based on appearance though, is equally not unknown to the history of mankind. In the early 19th century for instance, the Austrian physician Gall introduced the (pseudo-) science of phrenology, linking the morphology of the skull to the human character. With the use of his standard work "The Anatomy and Physiology of the Nervous System in General, and of the Brain in Particular" it became possible to predict ones future behaviour based on the shape of their skull (fig 6 & 7).[17, 18] Remarkably this "art" has survived to our modern day, even though Gall's theories were rejected as being dubious by many serious scientists of his time and notwithstanding the bad image it obtained after the Nazi's used its principles to justify their policy of racial discrimination.[19]

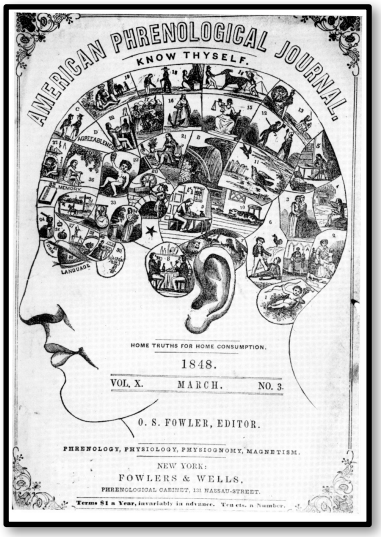


Fig 6. Front page of the American Phrenology Journal 1948

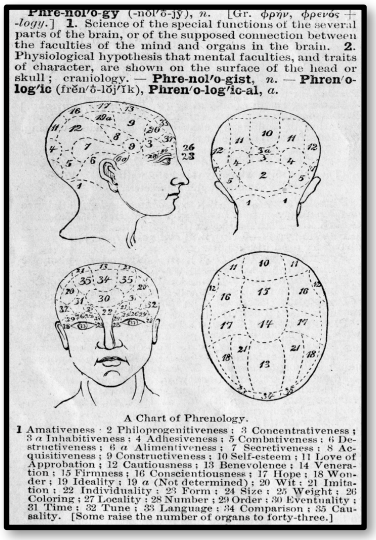


Fig 7. The skull and its corresponding area's of character

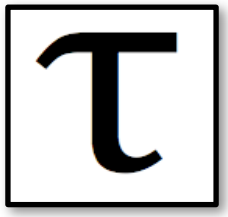
Despite all this, when it comes to appearance, the shape of the head always was and always will be an important factor. As early as in the classic tale of the Iliad condescending remarks are made towards people with an extraordinary appearance. Here Homer speaks of Thersites as being the uggliest man who ever

came to Ilium. His remarks; "pointed his head; sewn on the crown with thinnish wool" (Iliad, II, 219) very likely refer to a premature fusion of the metopic suture.[9, 20, 21] The classical signs of trigonocephaly can be appreciated on the image of Thersites on an ancient Greek vase (fig 8a), showing a strong resemblance to the child with metopic synostosis pictured in fig 8b.

Fig 8a. Detail of a Greek vase, with (from left to right) Odysseus, Agamemmon and Thersites.
b. His profile resembles that of the child with a metopic synostosis shown next to him.
c. The original vase (E196, The British Museum, London, UK).

In the Talmud, the body of Jewish civil and ceremonial law, trigonocephaly is specifically described as one of the physical defects that disqualify a priest from serving in the temple sanctuary in Jeruzalem. Amongst others, it proclaims that; "any man with a blemish shall not approach [the sanctuary], a blind or lame man or a man who is maimed [Hebrew charom, which signifies depression of the nasal bridge with hypotelorism]. More specifically, the Shakua is considered to be one of the maimed; "someone with a sloping or angular forehead, that is, an abruptly receding forehead in which a portion of the frontal area appears to be lacking".[22]

The Greek philosopher and founder of modern day medicine Hippocrates described trigonocephaly and its relationship to the cranial sutures as follows: "Men's heads are by no means all like to one another, nor are the sutures of the heads of all men constructed in the same form. Thus, whoever has a prominence in the anterior part of the head…..in him the sutures of the head take the form of the Greek letter 'tau', τ" (fig 9 & 10).[23, 24]



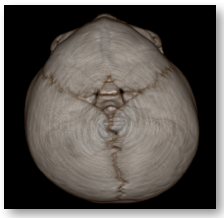


Fig 9 & 10. The Greek letter τ Hippocrates referred to can be seen in an axial view CT scan of a child with metopic suture synostosis

More recently there has been discussion whether Wolfgang Amadeus Mozart (1756-1792) had signs of metopic suture synostosis (fig 11 & 12). Puech et al. suggested such after examination of the skull on display in the Mozarteum in Salzburg, Austria. [25, 26] Several other authors have denied the conclusions of Puech et al. based on their own anthropometric observations (besides the fact that DNA studies of the skull have proved to be inconclusive whether or not it actually is the skull of Mozart).[15, 27-29] Personal inspection revealed a prominent frontal sinus as being the most likely cause of the slight frontal bossing over the caudal aspect of the metopic suture (fig 13).

Fig 11. Mozart at age 6 years

Fig 12. Superior view of the skull that is being kept at the Mozarteum in Salzburg, Austria

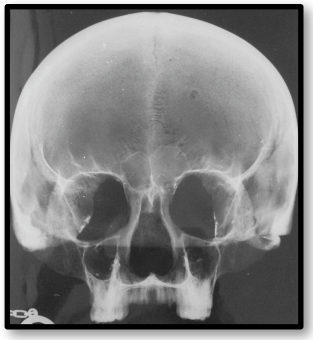


Fig 13. X-ray of the skull of Mozart showing the frontal sinus, which is the most likely cause of the metopic protruberance

EPIDEMIOLOGY

The incidence of metopic synostosis has been thought to be somewhere between 1:700 and 1:15.000 newborns.[16, 30] In series presenting an overview of more than 100 craniosynostotic cases, metopic synostosis accounted for 3 to 27% of the total, making it the third most common single suture synostosis after sagittal and unicoronal synostosis.(7, 31-38) The incidence seems to be on the rise though, with Selber et al. reporting an increase in their unit of 3,7% to 27,3% in the total number of craniosynostotic cases over a period of 30 years.[31] The male to female ratio is reported to be between 2:1[10, 32, 33] and 6,5:1[34], with Lajeunie et al. noting a ratio of 3,3:1 in the largest serie to date (237 cases). They also found a positive family history in 10 out of the 179 families (5,6%) and a 7,8% frequency of twins. Fifty-three of their cases (22,4%) were associated with other malformations (13 well defined syndromic cases and 40 cases with one or more malformations, but without a known syndrome).[16] Shillito found associated abnormalities in 19% of their 21 cases, with 9,5% presenting with multiple abnormalities.[35] Boulet et al. reported that, in their study of 854 children, maternal age and a birth weight of less than 2500grams was associated with a higher risk for metopic synostosis.[36]

ETIOLOGY

The etiology of craniosynostosis is largely unknown, but 3 theories predominantly arise:

1. Intrinsic bone malformation

The classical and most popular theory of premature suture fusion points towards osseous pathology early on in the pregnancy. This is believed to occur either by genetic,[37, 38] metabolic,[39] or pharmaceutical[16] means. In metopic synostosis especially these different etiological factors are all represented. In one reported case a Fibroblast Growth Factor Receptor 1 mutation was shown to be present in metopic synostosis.[40] Lajeunie et al. showed hereditary proof in 5,6% of their cases,[16] with others quoting the autosomal dominant penetration to be 2-5%.[41, 42] Thyroid hormone replacement therapy in case of hypothyroidism has been shown to cause (metopic) craniosynostosis[39, 43, 44] as has been the case with the use of the anticonvulsant drug Valproate during pregnancy.[16, 45]

2. Fetal head constrain

The second theory places the onset of the synostosis in the last phase of the pregnancy, when the head of the fetus can be constrained in the pelvic area. Graham and Smith described two cases of metopic synostosis believed to be the result of limited space for the fetal head (one was jammed in a bicornuate uturus, the other one between the legs of his two siblings).[46] More recently this theory was supported by Smartt et al., proving the principle in a mouse model.[47]

3. Intrinsic brain malformation

The third theory considers the brain to be the main reason behind the onset of craniosynotosis.[48, 49] The malformation of the frontal lobes would thus require only limited space in the anterior cranial vault, therefore providing a more restrained signal to the bone centers causing the suture to fuse prematurely. Findings of neurodevelopmental delays irrespective of corrective cranioplasty have further supported this theory.[50]

There seems to be ample proof for all three theories to be able to safely conclude that the etiology of metopic synostosis is multifactorial.

HISTORY OF TREATMENT

The first surgical correction for craniosynostosis, or cranioplasty, was reputably performed by Dr. L.C. Lane, professor of Surgery at the Cooper Medical College in San Francisco, in 1888.[9, 51] On the request of the mother, he performed a simple removal of the fused suture(s) in a case of microcephlia. The procedure went well, but unfortunately the child died 14 hours after surgery. Largely due to resentment of the godfather of American paediatrics Dr Jacobi, the referral of patients for surgical treatment was halted.[9] It wasn't until 1921 that the first report resurfaced that dealt with the surgical treatment of craniosynotosis, when Mehner published his technique of removing the fused cranial suture.[52] This was to be the method of choice for years to come, while the main problem appeared to be the prevention of early re-fusion of the suture.[35, 53] Matson subsequently published his technical notes on limited strip craniectomy in 6 cases of trigonocephaly in 1960, setting the standard for the next generation of (neuro)surgeons.[54] He commented that surgical correction for metopic synostosis was only of cosmetic value and only worth it if carried out in the first 4 months of life. Two years later Anderson advocated doing a simple cranial vault procedure before the age of 3 months but only if the child was not retarded or suffering from other major anomalies like heart disorders.[8] In 1968 Shillito et al. reported on 519 cranioplasties preformed from January 1929 to December 1966.[35] In the largest series to that date, they stimulated early operative treatment to "provide at minimal risk the best chances for the brain to expand the skull into its normal configuration". This coincided with the publication of the pioneering work of Paul Tessier in 1967, making the surgical treatment of craniosynotosis and its sequelae more common practise.[55]

RECENT EVOLUTIONS OF TREATMENT

There has been one report describing the natural history of trigonocephaly to be self-limiting, although nobody since has noticed the same.[6, 56, 57] Treatment therefore, is surgical. Due to claims of better intellectual outcome, the operative correction is generally performed before the age of one.[7, 33-35, 58-62] Simple suturectomy is nowadays considered to be insufficient to correct the complex three dimensional growth restrictions that result from metopic synostosis.[7, 10, 63-65] Hoffman and Mohr published a paper in 1976 on their technical notes regarding the correction of trigonocephaly, which involved the advancement of the lateral canthal segments of the supraorbital regions.[63] Marchac followed in 1978 with his classic paper on correction of the forehead using the "floating forehead technique" combined with remodelling of the supra orbital bandeau.[64] Several authors have since modified this technique,[10, 12, 13, 33, 34, 58, 66, 67] some with emphasis on the prevention of postoperative temporal hollowing.[68-73] Others have ventured into different directions in their quest to correct these deformities with minimal risk and maximal result. Distraction osteogenesis with conventional screws or with springs has been introduced and has been gaining wider acceptance over the last years, especially with regards to the correction of hypotelorism, even though there has been some debate whether this hypotelorism really needs to be corrected.[74] Some have noted the deformity to persist over the years,[10, 14] while others have adjusted their operative techniques with success.[67, 75, 76] Nevertheless, the role of springs in moving the orbits apart has been explored with success.[77-79] The use of minimal invasive endoscopic surgery techniques is on the rise since the early 90's, but still controversial due to the technical limitations of those procedures (strip craniectomy only), although Hinojosa has recently attempted to address those limitations.[80-84]

EVALUATION OF AESTHETIC RESULTS

Anderson presented the results of 107 cases of metopic and coronal synostosis in 1981, advising "that craniofacial operations for synostosis should be as extensive as necessary'.[7] After that, Freide et al. were one of the first to attempt an aesthetic evaluation of their treatment for metopic synostosis.[10] Their retrospective review of 11 cases consisted of 6 operated and 5 non-operated children with metopic synostosis. Advancement and straightening of supraorbital bone contour was performed in all 6 cases. Three to four years after surgery, the osteotomy lines where hardly found on palpation except temporally where the tongue in groove advancement sometimes yielded slight bone irregularity. They concluded that, since minor characteristics were still present after such a long time, a modification seemed appropriate to enhance restitution of forehead width and morphology of the temporal regions. Cohen et al. noted none or minor irregularities in 53% of their 17 cases in which photographic analysis was done. Their reoperation rate was 18%.[85] Posnick et al. investigated structural improvements of the periorbital region following corrective surgery using CT data in 10 patients, concluding that "anterior cranial vault and lateral orbital wall positions were corrected successfully and remained in good position despite subsequent growth. The orbital hypotelorism, although improved, remained undercorrected".[14] Havlik et al. adjusted their technique based on these same issues of correction of hypotelorism and prevention of temporal hollowing in 10 cases with severe trigonocephaly, using an midline interposition bonegraft and temporal extension graft to reduce these problems.[75] In 2002 Hinojosa commented on their series of 28 cases, grading as high as 85% good to excellent cosmetic results with an average follow-up of a little over 2 years (27 months).[86] Aryan et al. noticed a recurrence of the midline ridge in 3 out of their 39 cases, requiring a reoperation in two.[66] Hilling et al. remarked that results were persistently good over the years if the operation managed to achieve good reposition of the forehead in the first place.[87] Greenberg et al. recently found a 15% reoperation rate in their 50 cases, again mainly for correction of temporal hollowing.[57] Following on from Havlik et al., Selber et al. reviewed their 68 metopic synostosis patients and concluded that preoperative frontal irregularities and reduced preoperative intercanthal distance predisposed to inferior aesthetic outcome, while interpositional bonegrafting reduced the postoperative rate of temporal hollowing.[67, 75]

NEUROPSYCHOLOGICAL DEVELOPMENT

Of all the single suture synostoses, children with metopic synostosis have shown to be linked with the highest percentage of neurodevelopmental problems. Shillito et al., in their 1968 review of 519 cases, noted that "mental retardation was twice as high (4,8%) compared to children with sagittal or coronal synostosis".[35] Anderson in 1981 reported on a retardation rate of 17,9% in their population of trigonocephalies.[7] Different authors have since described neurodevelopmental delays, ranging from 15% to as high as 61%.[58, 66, 88, 89] Many of these problems do not become apparent until the children reach a school going age, where they are positioned into more intellectually demanding surroundings combined with higher expectancies of social interaction.[90]

Elevated intra cranial pressure (ICP) has been linked to a reduction of IQ.[91-93] Levels of 8 to 20% of elevated ICP in single-suture synostosis have been reported.[94-97] Shillito et al. noted an increased ICP in 19% of their 21 metopic cases, 18 of which were operated on. In their series this percentage was second only to the percentage in cases of multiple suture synostoses (41%). They did not however directly measure the pressure: seperation of uninvolved sutures on x-ray, the presence of a beaten copper pattern or papillary edema, and marked irritability (only if it disappeared after surgery) were considered to be signs of elevated ICP.[35] Although some authors have claimed to see no developmental effect whatsoever,[10, 54] IQ inhibitions were reported by several units,[61, 88] while others noticed the effects to largely be at the level of neurodevelopmental disorders.[50, 85, 89, 90, 98-101] Boterro et al. for instance tested 76 children with metopic synostosis and showed developmental delay in 32% of operated children. In the (often milder) unoperated children in their series this was 23%.[98] The fact that an increased prevalence of these delays is also seen in unoperated children supports the theory that they primarily originate in the brain and might not be a direct result of the craniosynostosis acting as a growth restrictor.[50, 102, 103]

AIM OF THIS THESIS

This thesis aims to give a global overview of different aspects of metopic synostosis. The study investigated epidemiological, genetic, surgical, radiological, as well as psychological aspects of this entity:

In *Chapter 2*, a multicenter study is presented in which the increase in prevalence of metopic synostosis is described, which was seen between 1997 and 2006 in 7 different craniofacial units irrespective of each other, spread out all over Europe.

Chapter 3 reports on the genetic background of a child with trigonocephaly who was shown to posses the Pro250Arg genetic mutation, making it the world's first published case of Muenke syndrome with a metopic synostosis.

Chapter 4 focuses on the (lack of) periorbital growth after corrective surgery for metopic synostosis.

Chapter 5 gives further insight into the processes behind the origin of temporal hollowing, so often present at a later age in these patients.

Chapter 6 provides a closer view on the intracranial abnormalities seen in children with metopic synostosis.

Chapter 7 investigates the dysfunction of the frontal lobes of the brain as expressed by neurodevelopmental disorders like Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder.

The following hypotheses were formulated at the start of this research:

1. The incidence of metopic synostosis is increasing.
2. There is no need to surgically correct the hypotelorism seen in relation to metopic synostosis.
3. Postoperative temporal hollowing is the result of a temporal bone growth restriction.
4. The frontal lobes of the brain are malformed in metopic synostosis.
5. Metopic synostosis is related to frontal lobe dysfunction.

REFERENCES

1. Welcker H. Untersugungen uber wachstum und bau des menschlichen Schädels. Leipzig: Engelmann, 1862.
2. Weinzweig J, Kirschner RE, Farley A, et al. Metopic synostosis: Defining the temporal sequence of normal suture fusion and differentiating it from synostosis on the basis of computed tomography images. Plast Reconstr Surg 2003: 112: 1211-8.
3. Vu HL, Panchal J, Parker EE, Levine NS, Francel P. The timing of physiologic closure of the metopic suture: a review of 159 patients using reconstructed 3D CT scans of the craniofacial region. J Craniofac Surg 2001: 12: 527-32.
4. Virchow R. Über den Cretinismus, namentlich in Franken, und über pathologische Schädelformen. Verh Phys Med Gesell 1851: 2: 230-70.
5. David DJ, Posswillo D, Sompson D. The craniosynostosis: causes, natural history and management. Springer-Verlag, 1992.
6. Zumpano MP, Carson BS, Marsh JL, Vanderkolk CA, Richtsmeier JT. Three-dimensional morphological analysis of isolated metopic synostosis. Anat Rec 1999: 256: 177-88.
7. Anderson FM. Treatment of coronal and metopic synostosis: 107 cases. Neurosurgery 1981: 8: 143-9.
8. Anderson FM, Gwinn JL, Todt JC. Trigonocephaly. Identity and surgical treatment. J Neurosurg 1962: 19: 723-30.
9. Cohen M. Craniosynostosis; diagnosis, evaluation and management. New York: Raven Press, 1986.
10. Friede H, Alberius P, Lilja J, Lauritzen C. Trigonocephaly: clinical and cephalometric assessment of craniofacial morphology in operated and nontreated patients. Cleft Palate J 1990: 27: 362-7; discussion 68.
11. Strickler M., van der Meulen J., Rahael B., Mazolla R. Craniofacial malformations. Edinburgh, London, Melbourne, New York: Churchill Livingston, 1990.
12. Sadove AM, Kalsbeck JE, Eppley BL, Javed T. Modifications in the surgical correction of trigonocephaly. Plast Reconstr Surg 1990: 85: 853-8.
13. Eppley BL, Sadove AM. Surgical correction of metopic suture synostosis. Clin Plast Surg 1994: 21: 555-62.

14. Posnick JC, Lin KY, Chen P, Armstrong D. Metopic synostosis: quantitative assessment of presenting deformity and surgical results based on CT scans. Plast Reconstr Surg 1994: 93: 16-24.
15. Kolar JC, Salter EM. Preoperative anthropometric dysmorphology in metopic synostosis. Am J Phys Anthropol 1997: 103: 341-51.
16. Lajeunie E, Le_Merrer M, Marchac D, Renier D. Syndromal and nonsyndromal primary trigonocephaly: analysis of a series of 237 patients. American Journal of Medical Genetics 1998: 75: 211-5.
17. Wikipedia. http://en.wikipedia.org/wiki/Cognitive_neuroscience.
18. Phrenology. http://www.phrenology.org/.
19. Ward J. The Student's Guide to Cognitive Neuroscience. Psychology Press, 2006.
20. Günther FK. Rassengeschichte des hellenischen und des römischen Volkes. Mit einem Anhang: Hellenische und römische Köpfe nordischer Rasse. Munich: Lehmanns Verlag, 1929.
21. Günther FK. Rassengeschichte des hellenischen und des römischen Volkes. Mit einem Anhang: Hellenische und römische Köpfe nordischer Rasse. Pähl: Verlag Hohe Warte, 1959.
22. Shapiro R. Craniosynostosis in the Talmud. Radiology 1989: 172: 230.
23. Hippocrates. On injuries of the head. Med Classics 1938: 3: 145-60.
24. Dimopoulos VG, Machinis TG, Fountas KN, Robinson JS. Head injury management algorithm as described in Hippocrates' "peri ton en cephali traumaton". Neurosurgery 2005: 57: 1303-5; discussion 03-5.
25. Puech B, Puech PF, Tichy G, Dhellemmes P, Cianfarani F. Craniofacial dysmorphism in Mozart's skull. J Forensic Sci 1989: 34: 487-90.
26. Puech PF, Puech B, Tichy G. Identification of the cranium of W.A. Mozart. Forensic Sci Int 1989: 41: 101-10.
27. Massimi L, Di Rocco C. Mozart: a metropolitan legend with pediatric neurosurgical implications. Childs Nerv Syst 2006: 22: 451-3.
28. Czorny A, Ricbourg B. [No, Mozart was not trigonocephalic]. Ann Chir Plast Esthet 1992: 37: 321-8.
29. Hauser G, Kritscher H. Brief communication: the skull attributed to Mozart--craniosynostosis or not? Am J Phys Anthropol 1994: 94: 263-8.

30. Alderman BW, Fernbach SK, Greene C, Mangione EJ, Ferguson SW. Diagnostic practice and the estimated prevalence of craniosynostosis in Colorado. Arch Pediatr Adolesc Med 1997: 151: 159-64.
31. Selber J, Reid RR, Chike-Obi CJ, et al. The changing epidemiologic spectrum of single-suture synostoses. Plast Reconstr Surg 2008: 122: 527-33.
32. Genitori L, Cavalheiro S, Lena G, Dollo C, Choux M. Skull base in trigonocephaly. Pediatr Neurosurg 1991: 17: 175-81.
33. DiRocco C, Caldarelli M, Ceddia A, Iannelli A, Velardi F. [Craniostenosis. Analysis of 161 cases surgically treated during the first year of life]. Minerva Pediatr 1989: 41: 393-404.
34. Dhellemmes P, Pellerin P, Lejeune JP, Lepoutre F. Surgical treatment of trigonocephaly. Experience with 30 cases. Childs Nerv Syst 1986: 2: 228-32.
35. Shillito J, Jr., Matson DD. Craniosynostosis: a review of 519 surgical patients. Pediatrics 1968: 41: 829-53.
36. Boulet SL, Rasmussen SA, Honein MA. A population-based study of craniosynostosis in metropolitan Atlanta, 1989-2003. Am J Med Genet A 2008: 146A: 984-91.
37. Wilkie AO. Craniosynostosis: genes and mechanisms. Hum Mol Genet 1997: 6: 1647-56.
38. Wilkie AO, Bochukova EG, Hansen RM, et al. Clinical dividends from the molecular genetic diagnosis of craniosynostosis. Am J Med Genet A 2007: 143A: 1941-9.
39. Penfold JL, Simpson DA. Premature craniosynostosis-a complication of thyroid replacement therapy. J Pediatr 1975: 86: 360-3.
40. Kress W, Petersen B, Collmann H, Grimm T. An unusual FGFR1 mutation (fibroblast growth factor receptor 1 mutation) in a girl with non-syndromic trigonocephaly. Cytogenet Cell Genet 2000: 91: 138-40.
41. Frydman M, Kauschansky A, Elian E. Trigonocephaly: a new familial syndrome. Am J Med Genet 1984: 18: 55-9.
42. Hennekam RC, Van den Boogaard MJ. Autosomal dominant craniosynostosis of the sutura metopica. Clin Genet 1990: 38: 374-7.
43. Johnsonbaugh RE, Bryan RN, Hierlwimmer R, Georges LP. Premature craniosynostosis: A common complication of juvenile thyrotoxicosis. J Pediatr 1978: 93: 188-91.

44. Rasmussen SA, Yazdy MM, Carmichael SL, et al. Maternal thyroid disease as a risk factor for craniosynostosis. Obstet Gynecol 2007: 110: 369-77.
45. Ardinger HH, Atkin JF, Blackston RD, et al. Verification of the fetal valproate syndrome phenotype.
Am J Med Genet 1988: 29: 171-85.
46. Graham JM, Jr., Smith DW. Metopic craniostenosis as a consequence of fetal head constraint: two interesting experiments of nature.
Pediatrics 1980: 65: 1000-2.
47. Smartt JM, Jr., Karmacharya J, Gannon FH, et al. Intrauterine fetal constraint induces chondrocyte apoptosis and premature ossification of the cranial base.
Plast Reconstr Surg 2005: 116: 1363-9.
48. Riemenschneider PA. Trigonocephaly. Radiology 1957: 68: 863-5.
49. Moss ML. The pathogenesis of premature cranial synostosis in man.
Acta Anat (Basel) 1959: 37: 351-70.
50. Kapp-Simon KA, Speltz ML, Cunningham ML, Patel PK, Tomita T. Neurodevelopment of children with single suture craniosynostosis: a review.
Childs Nerv Syst 2007: 23: 269-81.
51. Lane LC. Pioneer craniectomy for relief of mental inbecility due to premature suture closure and microcephalus. JAMA 1892: 18: 49-50.
52. Mehner A. Beitrage zu den Augenveranderungen bei der Schadeldeformität des sog. Turmschädels mit besonderer Berucksichtigung des Rontgenbildes.
Klin Monatsbl Augenheilkd 1921: 61: 204.
53. Anderson FM, Johnson FL. Craniosynostosis; a modification in surgical treatment. Surgery 1956: 40: 961-70.
54. Matson DD. Surgical treatment of congenital anomalies of the coronal and metopic sutures. Technical note. J Neurosurg 1960: 17: 413-17.
55. Tessier P. [Total facial osteotomy. Crouzon's syndrome, Apert's syndrome: oxycephaly, scaphocephaly, turricephaly]. Ann Chir Plast 1967: 12: 273-86.
56. Dominguez R, Oh KS, Bender T, Girdany BR. Uncomplicated trigonocephaly. A radiographic affirmation of conservative therapy.
Radiology 1981: 140: 681-8.
57. Greenberg BM, Schneider SJ. Trigonocephaly: surgical considerations and long term evaluation. J Craniofac Surg 2006: 17: 528-35.
58. Collmann H, Sorensen N, Krauss J. Consensus: trigonocephaly.
Childs Nerv Syst 1996: 12: 664-8.

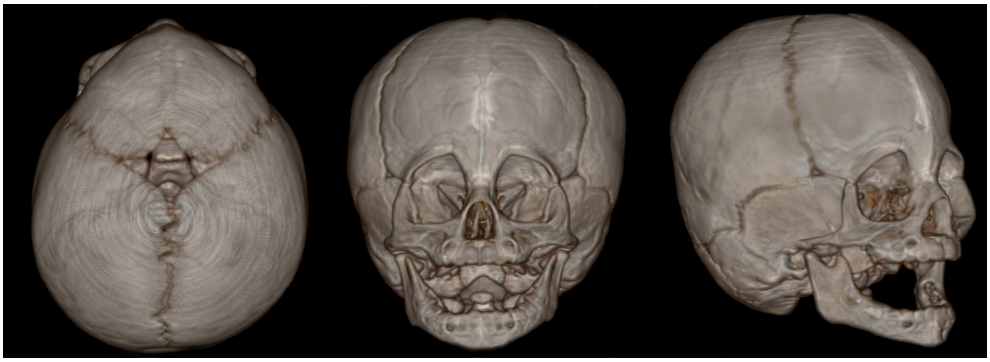
59. Marchac D, Renier D, Broumand S. Timing of treatment for craniosynostosis and facio-craniosynostosis: a 20-year experience.
Br J Plast Surg 1994: 47: 211-22.
60. McCarthy JG, Epstein F, Sadove M, Grayson B, Zide B. Early surgery for craniofacial synostosis: an 8-year experience.
Plast Reconstr Surg 1984: 73: 521-33.
61. Renier D, Lajeunie E, Arnaud E, Marchac D. Management of craniosynostoses. Childs Nerv Syst 2000: 16: 645-58.
62. Whitaker LA, Bartlett SP, Schut L, Bruce D. Craniosynostosis: an analysis of the timing, treatment, and complications in 164 consecutive patients.
Plast Reconstr Surg 1987: 80: 195-212.
63. Hoffman HJ, Mohr G. Lateral canthal advancement of the supraorbital margin. A new corrective technique in the treatment of coronal synostosis.
J Neurosurg 1976: 45: 376-81.
64. Marchac D. Radical forehead remodeling for craniostenosis.
Plast Reconstr Surg 1978: 61: 823-35.
65. Delashaw JB, Persing JA, Park TS, Jane JA. Surgical approaches for the correction of metopic synostosis. Neurosurgery 1986: 19: 228-34.
66. Aryan HE, Jandial R, Ozgur BM, et al. Surgical correction of metopic synostosis. Childs Nerv Syst 2005: 21: 392-8.
67. Selber J, Reid RR, Gershman B, et al. Evolution of operative techniques for the treatment of single-suture metopic synostosis. Ann Plast Surg 2007: 59: 6-13.
68. Albin RE, Hendee RW, Jr., O'Donnell RS, Majure JA. Trigonocephaly: refinements in reconstruction. Experience with 33 patients.
Plast Reconstr Surg 1985: 76: 202-11.
69. Marsh JL, Schwartz HG. The surgical correction of coronal and metopic craniosynostoses. J Neurosurg 1983: 59: 245-51.
70. Oh AK, Greene AK, Mulliken JB, Rogers GF. Prevention of temporal depression that follows fronto-orbital advancement for craniosynostosis.
J Craniofac Surg 2006: 17: 980-5.
71. Persing JA, Mayer PL, Spinelli HM, Miller L, Criscuolo GR. Prevention of "temporal hollowing" after fronto-orbital advancement for craniosynostosis.
J Craniofac Surg 1994: 5: 271-4.

72. Matic DB, Kim S. Temporal hollowing following coronal incision: a prospective, randomized, controlled trial.
Plast Reconstr Surg 2008: 121: 379e-85e.
73. Webster K, Dover MS, Bentley RP. Anchoring the detached temporalis muscle in craniofacial surgery. J Craniomaxillofac Surg 1999: 27: 211-3.
74. Fearon JA, Kolar JC, Munro IR. Trigonocephaly-associated hypotelorism: is treatment necessary? Plast Reconstr Surg 1996: 97: 503-9; discussion 10-11.
75. Havlik RJ, Azurin DJ, Bartlett SP, Whitaker LA. Analysis and treatment of severe trigonocephaly. Plast Reconstr Surg 1999: 103: 381-90.
76. McCarthy JG, Bradley JP, Longaker MT. Step expansion of the frontal bar: correction of trigonocephaly. J Craniofac Surg 1996: 7: 333-5.
77. Lauritzen CG, Davis C, Ivarsson A, Sanger C, Hewitt TD. The evolving role of springs in craniofacial surgery: the first 100 clinical cases.
Plast Reconstr Surg 2008: 121: 545-54.
78. Maltese G, Tarnow P, Lauritzen CG. Spring-assisted correction of hypotelorism in metopic synostosis. Plast Reconstr Surg 2007: 119: 977-84.
79. Davis C, Lauritzen CG. Frontobasal suture distraction corrects hypotelorism in metopic synostosis. J Craniofac Surg 2009: 20: 121-4.
80. Hinojosa J, Esparza J, Garcia-Recuero I, Romance A. [Endoscopically assisted fronto-orbitary correction in trigonocephaly]. Cir Pediatr 2007: 20: 33-8.
81. Murad GJ, Clayman M, Seagle MB, et al. Endoscopic-assisted repair of craniosynostosis. Neurosurg Focus 2005: 19: E6.
82. Barone CM, Jimenez DF. Endoscopic craniectomy for early correction of craniosynostosis. Plast Reconstr Surg 1999: 104: 1965-73; discussion 74-5.
83. Jimenez DF, Barone CM. Endoscopic craniectomy for early surgical correction of sagittal craniosynostosis. J Neurosurg 1998: 88: 77-81.
84. Hinojosa J, Esparza J, Munoz MJ. Endoscopic-assisted osteotomies for the treatment of craniosynostosis. Childs Nerv Syst 2007: 23: 1421-30.
85. Cohen SR, Maher H, Wagner JD, et al. Metopic synostosis: evaluation of aesthetic results. Plast Reconstr Surg 1994: 94: 759-67.
86. Hinojosa J, Esparza J, Munoz MJ, et al. Surgical treatment of trigonocephalies and associated hypoteleorbitism. Neurocirugia (Astur) 2002: 13: 437-45.
87. Hilling DE, Mathijssen IM, Vaandrager JM. Aesthetic results of fronto-orbital correction in trigonocephaly. J Craniofac Surg 2006: 17: 1167-74.

88. Oi S, Matsumoto S. Trigonocephaly (metopic synostosis). Clinical, surgical and anatomical concepts.
Childs Nerv Syst 1987: 3: 259-65.
89. Sidoti EJ, Jr., Marsh JL, Marty-Grames L, Noetzel MJ. Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 1996: 97: 276-81.
90. Kapp-Simon KA. Mental development and learning disorders in children with single suture craniosynostosis. Cleft Palate Craniofac J 1998: 35: 197-203.
91. Inagaki T, Kyutoku S, Seno T, et al. The intracranial pressure of the patients with mild form of craniosynostosis. Childs Nerv Syst 2007: 23: 1455-9.
92. Shimoji T, Tomiyama N. Mild trigonocephaly and intracranial pressure: report of 56 patients. Childs Nerv Syst 2004: 20: 749-56.
93. Siddiqi SN, Posnick JC, Buncic R, et al. The detection and management of intracranial hypertension after initial suture release and decompression for craniofacial dysostosis syndromes.
Neurosurgery 1995: 36: 703-8; discussion 08-9.
94. Renier D, Sainte-Rose C, Marchac D. Intracranial pressure in craniosynostose. In Marchac D, ed. Craniofacial Surgery. Berlin: Springer-Verlag, 1987.
95. Tamburrini G, Caldarelli M, Massimi L, Santini P, Di Rocco C. Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Childs Nerv Syst 2005: 21: 913-21.
96. Eide PK, Helseth E, Due-Tonnessen B, Lundar T. Assessment of continuous intracranial pressure recordings in childhood craniosynostosis.
Pediatr Neurosurg 2002: 37: 310-20.
97. Gault DT, Renier D, Marchac D, Jones BM. Intracranial pressure and intracranial volume in children with craniosynostosis.
Plast Reconstr Surg 1992: 90: 377-81.
98. Bottero L, Lajeunie E, Arnaud E, Marchac D, Renier D. Functional outcome after surgery for trigonocephaly.
Plastic and Reconstructive Surgery 1998: 102: 952-8; discussion 59-60.
99. Kapp-Simon KA, Figueroa A, Jocher CA, Schafer M. Longitudinal assessment of mental development in infants with nonsyndromic craniosynostosis with and without cranial release and reconstruction.
Plast Reconstr Surg 1993: 92: 831-9; discussion 40-1.

100. Kuper BD. Behaviour Patterns Among Children With a History of Metopic Synostosis. 2000: Doctor of Philosophy: 100.
101. Warschausky S, Angobaldo J, Kewman D, et al. Early development of infants with untreated metopic craniosynostosis.
Plast Reconstr Surg 2005: 115: 1518-23.
102. Aldridge K, Kane AA, Marsh JL, et al. Relationship of brain and skull in pre- and postoperative sagittal synostosis. J Anat 2005: 206: 373-85.
103. Aldridge K, Marsh JL, Govier D, Richtsmeier JT. Central nervous system phenotypes in craniosynostosis. J Anat 2002: 201: 31-9.

C H A P T E R T W O



The Increase of Metopic Synostosis; a pan-European Observation

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ABSTRACT

Background: Metopic synostosis is thought to have an incidence of about 1 in 15.000 births. Traditionally this makes it the third most frequent single-suture craniosynostosis, after scaphocephaly (1 in 4200-8500) and plagiocephaly (1 in 11.000). Our units have, independently from each other, noted a marked increase in the number of metopic synostosis over the recent years.

Methods: pan-European, retrospective epidemiological study on the number of cases with metopic synostosis born between January 1, 1997 and January 1, 2006. This number was compared to the prevalence of scaphocephaly, the most frequently seen craniosynostosis.

Results: In the 7 units a total of 3240 craniosynostosis were seen from 1997 until 2006. Forty-one percent (n = 1344) of those were sagittal synostosis, and 23% were metopic synostosis (756). There was a significant increase of the absolute number as well as of the percentage of metopic synostosis over these years (regression analysis, $p = 0.017$, $R^2 = 0.578$) as opposed to a non-significant increase in the percentage of sagittal synostosis ($p > 0.05$, $R^2 = 0.368$). The most remarkable increase occurred around 2000-2001, with the average of metopics being 20.1% from 1997-2000 and 25.5% from 2001-2005 (Independent t-test, $p = 0.002$). The sagittal synostosis showed a smaller and non-significant increase in the same years: from 39.9% in 1997-2000 leading up to 42.5% in 2001-2005 (Independent t-test, $p > 0.05$).

Conclusions: The number of metopic synostosis has significantly increased over the reviewed period in all of our units, both in absolute numbers as in comparison to the total number of craniosynostosis.

BACKGROUND

Premature closure of the metopic suture results in a growth restriction of the frontal bones, which leads to a skull malformation known as trigonocephaly. Typically, a wedge shaped forehead is seen due to the supra orbital recession, which is combined with hypotelorism. The volume of the anterior cranial fossa is reduced, even though the total skull volume is often unrestricted.[1] Metopic synostosis is linked with a high level of neurodevelopmental delays. Theories on the etiology of these delays range from a reduced volume of the anterior cranial fossa to intrinsic malformations of the brain.[2-6]

Premature closure of the sagittal suture results in a growth restriction in the coronal direction, which leads to a skull malformation known as scaphocephaly. The skullshape is elongated and narrow with a ridge running along the sagittal suture (hence the reference to the hull and keel of a boat). Sagittal synostosis is thought to be the most benign form of synostosis, although marked developmental delays have recently been reported.[5-7]

Metopic synostosis is thought to have an incidence of about 1 in 15.000 live births.[8] Traditionally this makes it the third most frequent single-suture craniosynostosis, after scaphocephaly (1 in 4200[9]-8500[10]) and plagiocephaly (1 in 11.000[11, 12]). A limited number of authors have reported on the prevalence of craniosynostosis. The relative percentages derived from several publications reporting on 100 cases or more are listed in table I. In recent years our units have independently from each other, noticed a rise in the number of metopic synostosis cases, relative to other synostotic skull malformations.

Authors	Year	Total number of cases	Sagittal	Metopic
Anderson & Geiger[12]	1965	204	57%	10%
Shillito & Matson[13]	1968	519	55%	3%
Hunter & Rudd[9]	1977	370	55%	4%
Montaut & Stricker[15]	1977	158	22%	8%
Marchac & Renier[16]	1994	1247	39%	10%
Breugem & Zeeman[17]	1999	154	29%	11%
Kadri & Mawla[18]	2004	116	22%	24%

Table I. Prevelance numbers of sagittal and metopic synostosis quoted in the literature. Percentages compared to total number of craniosynostosis

MATERIAL AND METHODS

This was a pan-European, retrospective epidemiological study on the number of cases with metopic synostosis born between January 1, 1997, and January 1, 2006. Diagnosis of metopic synostosis was made by a combination of physical (the presence of hypotelorism and a wedge-shaped forehead due to a marked bilateral supra-orbital and temporal retrusion) and radiographic examination (hypotelorism, bilateral highrise of the sphenoid wing, teardrop shaped orbits and an increased bony deposit in the metopic suture area). The number of metopic synostosis was compared to the number of sagittal synostosis, the most frequently seen craniosynostosis, and data were analysed using Linear Regression and Independent t-tests.

RESULTS

Between January 1, 1997 and January 1, 2006, a total number of 3240 cases of craniosynostosis were seen in the seven participating units (table II). Forty-one percent of those were sagittal synostosis (1344), and 23% were metopic synostosis (756). There was a significant increase of the absolute number as well as of the percentage of metopic synostosis over these years (regression analysis, $p = 0.017$, $R^2 = 0.578$) as opposed to a non-significant increase in the percentage of sagittal synostosis ($p > 0.05$, $R^2 = 0.368$). The most remarkable increase occurred around 2000-2001, with the average of metopics being 20.1% from 1997-2000 and 25.5% from 2001-2005 (Independent t-test, $p = 0.002$). The sagittal synostosis showed a more limited and therefore non-significant increase in the same years: from 39.9% in 1997-2000 leading up to 42.5% in 2001-2005 (Independent t-test, $p > 0.05$) (fig 1).

	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
Children's Hospital Birmingham (UK)										
Metopics	2	3	3	6	7	9	21	16	12	79
Sagittal	0	6	5	7	15	12	19	21	17	102
Total synostosis	14	22	16	22	35	29	62	55	49	304
Radcliffe Infirmary Oxford (UK)										
Metopics	3	11	6	10	9	7	9	8	11	74
Sagittal	13	13	13	17	15	23	13	16	15	138
Total synostosis	32	43	49	57	36	48	40	39	40	384
Alderhey Hospital Liverpool (UK)										
Metopics	4	9	6	8	13	5	9	10	10	74
Scaphoids	3	7	9	8	11	9	13	13	9	82
Total	19	28	26	26	30	18	27	29	24	227
Hospital Materno-Infantil 12 de Octubre Madrid (ES)										
Metopics	3	4	4	0	5	4	3	10	10	43
Sagittal	12	15	16	20	21	25	9	15	25	158
Total synostosis	25	36	29	27	31	41	21	36	44	290
University Hospital Maastricht (NL)										
Metopics	1	0	1	0	1	2	3	1	3	12
Sagittal	1	0	0	0	1	0	2	1	1	6
Total synostosis	2	0	1	0	3	2	5	3	4	20
Hôspital Necker-Enfants Malades Paris (FR)										
Metopics	39	31	38	38	41	50	33	52	30	352
Sagittal	62	69	65	62	72	83	75	70	71	629
Total synostosis	156	147	160	169	172	196	158	172	159	1489
Sophia Children's Hospital Rotterdam (NL)										
Metopics	8	13	4	9	17	17	21	16	17	122
Sagittal	18	25	34	25	17	26	32	23	29	229
Total synostosis	37	62	61	46	60	58	79	60	63	526
Total numbers										
Metopics	60	71	62	71	93	94	99	113	93	756
Sagittal	109	135	142	139	152	178	163	159	167	1344
Total synostosis	285	338	342	347	367	392	392	394	383	3240
Total percentages										
Metopics	21%	21%	18%	20%	25%	24%	25%	29%	24%	23%
Sagittal	38%	40%	42%	40%	41%	45%	42%	40%	44%	41%

Table II. Absolute numbers and percentages per participating craniofacial unit.

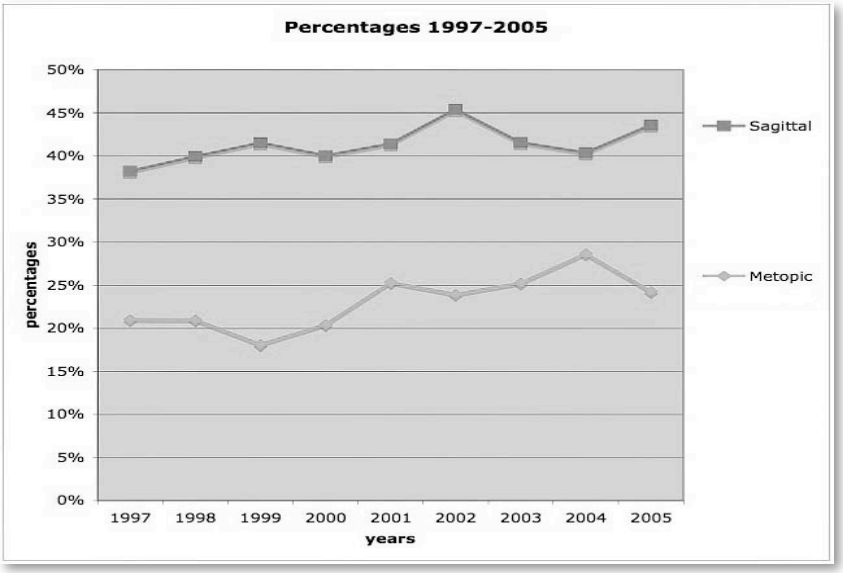


Fig 1. Percentages of sagittal and metopic synostosis seen between jan 1997 and jan 2006

DISCUSSION

The incidence of craniosynostosis has always been uncertain. Usually authors relate the prevalence seen in their unit to the regional birth rate, which leaves the un-referred cases unaccounted for. Raised awareness of craniosynostosis because of, for instance, media attention or the internet, could therefore possibly explain the steady overall rise in craniosynostosis cases over the years. Another factor could be, for instance, the increase in average paternal age at time of conception, which has shown to be of influence on the incidence of syndromic synostosis like Crouzon, Apert's and Pfeiffer syndromes.[13, 14] In the Netherlands, for instance, the number of fathers over the age of 40 years increased from 9% in 1990 to 11% in the year 2000.[15]

If any of these theories would be true, then how can we explain the difference seen between the significant rise of metopic synostosis compared to the total number of craniosynostosis as opposed to the non-significant rise of sagittal synostosis compared with this total? One would expect a raised awareness to have an effect on all forms of craniosynostosis and especially on the milder phenoptypes. Because this argument is also valid for the other theories, none of the factors mentioned above seem to have a plausible explanation for the significant rise in metopics as

opposed to the non-significant rise in sagittal synostosis.
Several midline defects (such as cleft lip and palate or neural tube defects) have been linked to the maternal homocysteine metabolism, which is influenced by intake levels of folic acid.[16, 17] Periconceptual supplementation of folic acid has been proven to play a role in the prevention of these defects.[18, 19] Because metopic synostosis is considered to be a midline defect, an investigation into the role of folic acid on its etiology would be a logical and interesting next step. Periconceptual folic acid supplementation (400µg to 500µg per day, from 4 weeks before until 8 weeks after conception) however, is advocated in the Netherlands since 1998.[20] Around one third of women follow this advice. In France though the periconceptual supplementation of folic acid is not advocated. As a result the majority of women do not have additional folic acid intake beyond their normal dietary intake.[21] Despite this difference, the same increase was seen in France as in the Netherlands, which makes the influence of folic acid on this process less likely.

Limitations of this study

The units involved in this review do not claim to see and treat all conceivable cases of craniosynostosis in their respective countries or indeed in the whole of Europe. Absolute figures regarding incidence of these types of craniosynostosis can therefore not be concluded from these data.

Conclusion

The number of metopic synostosis has significantly increased over the reviewed period of 9 years (from 1997 to 2006) in all of our units, both in absolute numbers as in comparison to the total number of craniosynostosis seen by us. The most remarkable increase occurred in 2001. This increase in metopic synostosis remains unexplained.

Remarks

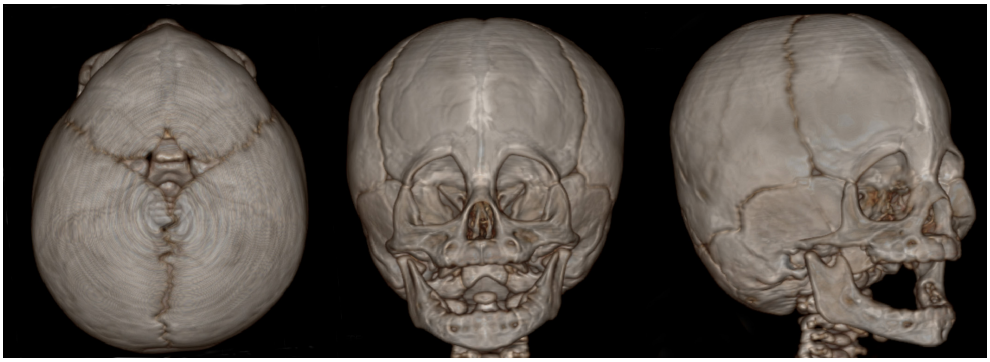
The results of this study have previously been presented at the XII Biennial International Congress of the International Society of CranioFacial Surgery (ISCFS) on August 25 2007 in Salvador, Bahia, Brazil.

REFERENCES

1. Gault DT, Renier D, Marchac D, Ackland FM, Jones BM. Intracranial volume in children with craniosynostosis. J Craniofac Surg 1990: 1: 1-3.
2. Shimoji T, Shimabukuro S, Sugama S, Ochiai Y. Mild trigonocephaly with clinical symptoms: analysis of surgical results in 65 patients. Childs Nerv Syst 2002: 18: 215-24.
3. Wilke TA, Gubbels S, Schwartz J, Richman JM. Expression of fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3) in the developing head and face. Dev Dyn 1997: 210: 41-52.
4. Tamburrini G, Caldarelli M, Massimi L, Santini P, Di Rocco C. Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Childs Nerv Syst 2005: 21: 913-21.
5. Speltz ML, Kapp-Simon KA, Cunningham M, Marsh J, Dawson G. Single-suture craniosynostosis: a review of neurobehavioral research and theory. J Pediatr Psychol 2004: 29: 651-68.
6. Kapp-Simon KA, Speltz ML, Cunningham ML, Patel PK, Tomita T. Neurodevelopment of children with single suture craniosynostosis: a review. Childs Nerv Syst 2007: 23: 269-81.
7. Kapp-Simon KA. Mental development and learning disorders in children with single suture craniosynostosis. Cleft Palate Craniofac J 1998: 35: 197-203.
8. Lajeunie E, Le Merrer M, Marchac D, Renier D. Syndromal and nonsyndromal primary trigonocephaly: analysis of a series of 237 patients. Am J Med Genet 1998: 75: 211-5.
9. Hunter AG, Rudd NL. Craniosynostosis. I. Sagittal synostosis: its genetics and associated clinical findings in 214 patients who lacked involvement of the coronal suture(s). Teratology 1976: 14: 185-93.
10. David JD, Poswillo D, Simpson D. The craniosynostoses: causes, natural history and management. New York: Springler, 1982.
11. Cohen MM. Craniosynostosis: diagnosis, evaluation, and management. New York: Raven Press, 1986.
12. Cohen M. Craniosynostosis: diagnosis, evaluation, and management. New York: Oxford Press, 2000.
13. Glaser RL, Broman KW, Schulman RL, et al. The paternal-age effect in Apert syndrome is due, in part, to the increased frequency of mutations in sperm. Am J Hum Genet 2003: 73: 939-47.

14. Glaser RL, Jiang W, Boyadjiev SA, et al. Paternal origin of FGFR2 mutations in sporadic cases of Crouzon syndrome and Pfeiffer syndrome. Am J Hum Genet 2000: 66: 768-77.
15. Latten J. Steeds later vader. 2002.
16. Steegers-Theunissen RP, Boers GH, Trijbels FJ, Eskes TK. Neural-tube defects and derangement of homocysteine metabolism. N Engl J Med 1991: 324: 199-200.
17. Wong WY, Eskes TK, Kuijpers-Jagtman AM, et al. Nonsyndromic orofacial clefts: association with maternal hyperhomocysteinemia. Teratology 1999: 60: 253-7.
18. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. Jama 2001: 285: 2981-6.
19. Wilcox AJ, Lie RT, Solvoll K, et al. Folic acid supplements and risk of facial clefts: national population based case-control study. Bmj 2007: 334: 464.
20. Verhoef P, Katan MB. [Uncertain effects of folic acid on disorders other than neural-tube defects]. Ned Tijdschr Geneeskd 2006: 150: 1439-42.
21. Chevrier C, Perret C, Bahuau M, et al. Fetal and maternal MTHFR C677T genotype, maternal folate intake and the risk of nonsyndromic oral clefts. Am J Med Genet A 2007: 143: 248-57.

C H A P T E R T H R E E



Trigonocephaly in Muenke Syndrome

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ABSTRACT

Saethre-Chotzen syndrome is caused by mutations in the TWIST gene at 7p21.2. However, Muenke et al. [(1997); Am J Hum Genet 91: 555-564] described a new subgroup carrying the Pro250Arg mutation in the fibroblast growth factor receptor (FGFR) 3 gene on 4p16. Uni or bi-coronal synostosis appears to be the main clinical finding in both syndromes. We observed Trigonocephaly as a new manifestation in Muenke syndrome. As a consequence we routinely perform mutation analysis of the FGFR1, 2 and 3 genes in children with non-syndromic trigonocephaly.

Key words: Muenke syndrome; Saethre-Chotzen syndrome; trigonocephaly; metopic synostosis; craniosynostosis; new phenotype; FGFR3 Pro250Arg mutation

INTRODUCTION

The Saethre-Chotzen syndrome [1, 2] typically presents with a uni or bicoronal craniosynostosis, facial asymmetry, ptosis and hand anomalies, consisting of brachydactyly, cutaneous syndactyly between digits 2 and 3 and clinodactyly of digit 5.[3-5] Saethre-Chotzen syndrome families, with an autosomal dominant inheritance pattern, show complete penetrance with variable expression. This syndrome is due to TWIST gene mutations at 7p21.2.[6-8] In 1997 Muenke et al.[9] described a new subgroup of Saethre-Chotzen patients (called Muenke syndrome), carrying the Pro250Arg mutation in the fibroblast growth factor receptor (FGFR 3) gene at 4p16. This is an autosomal dominant trait with reduced penetrance and very variable expressivity. The main clinical finding in both syndromes appears to be the coronal synostosis. Due to its variability in expression, Muenke syndrome is only distinguishable from Saethre-Chotzen syndrome by genetic analysis. Here we describe trigonocephaly as a new clinical finding in Muenke syndrome.

CLINICAL REPORT

The patient was born after an uncomplicated pregnancy as the second child of non-consanguineous healthy parents. Because of metopic suture prominence he was referred to our craniofacial unit. We saw the typical manifestations resulting from a premature fusion of the metopic suture. The wedge shaped forehead was accentuated by bilateral supra-orbital retrusions with a marked hypotelorism. A deformational occipital plagiocephaly was also noted. A 3D-CT scan (fig. 1, 2) confirmed the diagnosis. The boy underwent a fronto-supraorbital advancement and remodelling at 11 months. Cranioplasty and postoperative recovery passed without complications. However, during follow-up he was diagnosed with a hearing impairment. Physiotherapy evaluation showed a motor delay of approximately 5 months.

As a standard procedure blood was taken for DNA-analysis. Direct sequence analysis of exons 7, 10, 13, 15 and 19 of the FGFR3 gene showed the presence of the Pro250Arg mutation. After genetic counselling, DNA analysis of the parents was performed. The Pro250Arg mutation was also present in the mother with barely detectable sequelae of a bicoronal synostosis.

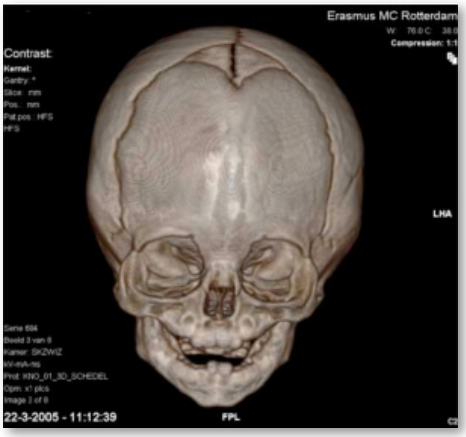

Fig 1. Preoperative 3D CT scan showing typical wedged forehead and hypotelorism.

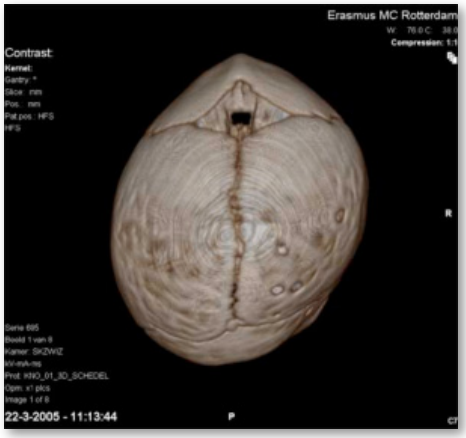

Fig 2. Preoperative 3D CT scan showing metopic synostosis and positional plagiocephaly.

DISCUSSION

In the Saethre-Chotzen and Muenke syndromes the most prominent finding is the craniosynostosis of one or both coronal sutures. However, in 1992 a case of Saethre-Chotzen with trigonocephaly was presented by Cristofori and Filippi.[10] Their diagnostic conclusion was based on clinical and neuroradiological findings alone (using a 1975 diagnostic criteria frequency list for Saethre-Chotzen syndrome).[11] On review one is left with considerable doubt whether this diagnosis was justified. Nowadays, genetic analysis can be used to support clinical observations. Others have already advocated the routine use of FGFR mutational screening in children with non-syndromic trigonocephaly.[12, 13] The finding of the FGFR3 Pro250Arg mutation in this case of trigonocephaly supports that view.

REFERENCES

1. Chotzen F. Eine eigenartige familiäre entwicklungsstörung. (Akrocephalosyndactylie, dysostosis craniofacialis und hypertelorismus). Monatsschr Kinderheilk 1933: 55: 97-122.
2. Saethre. Ein beitrag zum Turmschädelproblem (patho-genese, erblichkeit und symptomatologie). Dtsch Z Nerven-heilk 1930: 117: 533-55.
3. Anderson PJ, Hall CM, Evans RD, Hayward RD, Jones BM. The hands in Saethre-Chotzen syndrome. J Craniofac Genet Dev Biol 1996: 16: 228-33.
4. de Heer IM, de Klein A, van den Ouweland AM, et al. Clinical and genetic analysis of patients with Saethre-Chotzen syndrome. Plast Reconstr Surg 2005: 115: 1894-902; discussion 903-5.
5. El Ghouzzi V, Lajeunie E, Le Merrer M, et al. Mutations within or upstream of the basic helix-loop-helix domain of the TWIST gene are specific to Saethre-Chotzen syndrome. Eur J Hum Genet 1999: 7: 27-33.
6. Brueton LA, van Herwerden L, Chotai KA, Winter RM. The mapping of a gene for craniosynostosis: evidence for linkage of the Saethre-Chotzen syndrome to distal chromosome 7p. J Med Genet 1992: 29: 681-5.
7. Reardon W, McManus SP, Summers D, Winter RM. Cytogenetic evidence that the Saethre-Chotzen gene maps to 7p21.2. Am J Med Genet 1993: 47: 633-6.
8. Rose CS, King AA, Summers D, et al. Localization of the genetic locus for Saethre-Chotzen syndrome to a 6 cM region of chromosome 7 using four cases with apparently balanced translocations at 7p21.2. Hum Mol Genet 1994: 3: 1405-8.
9. Muenke M, Gripp KW, McDonald-McGinn DM, et al. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. Am J Hum Genet 1997: 60: 555-64.
10. Cristofori G, Filippi G. Saethre-Chotzen syndrome with trigonocephaly. Am J Med Genet 1992: 44: 611-4.
11. Pantke OA, Cohen MM, Jr., Witkop CJ, Jr., et al. The Saethre-Chotzen syndrome. Birth Defects Orig Artic Ser 1975: 11: 190-225.
12. Kress W, Petersen B, Collmann H, Grimm T. An unusual FGFR1 mutation (fibroblast growth factor receptor 1 mutation) in a girl with non-syndromic trigonocephaly. Cytogenet Cell Genet 2000: 91: 138-40.

13. Tartaglia M, Bordoni V, Velardi F, et al. Fibroblast growth factor receptor mutational screening in newborns affected by metopic synostosis. Childs Nerv Syst 1999: 15: 389-93; discussion 93-4.

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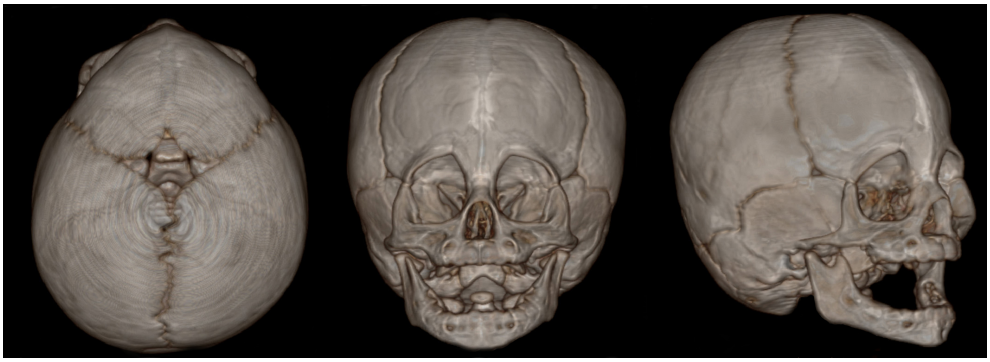

Bitemporal Depressions following Cranioplasty for Trigonocephaly

a long term evaluation of (supra) orbital growth in 92 cases

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ABSTRACT

Introduction: Long-term results after cranioplasty for trigonocephaly often show bitemporal depressions and a residual hypotelorism. Both findings fuel the perception that the growth of the periorbital region and the forehead as a whole continues to be restricted, even after correction. The aim of this study is to evaluate the growth process of the peri-orbital region after correction for trigonocephaly in the long term.

Materials & Methods: From 1986 to 2004, 123 patients underwent a cranioplasty for the correction of trigonocephaly. Cephalometric analysis was performed on the radiographs taken at presentation and on the last available radiograph before the age of 6 years (92 posteroanterior and 93 lateral cephalograms). Cephalic landmarks were used to analyse the growth of the forehead: Mo (medial orbital wall), Lo (lateral orbital wall), Losp (crosspoint between lateral orbital wall and sphenoid) and Eu (most lateral point of the skull). Due to lack of standardized cephalograms, growth ratios were used instead of absolute numbers.

Results: The Eu-Eu growth rate was higher than the Lo-Lo rate, which in its turn surpassed the Losp-Losp rate. An initial undercorrection of the hypotelorism was noted, followed by an increased limited auto-correction. A higher Mo-Mo growth rate was noted in the group operated after one year of age.

Conclusions: Increased inter-orbital growth accounts for an autocorrection of the residual hypotelorism. The growth rate of the antero-temporal area (Losp) was shown to be the lowest, which could explain the bitemporal depressions so often seen after a fronto-supra-orbital cranioplasty.

Keywords: Trigonocephaly, forehead growth, long-term results, bitemporal depressions, hypotelorism

INTRODUCTION

Premature ossification of the metopic suture results in a growth restriction of the frontal bones, which leads to a skull malformation known as trigonocephaly. Typically there is a wedge shaped forehead due to the bony bilateral supra orbital retrusion, which is combined with a mild hypotelorism (fig 1). Traditionally, concerns about neurobehavioural development, increased intracranial pressure as well as aesthetic considerations have prompted surgical intervention of this congenital malformation.[1, 2] The operative correction is indicated before the age of 12 months in order to prevent permanent developmental restrictions.[3-5]

At this time the intracranial volume is restored by means of a supra orbital and frontal bone remodelling and advancement. In the National Craniofacial Center at the Sophia Childrens Hospital of the Erasmus Medical Center (Rotterdam, The Netherlands), an average of 70 cranioplasties are performed each year. The number of trigonocephalies is increasing, rising up to 30% of single suture synostosis in 2005. All of these patients are entered into a follow-up scheme to monitor their growth and development until they are fully-grown.

On reflection of the long-term cosmetic results in our trigonocephalic group, bitemporal depressions seemed to be a common finding and a residual hypotelorism was also sometimes noted.[6] Both findings fuelled the perception that the growth of the periorbital region and the forehead as a whole continued to be restricted, even after correction. Other authors have previously reached this same conclusion[4, 6, 7] although autocorrection of hypotelorism has also been reported.[3]

The aim of this study was to evaluate the growth process of the peri-orbital region after correction for trigonocephaly in the long term.

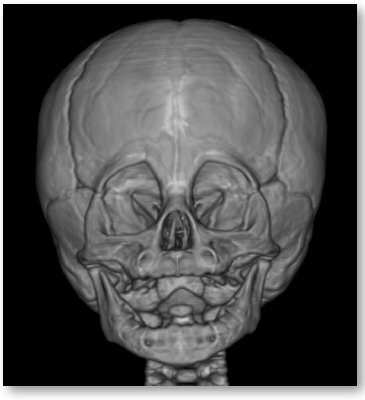


Fig 1. Metopic synostosis resulting in trigonocephaly (wedge-shaped forehead, supraorbital retrusion, hypotelorism)

Fig 2. Frontal and supraotbital osteotomy lines in cranioplasty for trigonocephaly

MATERIALS AND METHODS

Surgical technique

The standard technique for the correction of trigonocephaly performed at the National Craniofacial Center in the Sophia Childrens Hospital of the Erasmus Medical Center (Rotterdam, The Netherlands) is as follows: after the skin incision the skin and galeal layer on one side and periosteal layer on the other side are mobilised separately. The frontal bone is removed in one piece, followed by the supra-orbital bar (fig 2, fig 3a). An open wedge osteotomy is performed in the mid-line of this supra-orbital bar after which the angle between the orbits is corrected (fig 3b), increasing the inter-orbital distance in the process without the use of an interpositional bone graft. A unicortical posterior bone graft is used though to stabilise the mid-line open wedge osteotomy (fig 3c). Immediately lateral to the lateral orbital wall a closed wedge osteotomy is done which facilitates an increase of the fronto-temporal angle (fig 3d,e). The temporal fragments of the bar are then advanced in a tongue in groove fashion and subsequently fixed in their new position. The frontal bone is cut in the mid-line and remodelled to fit to the new shape of the supra-orbital bar. This usually results in the two halves being switched, followed by a 120 degrees rotation, leaving both coronal sutures in a parallel position to the supra-orbital osteotomy line (fig 4). With this procedure the volume of the anterior vault is restored and the morphological malformations are corrected. Early on in this series fixation was achieved by metal wiring but from 1999 onwards only absorbable sutures were used (2/0 and 3/0 vicryl®, polyglactine 910, Johnson & Johnson).

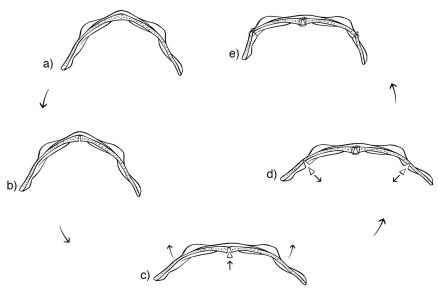


Fig 3. (a-e) Supraorbital remodeling

Fig 4. Skull after supraorbital advancement and remodeling

Cephalometric analysis

From 1986 to 2004, 123 patients underwent such a cranioplasty in our unit for the correction of trigonocephaly. The median age at operation was 11 months (mean = 12,6, range 4-188,5), whereas 70% had the surgery performed before the age of one year. According to our follow-up protocol, posteroanterior and lateral cephalograms are made at three months post cranioplasty, and subsequently at two-yearly intervals from the age of 2 until 6. Thereafter the interval increases to three years up to completion of growth at 18 years.

As the supra-orbital area is thought to cease growing after the age of 6, cephalometric analysis was performed on the postoperative radiographs available up to that age.[7-10] Loss or poor quality reduced the number of radiographs suitable for analysis and 92 posteroanterior and 93 lateral cephalograms were found to meet the inclusion criteria. All cephalograms were scanned and digitized using an Epson Expression 1680 Pro scanner at 300dpi. After reviewing the cephalometric literature a number of specific landmarks related to the forehead were identified (table I).[9, 11-19]

Landmark	Description	Source of normative value
Mo	Most medial point of medial orbital wall	Waitzman et al (1992)[32]
Lo	Most lateral point of lateral orbital wall	Waitzman et al (1992)[32]
LoSp	Junction of lateral orbital wall and sphenoid wing	Basyouni, Nanda (2000)[26]
Eu	Euryon: most lateral point of the cranium	Waitzman et al (1992)[32]
Eca	Most anterior point of neurocranium	Friede et al (1986)[34]
Ecp	Most posterior point of neurocranium	Friede et al (1986)[34]
Ecs	Most superior point of neurocranium	Friede et al (1986)[34]
Ba	Basion: most postroinferior point on anterior margin of foramen magnum	Friede et al (1986)[34]
Ratios	Lo-Lo/Eu-Eu	
	Lo-Lo/Mo-Mo	
	Eu-Eu/Mo-Mo	
	Eca-Ecp/Ecs-Ba	

Table 1. Landmarks on the facial skeleton

In order to determine the lateral expansion rate of the forehead over time, measurements needed to focus on interorbital distance and width of the forehead. The cephalic landmarks around the orbit (Mo, Lo, Losp) and the most lateral points of the skull (Eu) were used to analyse this on the PA radiographs (fig 5). As there were no standardized cephalograms made due to the age at which most of these patients presented themselves, we resolved to the use of growth ratios. The ratio's were compared to normal values as described by Waitzman and Basyouni.[20, 21]

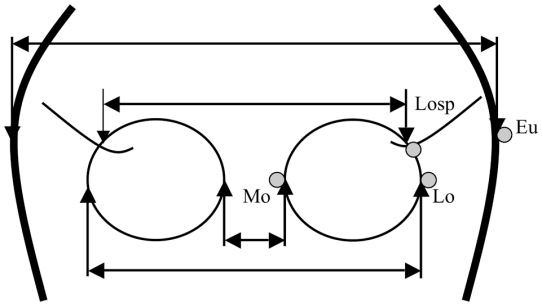


Fig 5. Schematic drawing of radiographic landmarks used (see table 1).

With the use of a cephalometric computerprogram (Viewbox 3.0 by dHal Software, Kifissia, Greece, 2003) all resulting landmarks were marked on each of the cephalograms. An automated cephalometric analysis was performed to evaluate the growth of the forehead after cranioplasty. To check the inter-observer variability, one-third of the cephalograms were examined by three different consultants (an orthodontist, a maxillofacial surgeon and a craniofacial plastic surgeon) after which Intraclass Correlation Coefficients (ICC) were determined (table II). Of the 123 patients in this study, only 115 patient files were available for evaluation. Factors related to the growth of the forehead (like gender, age at operation and skull circumference) were noted in this review.

Distance	ICC	Standard error
Eu-Eu	0.96	0.25
Losp-Losp	0.87	0.24
Lo-Lo	0.66	0.20
Mo-Mo	0.57	0.18

Table 2. Interclass Correlation Coefficient ($0 < ICC \leq 1$)

RESULTS

Growth ratios

Growth of the forehead and peri-orbital region was evaluated using the following ratios:

a) Eu-Eu/Lo-Lo growth ratio (fig 6)

This ratio, representing the relation between the widest point of the skull and the most lateral point of the orbit, was smaller than normal within the study group at the age of 1 year (1,50 as opposed to the normal value of 1,67). It increased towards the normal curve over the years reaching near normal levels at the age of 4 (1,59 compared to 1,61). From 4 to 6 years the difference increased again with the trigonocephaly curve falling down to 1,53 and the normal curve regaining height at 1,62.

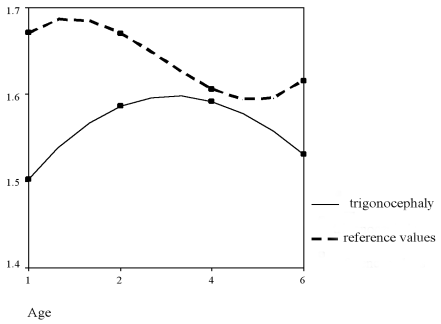


Fig 6. Eu-Eu/Lo-Lo growth ratio

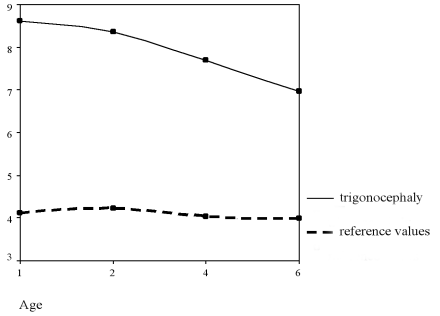


Fig 7. Lo-Lo/Mo-Mo growth ratio

b) Lo-Lo/Mo-Mo growth ratio (fig 7)

At the age of 1 with 8,6 this ratio in our trigonocephaly study group was more than double the normal of 4,1. The normal curve remained at a fairly stable level over the first 6 years, whereas our study group curve showed a steady decline in that same period.

c) Eu-Eu/Mo-Mo growth ratio (fig 8)

Both the trigonocephaly as well as the normal curve showed similar patterns, although the former did lie at a considerable higher level. The ratio was 12,9 at the age of 1 year (as opposed to 6,9 in normal subjects) and regressed towards the norm towards the end of our study period, settling down at 10,7 at 6 years, where 6,4 is normal.

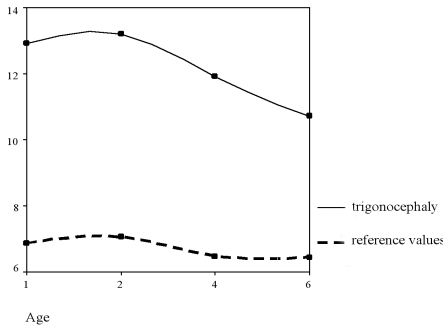


Fig 8. Eu-Eu/Mo-Mo growth ratio

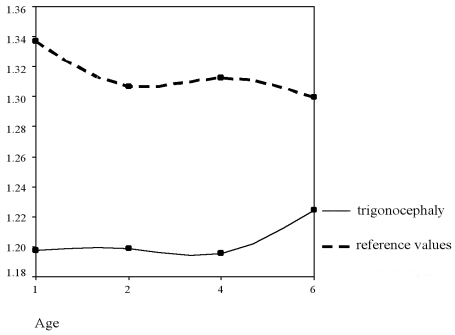


Fig 9. Eca-Ecp/Ecs-Ba growth ratio

d) Eca-Ecp/Ecs-Ba growth ratio (fig 9)

This is the only growth ratio derived from the lateral skull radiographs. As growth in the anterior-posterior axis of the skull (Eca-Ecp) was depicted against the growth in the inferior to superior axis, a fairly horizontal line was seen running parallel to, but just below the normal line. Where the normal ratio was running along between 1,30-1,34, the trigonocephalic ratio did not top the 1,22 mark (fig 9). This difference of 11% at the age of 1 year reduced over time to 6% at 6 years.

e) Losp

The junction of the lateral orbital wall and the sphenoid wing is very well distinguishable on posteroanterior radiographs. This makes it a stable and reproducible marker for periorbital growth evaluation. However, after being unsuccessful in finding normal reference values we could not use this point in relation to normal growth curves. A comparison to the other marker points, however, revealed a lower lateral expansion rate than both Eu and Lo, making it the slowest laterally growing marker point in our study group (fig 10).

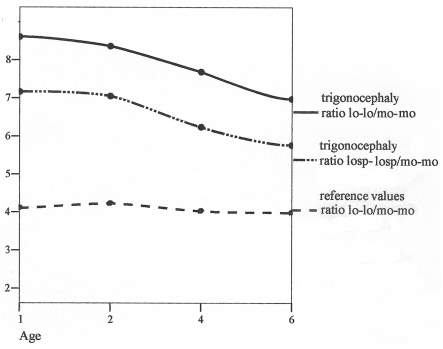


Fig 10. Losp-Losp/Mo-Mo growth ratio compared to Lo-Lo/Mo-Mo growth ratio

Timing of operation

The patients were operated at a mean age of 54 weeks of age (range 17 to 221 weeks). In 71,9% of cases the cranioplasty was performed according to protocol, which requires surgery to be performed between 9 and 12 months of age. 93% of patients were operated within 1,5 years (78 weeks) of age. Late surgery was due to late referral. Direct postoperatively all growth ratios differed significantly compared to normal, regardless of age at time of surgery ($p \leq 0{,}02$).
When comparing the growth in the group of children operated before the age of 1 to the ones operated at a later age, a significantly smaller (is a more normal) Eu-Eu/Mo-Mo ratio was noted in the latter group ($p \leq 0{,}001$). The skull circumference was not influenced by the metopic suture synostosis and stayed within normal range after surgery regardless of age at time of surgery.

Comorbidity

Analysis of patient notes (n = 115) revealed a presence of co-morbidity like polydactyly, hemifacial microsomia or a ventricular septal defect, in 57 cases (49,6%). The majority of those (n = 32, 27,6%) presented with only one other anomaly. The presence ($p \leq 0{,}001$) and number ($p \leq 0{,}001$) of additional congenital malformations had no significant effect on growth ratios.

Childbirth

There was a strong male predominance (82%) in our patient group, consistent with previous reports in the literature.[22-25] In 57% (66 cases) the pregnancy concluded with an uncomplicated vaginal delivery. In 11% (13 cases) the delivery was performed by using either forceps or vacuum extraction (the national rate in 2002 was 10%).[26] A caesarean section however, was necessary in 26% (30 cases), almost half of which were due to a slowly progressing delivery. This rate appeared to be almost double that of the normal population in the Netherlands (at 14% in 2002).[26]

Intraclass Correlation Coefficients

Intraclass Correlation Coefficients (ICC) determined to evaluate the inter-observer variability were found to be sufficient (table 2). The borderline values of the Lo and especially Mo ICC's are a logical result of their position along a vertical curvature, making a consistent judgement of these landmarks very difficult. The Mo ICC was further dampened by the repetitive but same error made by one of the consultants.

DISCUSSION

Landmarks and growth ratios

The aim of this study was to evaluate the growth process of the peri-orbital region after correction for trigonocephaly. In order to properly evaluate the growth process of the forehead in lateral direction one should rely on standardized landmarks visible on posteroanterior radiographs. The relative lack of well defined and stable landmarks make the cephalic evaluation of these radiographs difficult. Nevertheless, many landmarks have been described in the frontal and peri-orbital region.[11, 13, 15-17, 19] The landmarks used in this study (on the medial and lateral orbital wall, and on the most lateral skull border) were clearly recognizable in both pre and postoperative radiographs (table I, fig 5). Unfortunately we were unable to determine clear and reproducible landmarks in one of the areas we were especially interested in: the temporal area immediately lateral and posterior to the lateral orbital walls. This was mainly due to the presence of bone regeneration in these areas following the osteotomies, obscuring any landmarks that might have been clear before surgery. On the other hand, the landmark Losp, which lies on the anterior border of this area, was shown to be very reliable due to its nature of being a junction between two radiographic lines, namely the lateral orbital wall and the sphenoid wing. Growth ratios of Losp therefore, were considered to be indicators of the antero-temporal growth pattern and subsequently used in this study as marker for the growth of the temporal region.[19]

Orbital growthrate

Several authors have advocated the use of a interorbital bone graft to correct the hypotelorism associated with metopic synostosis.[27, 28] Havlik et al. even expanded up to a level where a reduction of the medial orbital wall was needed to achieve normal interorbital width.[28] McCarthy et al. suggested using a midline step advancement instead of a bone graft to achieve the same results.[29] Fearon et al. argued that expansion of the supraorbital bar would merely widen that bar and would not affect the true interorbital distance.[30]They noted in their group of 16 patients a statistically significant improvement in hypotelorism postoperatively that was greater than expected from normal growth curves.

As explained earlier, in our study group the hypotelorism was only dealt with by remodelling of the supraorbital area (fig 3a-e). This resulted in an undercorrection of the interorbital width in the early postoperative phase. Remarkably though, the

Lo-Lo/Mo-Mo growth ratio showed a steady decline over the years. Analysis of the ratios involving the medial orbital wall (Mo) revealed a persistently higher Mo-Mo growth ratio when compared to the fairly normal Lo-Lo and Eu-Eu rates, indicating a limited auto-correction of the hypotelorism in the years following the cranioplasty. This finding supports the aesthetic evaluation our trigonocephaly patients previously performed by Hilling et al..[6]

In the initial postoperative phase, the lateralisation of the lateral orbital wall was found to be slower than the increase in head width (fig 6). However, this difference slowly diminished over the first few years due to a catch up of the growth rate of the lateral orbital wall. Although the bi-orbital width continued to increase in the years thereafter, its lateral orbital wall growth rate did not manage to keep up with the rate at which the head widens, thus resulting in a relative restriction of the width of the peri-orbital forehead region.

Lo-Lo/Mo-Mo growth ratio clearly showed Mo-Mo expanding at a quicker pace than Lo-Lo (fig 7). As a result, the orbits slowly became less wide over the years while the interorbital width increased.

Bitemporal depressions

The occurrence of temporal depressions is a common finding following fronto-supra-orbital cranioplasty. Do temporal depressions also occur in unoperated trigonocephaly patients? The very limited number of reports on the natural history of trigonocephaly are not conclusive regarding the cosmetic results of a non-surgical treatment.[22, 23, 31-33] Friede et al. noted narrow foreheads in both operated and unoperated patients at 4 years of age[22] and others reported on spontaneous return of interorbital width to normal limits in non-operated cases.[23]

The postoperative occurrence of temporal depressions then is not only related to the cranioplasty, nor is it restricted to surgical correction of metopic suture synostosis alone. It is also observed after advancement cranioplasty for plagio- or brachycephaly.[3, 4, 25] It is therefore unlikely that these depressions are solely the result of restricted growth of the frontal bones in a lateral direction. Performing a double osteotomy in the temporal region to release the supra-orbital bandeau (fig 2) could very well have an inhibiting effect on the lateral expansion of the temporal area.

In order to understand the growth patterns of the temporal area, one should look at the Eu, Lo and Losp landmarks. In our study group the Eu-Eu growth rate was

higher than the Lo-Lo rate, which in its turn surpassed the Losp-Losp rate. In the lateral orbital region therefore, the antero-temporal region was shown to have the slowest rate of lateral expansion, which might account for the temporal depressions.

Overall skull growth rate

Gratz et al. followed 57 children for more than 12 months after surgery and found no circumferential growth restriction of the reshaped calvaria after surgical correction of craniosynostosis.[35] This was confirmed by the data in our study group, where the skull circumference appeared unaffected by the metopic suture synostosis, before as well as after surgery. Analysis of the Eca-Ecp/Ecs-Ba growth ratio however, revealed a slightly shorter skull than normal, which improved over time. It is conceivable that the coronal suture displacement, which occurs during surgery, has an inhibiting effect on the subsequent antero-posterior growth, resulting in a shorter skull.

Timing of operation

There have been several reports advocating corrective surgery before the age of one.[4-6] Most of our postoperative growth ratios though were not affected by the age at which the corrective surgery was performed. Only the Eu-Eu/Mo-Mo ratio was significantly smaller in the group operated after one year of age, suggesting a higher Mo-Mo growth rate. This indicates a quicker normalisation of the relative undercorrection of the hypotelorism when compared to the children operated before the age of one year.

Conclusions

The increase in interorbital width (Mo-Mo) occurs at a higher rate than normal. This results in an autocorrection of the residual hypotelorism after corrective cranioplasty for trigonocephaly. The rate at which the interorbital width increases also surpasses that of the expansion of the head width (Eu-Eu), which in turn supersedes the bi-orbital width growth rate (Lo-Lo). The growth rate of the antero-temporal area (Losp) was shown to be the lowest, which could explain the bitemporal depressions so often seen after a fronto-supra-orbital cranioplasty.

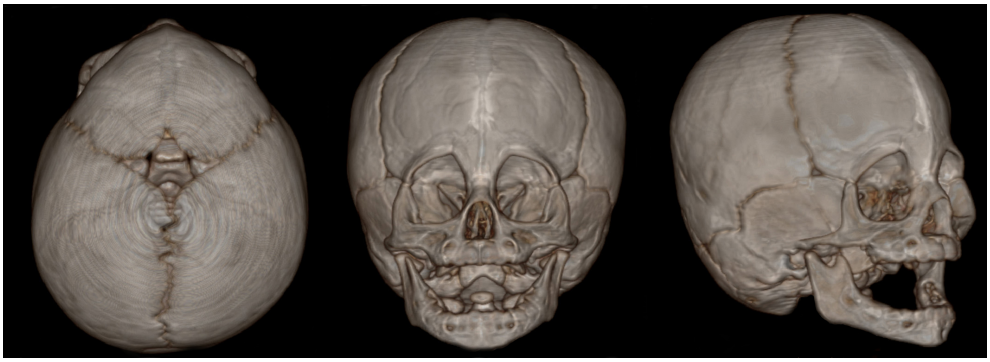
REFERENCES

1. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. J Neurosurg 1982: 57: 370-7.
2. Renier D, Marchac D. Craniofacial surgery for craniosynostosis: functional and morphological results. Ann Acad Med Singapore 1988: 17: 415-26.
3. McCarthy JG, Epstein F, Sadove M, Grayson B, Zide B. Early surgery for craniofacial synostosis: an 8-year experience. Plast Reconstr Surg 1984: 73: 521-33.
4. Whitaker LA, Bartlett SP, Schut L, Bruce D. Craniosynostosis: an analysis of the timing, treatment, and complications in 164 consecutive patients. Plast Reconstr Surg 1987: 80: 195-212.
5. Marchac D, Renier D, Broumand S. Timing of treatment for craniosynostosis and facio-craniosynostosis: a 20-year experience. Br J Plast Surg 1994: 47: 211-22.
6. Hilling DE, Mathijssen IM, Mulder PG, Vaandrager JM. Long-term aesthetic results of frontoorbital correction for frontal plagiocephaly. J Neurosurg 2006: 105: 21-5.
7. Whitaker LA, Morales L, Jr., Farkas LG. Aesthetic surgery of the supraorbital ridge and forehead structures. Plast Reconstr Surg 1986: 78: 23-32.
8. Farkas LG, Posnick JC, Hreczko TM, Pron GE. Growth patterns in the orbital region: a morphometric study. Cleft Palate Craniofac J 1992: 29: 315-8.
9. Farkas LG, Posnick JC, Hreczko TM. Anthropometric growth study of the head. Cleft Palate Craniofac J 1992: 29: 303-8.
10. Farkas LG, Posnick JC. Growth and development of regional units in the head and face based on anthropometric measurements. Cleft Palate Craniofac J 1992: 29: 301-2.
11. Posnick JC, Lin KY, Chen P, Armstrong D. Metopic synostosis: quantitative assessment of presenting deformity and surgical results based on CT scans. Plast Reconstr Surg 1994: 93: 16-24.
12. Lux CJ, Conradt C, Burden D, Komposch G. Transverse development of the craniofacial skeleton and dentition between 7 and 15 years of age: a longitudinal postero-anterior cephalometric study. Eur J Orthod 2004: 26: 31-42.
13. Kelly KM, Littlefield TR, Pomatto JK, Manwaring KH, Beals SP. Cranial growth unrestricted during treatment of deformational plagiocephaly. Pediatr Neurosurg 1999: 30: 193-9.
14. Ferrario VF, Sforza C, Poggio CE, Schmitz JH. Facial volume changes during normal human growth and development. Anat Rec 1998: 250: 480-7.

15. Carr M, Posnick JC, Pron G, Armstrong D. Cranio-orbito-zygomatic measurements from standard CT scans in unoperated Crouzon and Apert infants: comparison with normal controls. Cleft Palate Craniofac J 1992: 29: 129-36.
16. Bartlett SP, Grossman R, Whitaker LA. Age-related changes of the craniofacial skeleton: an anthropometric and histologic analysis. Plast Reconstr Surg 1992: 90: 592-600.
17. Athanasiou AvdM. Posteroanterior (frontal) cephalometry. London: Mosby-Wolfe, 1995.
18. Athanasiou AE, Miethke R, Van Der Meij AJ. Random errors in localization of landmarks in postero-anterior cephalograms. Br J Orthod 1999: 26: 273-84.
19. Athanasiou AE, Hack B, Enemark H, Sindet-Pedersen S. Transverse dentofacial structure of young men who have undergone surgical correction of unilateral cleft lip and palate: a posteroanterior cephalometric study. Int J Adult Orthodon Orthognath Surg 1996: 11: 19-28.
20. Waitzman AA, Posnick JC, Armstrong DC, Pron GE. Craniofacial skeletal measurements based on computed tomography: Part II. Normal values and growth trends. Cleft Palate Craniofac J 1992: 29: 118-28.
21. Basyouni AA NS. An atlas of transverse dimensions of the face. Michigan: Needham press, 2000.
22. Friede H, Alberius P, Lilja J, Lauritzen C. Trigonocephaly: clinical and cephalometric assessment of craniofacial morphology in operated and nontreated patients. Cleft Palate J 1990: 27: 362-7; discussion 68.
23. Dominguez R, Oh KS, Bender T, Girdany BR. Uncomplicated trigonocephaly. A radiographic affirmation of conservative therapy. Radiology 1981: 140: 681-8.
24. Dhellemmes P, Pellerin P, Lejeune JP, Lepoutre F. Surgical treatment of trigonocephaly. Experience with 30 cases. Childs Nerv Syst 1986: 2: 228-32.
25. Anderson FM. Treatment of coronal and metopic synostosis: 107 cases. Neurosurgery 1981: 8: 143-9.
26. Kwee A. Caesarean section in the Netherlands. Policy, prevention and long-term consequences 2005.
27. Sadove AM, Kalsbeck JE, Eppley BL, Javed T. Modifications in the surgical correction of trigonocephaly. Plast Reconstr Surg 1990: 85: 853-8.
28. Havlik RJ, Azurin DJ, Bartlett SP, Whitaker LA. Analysis and treatment of severe trigonocephaly. Plast Reconstr Surg 1999: 103: 381-90.
29. McCarthy JG, Bradley JP, Longaker MT. Step expansion of the frontal bar: correction of trigonocephaly. J Craniofac Surg 1996: 7: 333-5.
30. Fearon JA, Kolar JC, Munro IR. Trigonocephaly-associated hypotelorism: is treatment necessary? Plast Reconstr Surg 1996: 97: 503-9; discussion 10-11.
31. Ousterhout DK, Peterson-Falzone SJ. Long-term follow-up on a case of untreated trigonocephaly. Cleft Palate J 1990: 27: 72-5.

32. Hunter AG, Rudd NL, Hoffmann HJ. Trigonocephaly and associated minor anomalies in mother and son. J Med Genet 1976: 13: 77-9.
33. Hinojosa J, Esparza J, Munoz MJ, et al. Surgical treatment of trigonocephalies and associated hypoteleorbitism. Neurocirugia (Astur) 2002: 13: 437-45.
34. Friede H, Figueroa AA, Naegele ML, et al. Craniofacial growth data for cleft lip patients infancy to 6 years of age: potential applications. Am J Orthod Dentofacial Orthop 1986: 90: 388-409.

C H A P T E R F I V E



On the Origin of Bitemporal Hollowing

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INTRODUCTION

Trigonocephaly results from a premature ossification of the metopic suture. Inhibited lateral growth of the frontal bones leads to the typical wedge shaped forehead and bilateral supra orbital retrusion, which is combined with a mild hypotelorism (fig 1). The volumetric restrictions can be corrected by performing a fronto-supra-orbital advancement.[1, 2] This cranioplasty is thought to be indicated before the age of 12 months in order to prevent permanent intellectual restrictions due to the restricted intracranial volume.[3-5]

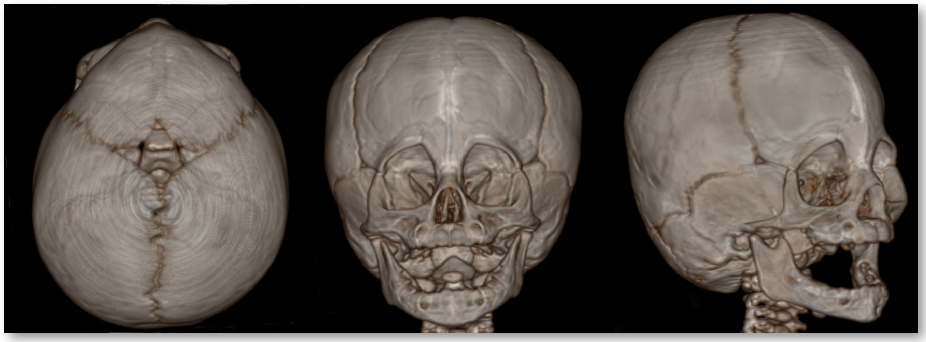

Fig 1. Typical trigonocephaly with triangular forehead, supraorbital retrusion, teardrop-shaped orbits and hypotelorism

Bitemporal hollowing is a common occurrence after surgical correction of metopic or coronal synostosis.[6-12] The hollowing is usually located just lateral and slightly cranial to the lateral apex of the eyebrow. Theories on its etiology focus either on bone or on soft tissue. Iatrogenic damage to the temporal bone for instance could result from the two osteotomies that are performed in that area in a parallel horizontal plane in order to mobilise the supraorbital bandeau (fig 2). The choice of operative technique could result in an underestimation of the lateral expansion needed to correct the initial dysmorphology. Some for instance suggested to increase the intraorbital distance by using an interpositional bonegraft, as a modification of the original description of the supraorbital bar remodelation.[9, 13-15] Furthermore, the posterior edge of the forehead in the temporal region could end up not extending sufficiently backwards enough to support or fill the temporal area, leaving a temporal depression.[6, 7] Finally, an intrinsic inhibition of the lateral growth expansion of the frontal bones could, even despite a faultless corrective procedure, eventually lead to the same temporal hollowing.[12]

Soft tissue etiology mainly focuses on the potential devascularisation of the temporal muscles following the mobilisation in order to get access to the temporal bones, which could result in muscle atrophy and loss of volume.[8] Alternatively, if after mobilisation of the muscle, its cranial border would be insufficiently re-attached it could end up in a more caudal position, thus rendering the muscles unable to fill the temporal area. Atrophy of the superficial temporal fat pad could be another explanation for the appearance of these depressions.[16]

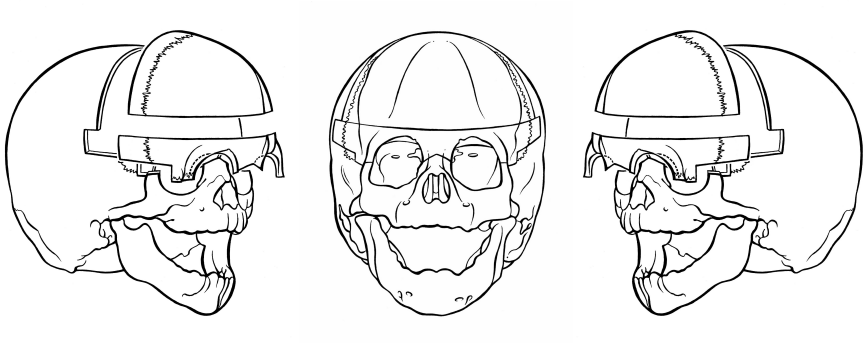

Fig 2. Osteotomy design for corrective cranioplasty for trigonocephaly

In order to determine whether the postoperative temporal hollowing is of bony or soft tissue origin, we conducted a study comparing periorbital bony growth with visual outcome following cranioplasty for metopic synostosis.

Materials and Methods

Patient characteristics

Case notes of patients with non-syndromic trigonocephaly who were treated surgically at our department between 1972 and 2004 were reviewed. Of these 184 patients, 6 were excluded because of the use of a non conventional operation technique and 11 because of incomplete medical files.

The following inclusion criteria were used for the photographic and radiographic panel assessment:

1. Complete treatment including follow up was done at the Sophia Children's Hospital,
2. Standardised postoperative AP photograph and PA cephalogram were available,
3. Both photograph and cephalogram were taken on the same day (to prevent interference by growth [17-20]) and at least 1 year postoperatively.

Of the 167 patients, 134 did not qualify according to these criteria, leaving only 33 to be included into this study. When multiple follow up moments were done, the most recent data were used.

The average age at operation was 11 months (mean 10,8 months, range 4-20 months), whereas 76% had the surgery performed before the age of 1 year. The average age at follow up was 38 months (mean 37,8 range 16-111 months).

Photographic assessment

Two medically trained panel members, neither of whom performed surgery in any of the children, independently evaluated the AP photographs on the presence and level of temporal hollowing. Scores of 0 (normal), 1 (moderate deformity), and 2 (severe deformity) were assigned and the average of both scores was used in the statistical analysis. [21]

Radiological assessment: cephalograms

Cephalometric measurements were done for all 33 patients. Due to difficulties in persistently achieving standardised cephalograms as a result of the age at which most of these patients were presented, growth ratios were used instead of absolute distances.[22] To determine the lateral growth ratios of the forehead, measurements were focused on interorbital distance and width of the forehead (table I). A number of specific landmarks related to the forehead were identified.[12, 19, 22-32] Two cephalic landmarks around the orbit (the medial orbital wall [Mo] and the crosspoint between the lateral orbital wall and the sphenoid [LoSp]) were used to measure the temporal growth (Table I, fig 3).[12]

In 18 of our 33 cases the cephalograms had previously been analyzed using an Epson Expression 1680 Pro scanner (Epson Inc, Long Beach, CA) at 300 dots per

Landmark	Description	Source of normative value
Mo	Most medial point of medial orbital wall	Waitzman et al[32]
Lo	Most lateral point of lateral orbital wall	Waitzman et al[32]
LoSp	Junction of lateral orbital wall and sphenoid wing	Basyouni, Nanda[26]
Eu	Euryon, most lateral point of the cranium	Waitzman et al[32]

Table 1. Radiographic Landmarks

inch (DPI).[12] With the use of a cephalometric computer program (Viewbox 3.0 by dHal Software; Kifissia, Greece), the landmarks were marked on each of these cephalograms. An automated cephalometric analysis was performed afterwards. Cephalograms of the remaining 15 cases were digitalised with a Diagnostic PRO Plus Film scanner running at 300dpi. The same landmarks were used as described above, and the computer program Image J (Wayne Rasband, National institute of health, USA) was used to determine the LoSp-LoSp and Mo-Mo growth ratios.

Both AP-photographs scores and cephalometric ratios were combined and statically analysed using SPS6 (SPS6 version 15.01; SPS6 Inc., Chicago, IL).

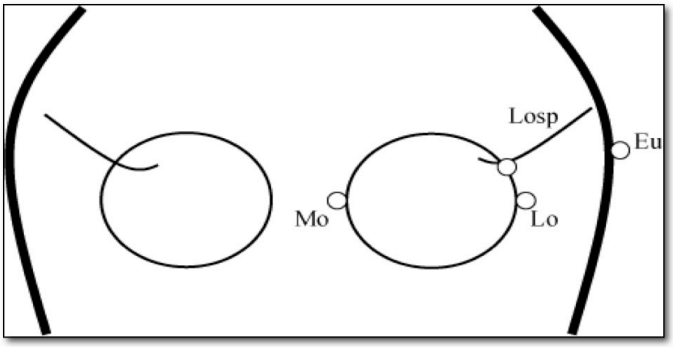

Fig 3. Schematic drawing of periorbital landmarks for forehead growth evaluation (table 1).

RESULTS

Photographic assessment

Of the reviewed postoperative photos, 15 were found to be normal, 15 scored a 1 (moderate temporal deformity), and three scored a 2 (severe deformity). The mean value of the postoperative photo scores showed a 5% decrease in comparison to the mean pre-operative photo score. [21]

Cephalomatric (LoSp - Mo ratio) vs photographic evaluation

The LoSp – Mo ratio, depicting temporal growth within our studied group, had a mean value of 5,4 (range 2,6- 8,0). The preoperative photo score was not a predictive factor for the postoperative growth ratio ($r = 0{,}171$).

Using a regression analysis, a significant negative correlation was found though between the postoperative photo score and the LoSp-Mo ratio. A low LoSp-Mo growth ratio therefore was a good predictive factor for a high postoperative photo score ($p = 0{,}014$), thus confirming the compatibility of these two methods of evaluation. A declining trend however was observed in the mean value of the LoSp-Mo ratio when the photo was scored higher (fig 4). The R^2 though, describing the accuracy of the regression line in relation to the higher end of real data points, was low ($R^2 = 0{,}179$).

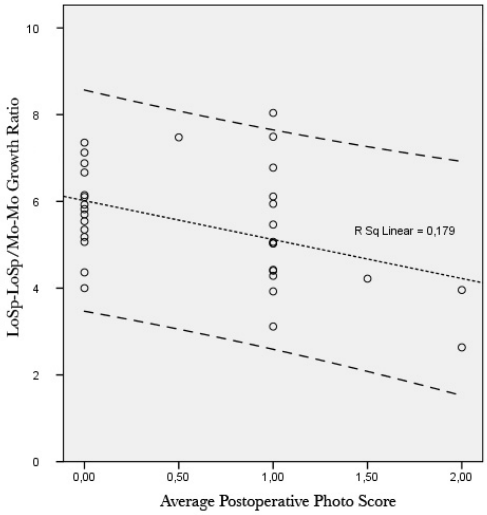

Fig 4. Linear regression analysis of photographic score versus orbital growth in the temporal region

Age at time of operation

The age at which time the operation was performed showed to have no significant correlation to the postoperative photographic evaluation (r = 0,331), nor did it have a significant influence on the height of the postoperative LoSp-LoSp/Mo-Mo growth ratio (r = 0,057).

Effect of surgical experience

The Spearman rank correlation showed a significant but weak negative correlation between the photo score and the date of surgery (r = -0,265, $p < 0.05$). Results seem to get better (with increased surgical experience) over the years.

Interclass correlation coefficient

The inter-observer variability in the evaluation of the 15 remaining cephalograms was tested using an Intraclass correlation coefficient (ICC). The coefficient was 0.985, which indicates nearly identical measurements between the different observers. ICC's of the rest of the radiographic and photographic evaluations were found to be sufficient in the original articles.[12, 21]

DISCUSSION

Skeletal growth

Several authors have reported on the occurrence of temporal hollowing following correction of the anterior cranial vault and supra-orbital bar in metopic or coronal synostosis.[8-11, 15] In addition, in our trigonocephalic population, evaluation of the long-term results revealed (bi)temporal hollowing to be a common finding.[12, 33] In search of the underlying cause, we initially undertook a radiographic analysis of the growth process of the forehead. For this we relied on standardised landmarks (on the medial and lateral orbital wall, and on the most lateral skull border) that were clearly recognisable in postoperative posteroanterior radiographs (table I, fig 3).[23-25, 27, 30, 31] Because of the presence of bone regeneration in the temporal area following the osteotomies, any landmarks that might have been clear before surgery were obscured, making a clear and reproducible evaluation difficult. On the other hand, the landmark LoSp is very reliable due to its nature of being a junction between two radiographic lines, namely the lateral orbital wall and the sphenoid wing. Since LoSp is located on the anterior border of the area most

associated with the hollowing, its growth ratios were considered to be good indicators of the antero-temporal growth pattern and subsequently used in this study as marker for the skeletal widening of the temporal region.[23]
Cephalometric analysis showed that the growth of the periorbital region and the forehead as a whole continued to be restricted, mostly so at the temporal region.[12]
In the initial postoperative phase, the lateralisation of the lateral orbital wall was found to be slower than the increase in head width. However, this difference slowly diminished over the first few years because of a catch up of the growth rate of the lateral orbital wall. Although the biorbital width continued to increase in the years thereafter, its lateral orbital wall growth rate did not manage to keep up with the rate at which the head widens, thus resulting in a relative restriction of the width of the temporal region.[12]
Photographic evaluation revealed a significant relation between the children with limited temporal growth ratios and those with significant temporal hollowing. Chronological photo evaluation showed a (non-significant) trend of deterioration of the temporal hollowing over time, confirming the hypothesis that bony growth inhibition plays a significant role in the postoperative appearance of these children.[21]

Muscle atrophy

The cranial origin of the temporal muscles is detached during the procedure in order to gain access to the temporal bone and lateral orbital wall. One could argue that this results in muscle atrophy due to devascularisation and denervation. From several studies on the vascularisation of the temporal muscle, it has become clear though that the muscle hardly relies on the transcranial blood supply coming in from the medial meningeal artery; it's main blood supply comes from the superficial temporal artery and the maxillary artery, both running superficial to the deep temporal fascia (and thus not disturbed by the dissection).[34] The same argument is true when applied to the innervation: the temporal branch of the facial nerve enters the muscle caudally and runs superficial to the periosteal layer along its entire length.[35] Muscle atrophy related to vascular or neural damage due to the dissection is unlikely to play a significant role based on these anatomical findings.

Superficial temporal fat pad atrophy

The second tissue that might be involved is the superficial temporal fat pad. This vulnerable tissue layer is positioned in between the superficial temporal fascia and the skin. Mobilisation of this layer while approaching the lateral orbital walls could damage its precarious vascularisation.[16, 36] Our approach however is purely subperiosteal, underneath the temporal muscle. Fat pad atrophy due to superficial dissection of the muscle is therefore not an issue in this population.

Surgical technique

One could argue that the temporal hollowing could be the result of the use of 2 osteotomies running parallel to each other in the temporal region (fig 2), although the hollowing usually occurs just above these lines.[12] We therefore looked at the results in our unilateral coronal synostosis group, in whom the same operative procedure is performed as is used in the metopic synostosis corrections. Despite a total frontal remodelling (with bilateral osteotomies) to correct this unilateral deformity, the temporal hollowing was invariably seen only on the affected side. This supports the theory of growth inhibition, which would be intrinsic to the synostotic bone and would appear irrelevant of the surgical procedure or technique. Remarkably though, it appeared that the presence of a temporal hollowing in the immediate postoperative period predisposed for the presence of a persistent temporal hollowing in the long term.[33] Surgical skill would play an important role in this scenario.

Oh et al[7] suggested that the hollowing was the result of an incorrect technique in making the frontal bone too short, thereby creating a lack of bone in the temporal region. In their series the hollowing disappeared after the introduction of bone grafts to fill in this temporal gap. Selber et al[37] came to similar conclusions after reviewing their 68 patients with metopic synostosis. Since our technique results in sufficient length of the posterior temporal segment of the frontal bone - where the actual hollowing is noted - (fig 2), we do not believe that a lack of bone is an issue in our group. Postoperative osteolysis however, might be an underlying cause, even though it would be difficult to explain why this would occur only at this specific localisation. Based on clinical and radiological observations in our population though, this did not seem to be a problem sizeable enough to be able to play a substantial role in the etiology of the temporal hollowing. Further radiological research would be needed to reach a definitive conclusion on this matter.

At the end of the procedure the temporal muscles are always reattached to the temporal crest from which they originate. Keeping the direction of muscle pull in mind, it is apparently clear that an insufficient fixation could lead to caudal misplacement of the muscle, thus leaving a hollowing in the temporal region.[6, 7, 38] We therefore requested parents to determine the muscle position in their children by palpating the muscle during jaw movement at the pre-designated locations (fig 5). A total of 97% of the parents could palpate the temporal muscle in the area just lateral to the orbit (point 2 of Fig. 5). Sadly, due to inconsistency of the measurements in our control group, we could not statistically validate these measurements of the parents. The remarkably high number of positive tests at point 2 however, does indicate the presence of a functional muscle in the area of hollowing in the vast majority of cases. In our study group, therefore, mal-positioning of the muscle seemed to play no role of importance in the etiology of the temporal hollowing.

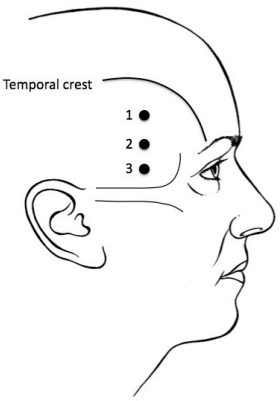

Fig 5. Schematic drawing of locations of temporal muscle palpation

Other operative factors

We did not find a statistically significant relation between the severity of the initial malformation and the postoperative result. The age at which time the corrective procedure was performed also showed to be of no significant relevance on growth or shape of the forehead in the years after surgery. The surgery seemed to be able to correct the deformation irrespective of the severity of the deformity, or the age at which the children presented. The amount and number of cases of postoperative temporal hollowing however did reduce while the surgeon became more experienced, suggesting a learning curve for the surgeon.[33]

Another factor that one must consider is the growth potential of the underlying brain. Several reports have confirmed the reduced size of the frontal lobes in metopic synostosis.[39, 40] Since brain expansion is one of the most potent stimulators of skull growth, an inhibition of the growth potential of the frontal lobes could be a contributing factor to the temporal hollowing.

Limitations of study

The preoperative radiographs were not standardised due to the young age at which these children present themselves, which resulted into the use of growth ratios instead of absolute values. Furthermore one could argue that the predictive value of the regression analysis regarding the relation between postoperative photographic evaluation and growth ratios is low due to the limited number of children with a severe hollowing. However, even despite this it proved to be statistically significant.

Conclusions

The aim of this study was to determine the etiology of temporal hollowing so often seen at visual evaluation of post cranioplasty patients. Bad postoperative visual evaluation scores correlated to reduced bone growth ratios in the same area. Temporal hollowing seems to be of bony origin and can be explained by skeletal growth inhibition in the affected area. When present immediate post operatively they seem to persist over the years, which makes surgical skill another factor of importance.

REFERENCES

1. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. J Neurosurg 1982: 57: 370-7.
2. Renier D, Marchac D. Craniofacial surgery for craniosynostosis: functional and morphological results. Ann Acad Med Singapore 1988: 17: 415-26.
3. Marchac D, Renier D, Broumand S. Timing of treatment for craniosynostosis and facio-craniosynostosis: a 20-year experience. Br J Plast Surg 1994: 47: 211-22.
4. Whitaker LA, Morales L, Jr., Farkas LG. Aesthetic surgery of the supraorbital ridge and forehead structures. Plast Reconstr Surg 1986: 78: 23-32.
5. McCarthy JG, Epstein F, Sadove M, Grayson B, Zide B. Early surgery for craniofacial synostosis: an 8-year experience. Plast Reconstr Surg 1984: 73: 521-33.
6. Persing JA, Mayer PL, Spinelli HM, Miller L, Criscuolo GR. Prevention of "temporal hollowing" after fronto-orbital advancement for craniosynostosis. J Craniofac Surg 1994: 5: 271-4.
7. Oh AK, Greene AK, Mulliken JB, Rogers GF. Prevention of temporal depression that follows fronto-orbital advancement for craniosynostosis. J Craniofac Surg 2006: 17: 980-5.
8. Greenberg BM, Schneider SJ. Trigonocephaly: surgical considerations and long term evaluation. J Craniofac Surg 2006: 17: 528-35.
9. Havlik RJ, Azurin DJ, Bartlett SP, Whitaker LA. Analysis and treatment of severe trigonocephaly. Plast Reconstr Surg 1999: 103: 381-90.
10. Friede H, Alberius P, Lilja J, Lauritzen C. Trigonocephaly: clinical and cephalometric assessment of craniofacial morphology in operated and nontreated patients. Cleft Palate J 1990: 27: 362-7; discussion 68.
11. Hinojosa J, Esparza J, Munoz MJ, et al. Surgical treatment of trigonocephalies and associated hypoteleorbitism. Neurocirugia (Astur) 2002: 13: 437-45.
12. van der Meulen J, Nazir P, Mathijssen I, et al. Bitemporal Depressions following Cranioplasty for Trigonocephaly: A Long-Term Evaluation of (Supra) Orbital Growth in 92 patients. J Craniofac Surg 2008: 19(1): 72-9.
13. Marchac D. Radical forehead remodeling for craniostenosis. Plast Reconstr Surg 1978: 61: 823-35.

14. Hoffman HJ, Mohr G. Lateral canthal advancement of the supraorbital margin. A new corrective technique in the treatment of coronal synostosis. J Neurosurg 1976: 45: 376-81.
15. Sadove AM, Kalsbeck JE, Eppley BL, Javed T. Modifications in the surgical correction of trigonocephaly. Plast Reconstr Surg 1990: 85: 853-8.
16. Kim S, Matic DB. The anatomy of temporal hollowing: the superficial temporal fat pad. J Craniofac Surg 2005: 16: 760-3.
17. Farkas LG, Posnick JC. Growth and development of regional units in the head and face based on anthropometric measurements. Cleft Palate Craniofac J 1992: 29: 301-2.
18. Farkas LG, Posnick JC, Hreczko TM. Growth patterns of the face: a morphometric study. Cleft Palate Craniofac J 1992: 29: 308-15.
19. Farkas LG, Posnick JC, Hreczko TM. Anthropometric growth study of the head. Cleft Palate Craniofac J 1992: 29: 303-8.
20. Farkas LG, Posnick JC, Hreczko TM, Pron GE. Growth patterns in the orbital region: a morphometric study. Cleft Palate Craniofac J 1992: 29: 315-8.
21. Hilling DE, Mathijssen IM, Vaandrager JM. Aesthetic results of fronto-orbital correction in trigonocephaly. J Craniofac Surg 2006: 17: 1167-74.
22. Athanasiou AE, Miethke R, Van Der Meij AJ. Random errors in localization of landmarks in postero-anterior cephalograms. Br J Orthod 1999: 26: 273-84.
23. Athanasiou AE, Hack B, Enemark H, Sindet-Pedersen S. Transverse dentofacial structure of young men who have undergone surgical correction of unilateral cleft lip and palate: a posteroanterior cephalometric study. Int J Adult Orthodon Orthognath Surg 1996: 11: 19-28.
24. Athanasiou vdM. Posteroanterior (frontal) cephalometry. London: Mosby-Wolfe, 1995.
25. Bartlett SP, Grossman R, Whitaker LA. Age-related changes of the craniofacial skeleton: an anthropometric and histologic analysis. Plast Reconstr Surg 1992: 90: 592-600.
26. Basyouni A. An Atlas of transverse dimensions of the face. Michigan: Needham press, 2000.
27. Carr M, Posnick JC, Pron G, Armstrong D. Cranio-orbito-zygomatic measurements from standard CT scans in unoperated Crouzon and Apert infants: comparison with normal controls. Cleft Palate Craniofac J 1992: 29: 129-36.

28. Ferrario VF, Sforza C, Poggio CE, Schmitz JH. Facial volume changes during normal human growth and development. Anat Rec 1998: 250: 480-7.
29. Kelly KM, Littlefield TR, Pomatto JK, Manwaring KH, Beals SP. Cranial growth unrestricted during treatment of deformational plagiocephaly. Pediatr Neurosurg 1999: 30: 193-9.
30. Lux CJ, Conradt C, Burden D, Komposch G. Transverse development of the craniofacial skeleton and dentition between 7 and 15 years of age, a longitudinal postero-anterior cephalometric study. Eur J Orthod 2004: 26: 31-42.
31. Posnick JC, Lin KY, Chen P, Armstrong D. Metopic synostosis: quantitative assessment of presenting deformity and surgical results based on CT scans. Plast Reconstr Surg 1994: 93: 16-24.
32. Waitzman AA, Posnick JC, Armstrong DC, Pron GE. Craniofacial skeletal measurements based on computed tomography: Part II. Normal values and growth trends. Cleft Palate Craniofac J 1992: 29: 118-28.
33. Hilling DE, Mathijssen IM, Mulder PG, Vaandrager JM. Long-term aesthetic results of frontoorbital correction for frontal plagiocephaly. J Neurosurg 2006: 105: 21-5.
34. Kadri PA, Al-Mefty O. The anatomical basis for surgical preservation of temporal muscle. J Neurosurg 2004: 100: 517-22.
35. Pinar YA, Govsa F. Anatomy of the superficial temporal artery and its branches: its importance for surgery. Surg Radiol Anat 2006: 28: 248-53.
36. Matic DB, Kim S. Temporal hollowing following coronal incision: a prospective, randomized, controlled trial. Plast Reconstr Surg 2008: 121: 379e-85e.
37. Selber J, Reid RR, Gershman B, et al. Evolution of operative techniques for the treatment of single-suture metopic synostosis. Ann Plast Surg 2007: 59: 6-13.
38. Webster K, Dover MS, Bentley RP. Anchoring the detached temporalis muscle in craniofacial surgery. J Craniomaxillofac Surg 1999: 27: 211-3.
39. Shimoji T, Tomiyama N. Mild trigonocephaly and intracranial pressure: report of 56 patients. Childs Nerv Syst 2004: 20: 749-56.
40. Collmann H, Sorensen N, Krauss J. Consensus: trigonocephaly. Childs Nerv Syst 1996: 12: 664-8.

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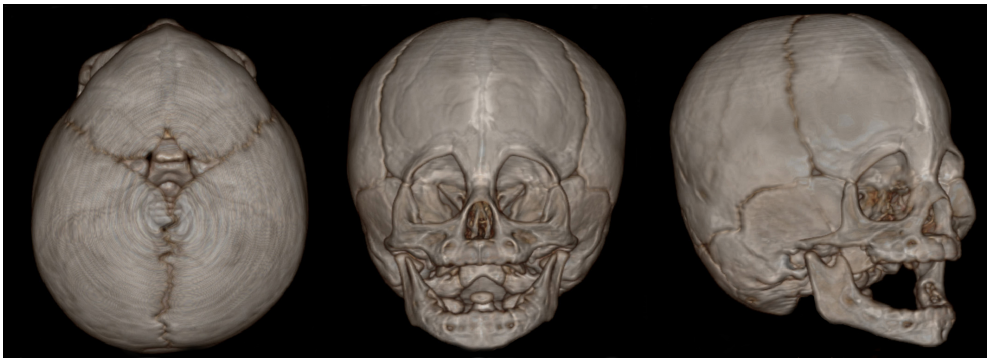

Intracranial Deformities in Metopic Synostosis

Submitted J Radiology

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INTRODUCTION

For years the focus in the treatment of craniosynostosis has been on the prevention of volumetric restriction, resulting from the premature ossification of one or more cranial sutures. When performed before the age of one, corrective surgery is thought to prevent cognitive limitations due to growth restrictions resulting in insufficient intracranial volume and subsequent raised intracranial pressure.[1-4] Several developmental outcome studies, focussing on the level of Intelligence Quotient (IQ) both before and after surgery, were in support of this theory. Interestingly enough though, while some papers reported on higher levels of IQ in children operated before the age of one year,[2, 3, 5, 6] others failed to find the same effect.[4, 7-11] During this analytical process however, several authors did notice some, more subtle, neurodevelopmental disorders occurring in all types of single suture synostosis.[4, 7, 9-15] Furthermore, a number of reports have recently been published that question the ability of surgery to correct these neurodevelopmental problems.[3, 4, 8, 9, 11-14, 16]

Especially metopic synostosis, over the last decade promoted into being the second most frequent type of craniosynostosis,[17] is associated with a relatively high level of neurodevelopmental problems.[3, 9, 12] These children display not only an increased incidence of speech and language developmental delays, but also disturbances of brain function that are believed to be specifically associated with frontal lobe dysfunction, like Attention Deficit - Hyperactivity Disorder (ADHD), Autism Spectrum Disorders and social incompetence.[14-16, 18, 19] These disorders seem to become more apparent when children reach school going age and are present irrespective of (normal) IQ or previous operations.[4, 9]

Many radiological abnormalities have been associated with craniosynostosis. As one would expect, most of these have been described in syndromal craniosynotosis. They range from ventriculomegaly and hydrocephalus to callosal anomalies or agenesis, hypoplasia/absence of the septum pellucidum, paucity or dysplasia of antero-mesial temporal white matter, distorsions of the cerebral cortex, pyramidal hypoplasia, hypoplasia/dysplasia of the hippocampus and parenchymal hemorrhage.[20, 21] Tokumaru et al. concluded that, while abnormalities in corpus callosum, septum pellucidum and hippocampus appeared to be primary brain disorders, the others were likely to be secondary to the bony growth

restrictions.[21]Previous radiological studies of children with nonsyndromal single suture synostosis have revealed similar abnormalities, although less outspoken. Carmel et al. reported on an ipsilateral decrease in the cerebrospinal fluid space with unilateral coronal synostosis. They also mentioned several CT findings in sagittal synostosis due to cerebrospinal fluid shifts producing small basal cisterns, an unusual prominent cistern over the frontal region and an increased size of the interhemispheric fissure.[22] Cohen described the presence of hydrocephalus also in isolated craniosynostosis.[23]

These neurodevelopmental and radiological findings seem to shed a new light on the classic hypothesis of volumetric restrictions being the sole reason for the developmental problems related to craniosynostosis. In order to investigate the relation between skull morphology and intrinsic malformations of the brain, we conducted a study into the preoperative radiological findings in metopic synostosis. Furthermore an attempt was made to quantify these abnormalities.

Materials and Methods

Study group

Eighty-nine children presented to the Dutch Craniofacial Unit with metopic synostosis between December 1994 and January 2006. In 11 cases we were not able to retrieve reliable CT scan data, leaving 78 cases to be included in this study with a mean age of 7,9 months (SD = 5,8). The missing cases were not significantly different with regards to diagnosis or number of associated anomalies ($p = 0{,}288$).

Control Group

A control group was compiled from the radiological archives of the Erasmus University Sophia Children's Hospital in order to enable a comparison of the intracranial CT scan data. Criteria for inclusion into this control group were; 1) age at time of CT scan < 2 years, 2) scans made after the year 2000, and 3) only trauma cases were included in which there were no intracranial findings that could be related to the trauma (like for instance a bleeding). Accidental findings that were not related to trauma (eg. corpus callosum agenesis) were allowed in order to prevent selection bias. The control group therefore consisted of 12 children with a mean age of 13,6 months (SD = 5,9). The age of the control group was significantly younger compared to the patient group ($p = 0{,}008$), while there were significantly more girls in the control group ($p = 0{,}03$).

3D CT scan

A 3-dimensional CT scan was made as part of the standard preoperative protocol. The mean age at time of this investigation was 8,15 months (SD 5,9 months, range 2-37 months). Three different scanners were used over this period (GE, Philips, Siemens). Slice thickness differed from 1,25 to 5mm, with an overlap varying from 0,1 to 1,3mm. All measurements (when applicable) were done in an axial plane running from Nasion to Occiput.

Frontal angle

The frontal angle was defined as the angle between the two lines drawn through Pterion (bilaterally) and Nasion, as described by Oi and Matsumoto in 1986 (fig 1). According to these calculations, a trigonocephaly was classified as being severe when presenting with an angle of less then 89 degrees, moderate when between 90-95 degrees, mild when between 96 and 103 degrees and normal when measuring 104 degrees or more.[24]

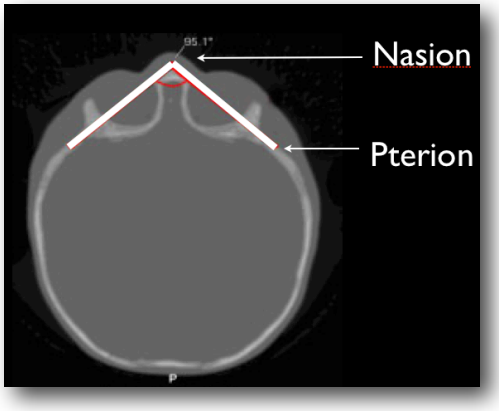


Fig 1. frontal angle

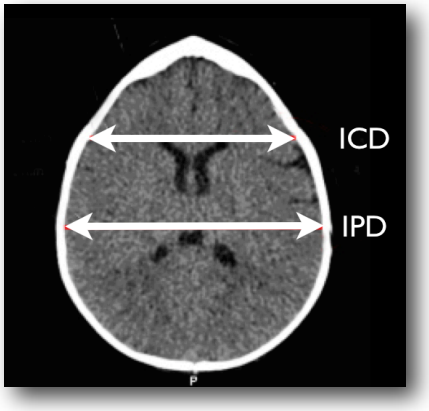


Fig 2. frontal stenosis

Frontal stenosis

This was defined as the ratio of the interparietal distance to the intercoronal distance according to the method introduced by Posnick et al. in 1994 and further modified by Bottero et al. (fig 2).[3, 25] Shimoji subsequently determined the IPD/ICD to be 1,21 in normal children.[19] These measurements were done on the same axial CT slices as mentioned above.

Intracranial evaluation

All preoperative CT scans were analysed by the same paediatric radiologist and a score was given to each of the aspects listed in table I. The central spinal fluid space was measured in millimeters at the smallest distance in between the frontal part of both hemispheres (bicaudate index). The arachnoid space was measured frontally at 1 cm lateral to the midline. The presence of a beaten copper pattern reduced spinal fluid space and compressed ventricles were considered to be signs of intracranial pressure elevation. Evaluation of frontal lobe development was classified into normal, mild hypoplasia and severe hypoplasia. The presence of Chiari malformations was investigated.

Statistical Analysis

Intracranial evaluation was compared between patients and controls using a Pearson Chi-square analysis. A students T-test was used to compare age differences between patient and control group, while an one sample T-test was used to measure the differences in frontal stenosis.

RESULTS

Frontal angle

The frontal angle was measured in 76 (out of 78) cases and ranged from 88,1 to 112,2 degrees (mean 98,9, SD 4,9) within our group. According to the classification of Oi and Matsumoto[24] one case presented with a severe angle 1 (1%), 20 (26%) cases were considered to be moderate, 47 (61%) cases were mild and 9 (12%) were categorised as being normal.

Frontal stenosis

In 76 cases the frontal stenosis was determined from the preoperative CT scan. The stenosis ranged from 1,03 to 1,38 (mean 1,24, SD 0,06) within our group. The mean frontal stenosis in the patient group (1,24) was significantly greater ($t = 4{,}32$, $p < 0{,}001$) compared to the frontal stenosis in healthy children (1,21) as reported by Bottero.

INTRACRANIAL EVALUATION

Of the 78 available patient CT-scans, 6 scans could not be assessed for differentiation between white and grey matter and the density of the brain parenchyma. There were no missing data for the other items of the intracranial evaluation.

The differentiation between white and grey matter was normal in all cases, as was the density of the brain parenchym. In 10% of patients the paediatric radiologist expressed a suspicion of elevated intracranial pressure, versus none in the control group. This was a non-significant difference ($p = 0{,}280$). Eight out of 78 patients showed a beaten copper pattern (10%), versus zero in the control group. Again, this difference was not significant ($p = 0{,}245$). There were no midline abnormalities (like corpus callosum malformations), nor were there any Chiari malformations present in our series. Overall spinal fluid space dilatation was apparent in 34 patients (44%), versus 2 out of 12 in the control group (17%)(non significant, $p = 0{,}076$).

A significant difference however was found when comparing the dilatation of the central ventricles between patients (40%) and controls (8%) ($p = 0{,}034$). Peripheral ventricular dilatation though did not differ significantly, 18% in patients versus 17% in controls ($p = 0{,}914$). Thirteen cases showed an increased arachnoid space (19%). There was no significant relation between the frontal angle or stenosis and the size or aspect of the ventricles.

Some form of frontal lobe hypoplasia was noted in a majority of cases (60%)(fig 3). This was subdivided in mild forms (56%) and severe forms (4%). No frontal lobe hypoplasia was found in any of the control CT's, resulting in a significant difference ($p < 0{,}001$). There was however no significant relation between the frontal angle and the severity of the frontal lobe agenesis ($p > 0{,}05$). The same was seen with regards to the relation between the frontal stenosis and the frontal lobe agenesis ($p > 0{,}05$). A total of 72% of children in our studied population presented with some form of intracranial abnormalities on their preoperative CT scan, which is significantly more then the 12% in our control group ($p < 0{,}001$).

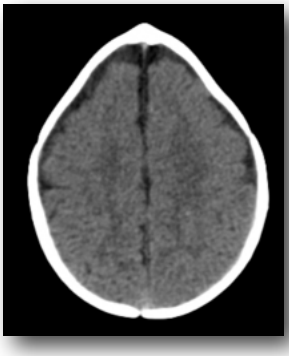


Fig 3. Frontal lobe hypoplasia

DISCUSSION

Functional brain disorders

Until recently, the functional brain disorders observed in craniosynostosis were generally thought to be secondary to the congenital growth disorders of the skull. Neurodevelopmental and neurobehavioural problems occurring in children with craniosynostosis despite corrective surgery however raise the question whether or not the brain itself is at the root of these problems.[9, 11, 20, 26] The role that fibroblastic growth factor receptors (FGFR) play in the development of both the skull [27, 28] and the underlying brain [29-32] makes this a very tempting hypothesis. Raybaud et al. for instance discussed the link between FGFR and white matter development by L1 cell adhesion molecule, which plays a role in the latter while needing FGFR to operate in a proper way.[20] Systematic screening of DNA in metopic patients however has proved to be relatively unproductive, despite some remarkable findings.[33-36]

The question therefore is whether one could quantify the intracranial abnormalities using computed tomography (CT) scans, which are routinely made in the work-up to corrective surgery for craniosynostosis in our clinic. Linking these data to neurobehaviour problems seen at a later age could possibly help in predicting future behaviour in these children.

Frontal angle & Frontal stenosis

Two methods are used in the literature when it comes to classifying the severity of metopic synostosis. The first method was introduced by Oi and Matsumoto in 1986, who measured the angle between two lines drawn from Pterion to Nasion in a group of 13 trigonocephaly patients and compared this to the angle seen in 43 normal children.[24] Posnick et al. took another approach and measured the inter-coronal distance in 10 patients and related these to an unknown number of age matched controls.[25] This second method was modified by Boterro et al. into a measure of frontal stenosis by incorporating the inter-parietal distance, thus creating the IPD/ICD ratio.[3]

When analysing our population the majority appeared to fall in the mild category according to the classification of Oi and Matsumoto, while 12% were even considered to have a normal frontal angle. Remarkably however, we did not find a significant relation between the severity of the frontal lobe hypoplasia and the

severity of the initial skull malformation (neither with the frontal angle nor with the ratio of stenosis). This is in contradiction with the assumption that the reduced volumetric demand of the brain induces the premature metopic synostosis.

Intracranial abnormalities

In metopic synostosis the reports on intracranial abnormalities are contradictive. One could expect abnormalities to be located in the frontal lobes, but some authors found that their population showed no abnormalities of brain or ventricles, besides the presence of slightly dilated frontal horns or partial effacement of the cisterns about the frontal lobes.[37] In contrary though, Boterro et al. reported on frontal subdural space distention (14%, amount not specified); hydrocephalus (4%) and anomalies of the corpus callosum (4%) in preoperative CT scans of 76 children.[3] In our group, 19% of cases presented with subdural space distention, but none of the subjects showed an anomaly of the corpus callosum. Ventricular distentions however, were seen in 44%. Remarkably, Tubbs et al. evaluated the CT scans of 50 children presenting with only metopic ridging and found Chiari I malformations in as high as 30% (while 9% is normal).[38] Again, contrary to these findings, no child in our study group was diagnosed with a Chiari malformation.

If one adheres to the theory of primal brain disorder being responsible for craniosynostosis to develop (a small frontal lobe only needs a small anterior vault), one would expect a marked reduction in the size of the frontal lobes in metopic synostosis. Several authors did comment on this before, although not in detail.[19, 39] We found frontal lobe hypoplasia to be present in the majority of cases, divided in mild (56%) and severe agenesis (4%). In this light it is interesting to realise that David et al. in 1996, followed by Shimoji et al. in 2004, investigated cerebral blood flow in metopic synostosis using single positron emission CT scans (SPECT), showing reduced flow in the frontal lobes, which subsequently improved after corrective surgery.[19, 40]

In general however it is important to note that 72% of children in our studied population presented with some form of intracranial abnormality on their preoperative CT scan, especially when taking onto account that the majority fell into the mild category of frontal angulation as mentioned above.

Further investigation is underway to relate these findings to the presence of neurodevelopmental disorders seen at a later age in this population. MRI would be an alternative method to judge the brain on possible intrinsic brain malformations, but this investigation is not a regular item in the treatment protocol of our unit.

CONCLUSIONS

Intracranial abnormalities were noted to be present in the majority of children with metopic synostosis. Most of them were located in or around the frontal lobes. This supports the theory that the neurodevelopmental disorders seen at a later age in this population are likely to be related to intrinsic brain developmental disorders. It also further undermines the classical theory of bone malformation being the sole etiological factor in the formation of (metopic) synostosis, pointing towards a distinct role of the brain in this process.

REFERENCES

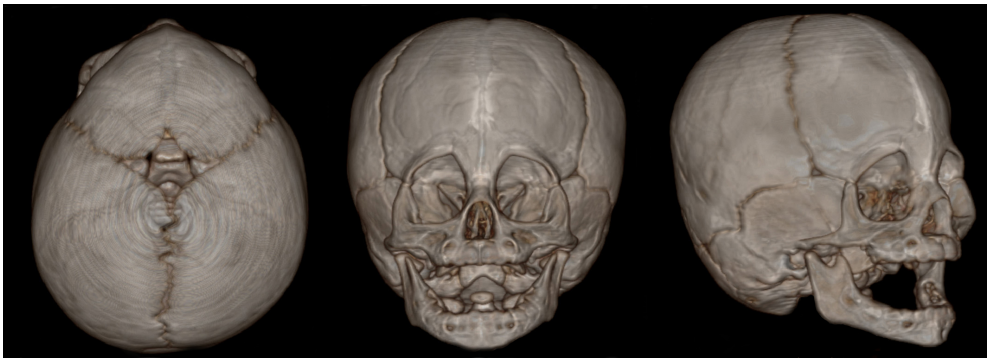
1. Arnaud E, Meneses P, Lajeunie E, et al. Postoperative mental and morphological outcome for nonsyndromic brachycephaly. Plast Reconstr Surg 2002: 110: 6-12; discussion 13.
2. Arnaud E, Renier D, Marchac D. Prognosis for mental function in scaphocephaly. J Neurosurg 1995: 83: 476-9.
3. Bottero L, Lajeunie E, Arnaud E, Marchac D, Renier D. Functional outcome after surgery for trigonocephaly. Plast Reconstr Surg 1998: 102: 952-8; discussion 59-60.
4. Da Costa AC, Walters I, Savarirayan R, et al. Intellectual outcomes in children and adolescents with syndromic and nonsyndromic craniosynostosis. Plast Reconstr Surg 2006: 118: 175-81; discussion 82-3.
5. Renier D, Brunet L, Marchac D. I.Q. and craniosynostosis: evolution in treated and untreated cases. 1987: 114-17.
6. Renier D, Lajeunie E, Arnaud E, Marchac D. Management of craniosynostoses. Childs Nerv Syst 2000: 16: 645-58.
7. Magge SN, Westerveld M, Pruzinsky T, Persing JA. Long-term neuropsychological effects of sagittal craniosynostosis on child development. J Craniofac Surg 2002: 13: 99-104.
8. Kapp-Simon KA, Figueroa A, Jocher CA, Schafer M. Longitudinal assessment of mental development in infants with nonsyndromic craniosynostosis with and without cranial release and reconstruction. Plast Reconstr Surg 1993: 92: 831-9; discussion 40-1.
9. Kapp-Simon KA. Mental development and learning disorders in children with single suture craniosynostosis. Cleft Palate Craniofac J 1998: 35: 197-203.
10. Lekovic GP, Bristol RE, Rekate HL. Cognitive impact of craniosynostosis. Semin Pediatr Neurol 2004: 11: 305-10.
11. Speltz ML, Kapp-Simon KA, Cunningham M, Marsh J, Dawson G. Single-suture craniosynostosis: a review of neurobehavioral research and theory. J Pediatr Psychol 2004: 29: 651-68.
12. Sidoti EJ, Jr., Marsh JL, Marty-Grames L, Noetzel MJ. Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 1996: 97: 276-81.

13. Becker DB, Petersen JD, Kane AA, et al. Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. Plast Reconstr Surg 2005: 116: 400-7.
14. Kelleher MO, Murray DJ, McGillivary A, et al. Behavioral, developmental, and educational problems in children with nonsyndromic trigonocephaly. J Neurosurg 2006: 105: 382-4.
15. Kapp-Simon KA, Speltz ML, Cunningham ML, Patel PK, Tomita T. Neurodevelopment of children with single suture craniosynostosis: a review. Childs Nerv Syst 2007: 23: 269-81.
16. Warschausky S, Angobaldo J, Kewman D, et al. Early development of infants with untreated metopic craniosynostosis. Plast Reconstr Surg 2005: 115: 1518-23.
17. van der Meulen J, van der Hulst R, van Adrichem L, et al. The increase of metopic synostosis; a pan-European observation. J Craniofacial Surg 2009, 20(2): 283-6
18. Kuper BD. Behaviour Patterns Among Children With a History of Metopic Synostosis. 2000: Doctor of Philosophy: 100.
19. Shimoji T, Tomiyama N. Mild trigonocephaly and intracranial pressure: report of 56 patients. Childs Nerv Syst 2004: 20: 749-56.
20. Raybaud C, Di Rocco C. Brain malformation in syndromic craniosynostoses, a primary disorder of white matter: a review. Childs Nerv Syst 2007: 23: 1379-88.
21. Tokumaru AM, Barkovich AJ, Ciricillo SF, Edwards MS. Skull base and calvarial deformities: association with intracranial changes in craniofacial syndromes. AJNR Am J Neuroradiol 1996: 17: 619-30.
22. Carmel PW, Luken MG, 3rd, Ascherl GF, Jr. Craniosynostosis: computed tomographic evaluation of skull base and calvarial deformities and associated intracranial changes. Neurosurgery 1981: 9: 366-72.
23. Cohen M. Radiological evaluation of craniosynostosis. In Cohen M, ed. Craniosynostosis; diagnosis, evaluation and management. New York: Raven Press, 1986: 210.
24. Oi S, Matsumoto S. Trigonocephaly (metopic synostosis). Clinical, surgical and anatomical concepts. Childs Nerv Syst 1987: 3: 259-65.
25. Posnick JC, Lin KY, Chen P, Armstrong D. Metopic synostosis: quantitative assessment of presenting deformity and surgical results based on CT scans. Plast Reconstr Surg 1994: 93: 16-24.

26. Noetzel MJ, Marsh JL, Palkes H, Gado M. Hydrocephalus and mental retardation in craniosynostosis. J Pediatr 1985: 107: 885-92.
27. Gripp KW, Zackai EH, Stolle CA. Mutations in the human TWIST gene. Hum Mutat 2000: 15: 479.
28. Kan SH, Elanko N, Johnson D, et al. Genomic screening of fibroblast growth-factor receptor 2 reveals a wide spectrum of mutations in patients with syndromic craniosynostosis. Am J Hum Genet 2002: 70: 472-86.
29. Oh LY, Denninger A, Colvin JS, et al. Fibroblast growth factor receptor 3 signaling regulates the onset of oligodendrocyte terminal differentiation. J Neurosci 2003: 23: 883-94.
30. Sleptsova-Friedrich I, Li Y, Emelyanov A, et al. fgfr3 and regionalization of anterior neural tube in zebrafish. Mech Dev 2001: 102: 213-7.
31. Wilke TA, Gubbels S, Schwartz J, Richman JM. Expression of fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3) in the developing head and face. Dev Dyn 1997: 210: 41-52.
32. Belluardo N, Wu G, Mudo G, et al. Comparative localization of fibroblast growth factor receptor-1, -2, and -3 mRNAs in the rat brain: in situ hybridization analysis. J Comp Neurol 1997: 379: 226-46.
33. Azimi C, Kennedy SJ, Chitayat D, et al. Clinical and genetic aspects of trigonocephaly: a study of 25 cases. Am J Med Genet A 2003: 117A: 127-35.
34. Jehee FS, Alonso LG, Cavalcanti DP, et al. Mutational screening of FGFR1, CER1, and CDON in a large cohort of trigonocephalic patients. Cleft Palate Craniofac J 2006: 43: 148-51.
35. Jehee FS, Johnson D, Alonso LG, et al. Molecular screening for microdeletions at 9p22-p24 and 11q23-q24 in a large cohort of patients with trigonocephaly. Clin Genet 2005: 67: 503-10.
36. van der Meulen J, van den Ouweland A, Hoogeboom J. Trigonocephaly in Muenke syndrome. Am J Med Genet A 2006: 140: 2493-4.
37. Dominguez R, Oh KS, Bender T, Girdany BR. Uncomplicated trigonocephaly. A radiographic affirmation of conservative therapy. Radiology 1981: 140: 681-8.
38. Tubbs RS, Elton S, Blount JP, Oakes WJ. Preliminary observations on the association between simple metopic ridging in children without trigonocephaly and the Chiari I malformation. Pediatr Neurosurg 2001: 35: 136-9.

39. Collmann H, Sorensen N, Krauss J. Consensus: trigonocephaly. Childs Nerv Syst 1996: 12: 664-8.
40. David LR, Wilson JA, Watson NE, Argenta LC. Cerebral perfusion defects secondary to simple craniosynostosis. J Craniofac Surg 1996: 7: 177-85.

C H A P T E R S E V E N



Psychopathology in Eighty-six Patients with Trigonocephaly

Submitted to J Pediatrics

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ABSTRACT

Background: Previous studies concerning the prevalence of psychopathology in patients with trigonocephaly have been hampered by methodological limitations, such as the use of non-validated instruments and not taking into account the role of intelligence (IQ) in psychopathology.

Objectives: The main objective of the present study was to assess the prevalences of features of Autism Spectrum Disorders (ASD-features), Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) in trigonocephalic patients, using validated instruments and by ruling out the confounding influence of IQ. Our second aim was to assess the association between extracranial anomalies and psychopathology in patients with trigonocephaly.

Methods: We performed a study in 86 trigonocephaly patients aged 4 to 18 at the Dutch Craniofacial Centre of the Erasmus Medical Centre in Rotterdam, the Netherlands. ASD-features were assessed using the Social Communication Questionnaire (SCQ). ADHD, ODD and CD were assessed with the Dutch Version of the Diagnostic Interview Schedule for Children – Parent Version 4th Edition DISC-IV-P. The presence of extracranial anomalies was determined by a clinician.

Results: Trigonocephalic patients were 4 times more likely to be intellectually disabled compared to children in the general population. Low IQ was significantly correlated with psychopathology. By stratifying the sample in IQ < 85 and IQ ≥ 85, our findings indicated a 64% versus 24% prevalence of psychopathology (ASD-features, ADHD, ODD, or CD). Extracranial anomalies were significantly correlated with lower IQ levels. However, when adjusted for IQ, the presence of extracranial malformations was not associated with an increased risk of psychopathology.

Conclusion: The relatively high prevalence of ASD-features, ADHD, and ODD in patients with trigonocephaly, seems to be mainly attributable to the increased likelihood of low intelligence levels in this group.

INTRODUCTION

Trigonocephaly has recently been promoted to the second most common type of single suture craniosynostosis.[43] The typically wedge shaped skull, when viewed from above, originates from a premature stenosis of the metopic suture followed by a bilateral growth restriction of the forehead (Fig 1). Furthermore, in a minority of patients, extracanial anomalies are present; such as finger deviations and/or extra digits, ear anomalies, maxillofacial abnormalities, or cardiac defects.

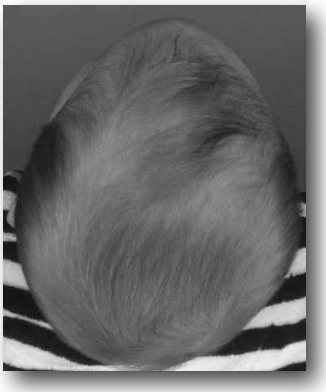


Fig 1. Trigonocephalic skull shape in a 9 months old child

Unlike other forms of single suture craniosynostosis, trigonocephaly has been associated with a high prevalence of problem behavior and cognitive deficits.[5,18,22,34-36] For example, Sidoti et al. (1996) reported that 33% of their sample of trigonocephalic patients showed problem behavior and/or cognitive problems, such as attention deficit/hyperactivity disorder (ADHD) aggressive behavior and intellectual disability (ID: IQ < 70).[36] Kelleher et al. (2006) described a 37% prevalence of ADHD and/or autism spectrum disorder (ASD) in 63 patients with non-syndromic trigonocephaly.[18] Bottero et al. (1998) reported that 31% of their sample of trigonocephalic patients (n = 76) showed problem behavior and/or intelligence quotients (IQ) lower than 90.[5] Patients with trigonocephaly and extracranial anomalies seem to have an even higher risk of problem behavior and ID when compared to trigonocephaly patients without extracranial anomalies.[5,22] Thus, previous studies have suggested that patients with trigonocephaly have an increased risk of ID and psychopathology. However, previous studies on children without craniosynostosis indicate that ID by itself is associated with an increased risk of psychopathology.[3,8,11,15,19,28,39] Multiple factors have been suggested to mediate the expression of psychopathology in children with ID, including psychological, familial, and social issues, as well as biological vulnerabilities such as genetic status.[9] Therefore, the association between trigonocephaly and psychopathology might be restricted to the subgroup of trigonocephalic patients with ID. So far, none of the studies on psychopathology in patients with trigonocephaly have considered this association between intelligence and

psychopathology. In other words, it is yet unclear if trigonocephaly affects the risk of psychopathology above and beyond the effect of intelligence. In addition, most previous studies on psychopathology in trigonocephaly did not provide information about the instruments that were used to assess psychopathology, or did not use validated instruments. This makes it difficult to judge the validity of their results.

In the present study we aimed to assess the prevalence of psychopathology in patients with trigonocephaly, using validated instruments and taking intelligence into account. Furthermore, we investigated whether having extracanial anomalies increased the risk of behavioral problems in patients with trigonocephaly.

METHODS

Patient population

The study sample consisted of 86 patients (72 males, 14 females), ranging in age from 4 to 18 years, presenting with metopic synostosis at the Dutch Craniofacial Centre of the Erasmus University Medical Centre in Rotterdam, The Netherlands. Patients were born between 1990 and 2005. All patients included in this study underwent fronto-supra-orbital remodellation and advancement operation (mean age of 11 months; SD = 4 months). Inclusion criteria for this study were: 1) a diagnosis of metopic synostosis confirmed on a 3D-CT-scan, and 2) Dutch as the first language. Ninety-one percent of all eligible patients (86 out of 94) agreed to participate in this study. The parents of two patients refused to participate because of the severe ID their children were suffering from. Another six parents did not participate because of limited access to transportation. Thirty percent of the included patients had extracanial anomalies as diagnosed by a clinician, including; visceral anomalies (27%), limb anomalies (54%), or a combination (19%).

Measures

Intelligence Quotient (IQ)

Depending on the age of the participant, intelligence was obtained with one of the four following intelligence tests. In 2-5 year old patients (n = 23), IQ was assessed using the Dutch version[47] of the Mullen Scales of Early Learning.[24] From the age of 5, intelligence was estimated using a four-subtest short form of the Dutch

Versions[21,40] of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale 3rd edition WAIS. In 5-7 year old children (n = 28) the WIPPSI was used, for 7-16 year old patients (n = 33), WISC-III[NL45] was used and for patients older than 16 years (n = 2), the WAIS[44] was used. All these intelligence tests have a mean score of 100 and a standard deviation (SD) of 15. Estimating IQ, by using a four-subtest short form of these intelligence scales, has shown good correlation with Full Scale IQ.[17,41,42]

Features of Autism Spectrum Disorders (ASD)

The Dutch translation[31] of the Social Communication Questionnaire (SCQ)[32] was used to screen for features of an ASD. The SCQ contains 40 items based on the Autism Diagnostic Interview – Revised (ADI-R)[23] that have been modified to be readily understandable by primary caregivers and that can be answered on a two-point scale (yes or no). Scores of 15 or more are considered deviant [31,32], and will be referred to as ASD-problems. The SCQ has good reliability and validity.[31,32]
Data on ASD-features were missing for 4 patients, resulting in a final sample of 82 for the ASD analyses (mean age 7.1 years, SD 3.0).

Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)

To determine the presence or absence of ADHD, ODD, and CD, the Dutch version of the Diagnostic Interview Schedule for Children – Parent Version 4th Edition (DISC-IV-P), was used.[10] The DISC-IV-P is a highly structured diagnostic parental interview, designed to generate DSM-IV diagnoses by ascertaining the presence or absence of symptoms. The DISC-IV-P can assess 34 child and adolescent psychiatric diagnoses, which are arranged into different modules. In this study only the module to assess Disruptive Behavior Disorders was used. This module requires a minimal age of 6 years of the child. Studies have demonstrated moderate to good test-retest reliability, and moderate to good agreement with evaluations by clinicians.[33]
Since 25 patients had not yet reached the age of 6 during the data collection period, the DISC-IV-P data are missing for this group. Another 4 patients were excluded from the analysis because of missing items, resulting in a final sample of 57 patients (mean age 8.1 years, SD 2.86) for analyses on ADHD, ODD, and CD.

Statistics

Analyses were conducted in three phases. Firstly, we assessed the difference in the prevalences of ID and borderline intellectual functioning between trigonocephalic patients and the general population by comparing the IQ levels of patients with the distribution for the general population using binomial tests. Secondly, Pearson's correlations were computed between IQ scores and the continuous scores on ASD-features, ADHD, ODD, and CD. Subsequently, prevalences of ASD-problems, ADHD, ODD, and CD were determined using the dichotomized scale scores. In case of significant correlations between any of the scale scores and IQ, prevalences were assessed in subgroups based on IQ. In that case, patients were divided into two groups; group 1, IQ < 85 and group 2, IQ ≥ 85. Thirdly, partial correlation analyses were performed to assess the association of extracanial anomalies with continuous scores on ASD-features, ADHD, ODD, and CD, adjusted for IQ.

RESULTS

Sample characteristics

Descriptive information on the outcome variables is provided in Table 1. Mean intelligence quotient of the sample was 99.5 (range 50-147; SD 22.2). Intellectual disability, defined as an IQ of two standard deviations below the mean (IQ < 70), was present in 12% of the patients. This is a significantly higher prevalence ($p < 0.001$) compared to the expected 2.5% that is found in the general population according to the normal distribution. In contrast, borderline intellectual functioning (defined as having an IQ between 70 and 85) was present in 14% of the patients, which is not significantly different ($p = 0.39$) from the expected 13.5% in the general population. Overall, low IQ (<85) was present in 23% of the patients. The prevalence of ASD-problems was 15%. When all trigonocephaly patients with information on the DISC-IV-P were considered (n = 57), the prevalence of ADHD was 14%, the prevalence of ODD was 19%, and the prevalence of CD was 4%. When ADHD, ODD and CD were combined in a composite measure, 26% of the patient sample presented with scores in the deviant range. When also low IQ (<85) and ASD-problems were included in this composite measure, 39% percent of the sample had deviant scores on one or more of the outcomes.

Intelligence and features of Autism Spectrum Disorders

A significant correlation between IQ and SCQ-scores (r = -0.50; $p < 0.001$), indicated that patients with lower IQ scores had a higher level of autistic features than patients with higher IQ-scores. Stratified by intelligence (IQ < 85 and IQ ≥ 85), our findings indicated ASD-problems in 40% of the patients with IQ < 85, and in 6% of the patients with IQ ≥ 85. All group scores are shown in Table 1.

Intelligence and ADHD, ODD, CD

Intelligence and ADHD were significantly correlated (r = -0.36; $p < 0.01$). Likewise, there was a significant correlation between IQ and ODD (r = -0.34; $p < 0.05$). This indicates that low IQ is associated with a higher risk of ADHD and ODD. IQ was not significantly correlated with CD (r = -0.19; $p= 0.18$). In the group "IQ < 85" prevalences of ADHD, ODD, and CD were 27%, 55%, and 9%, respectively. In the group "IQ ≥ 85" prevalences for ADHD, ODD and CD were 11%, 11%, and 2% respectively. Findings are presented in Table 1.

Extracranial anomalies in trigonocephaly

Trigoncephalic patients with extracanial anomalies (n = 26) had a mean IQ score of 89.3 (SD 22.2), which was significantly lower compared to the mean IQ score of trigonocephalic patients without extracranial anomalies (n = 60) who had a mean IQ of 104.4 (SD 20.4) ($t = 3.1$; $df = 84$; $p = 0.03$). ID was significantly more prevalent ($Chi^2 = 8.1$; $df = 1$; $p < 0.05$) in trigonocephalic patients with extracranial anomalies (27%) when compared to trigonocephalic patients without extracranial anomalies (5%). When intelligence was taken into account, no significant associations were found between the absence or presence of extracranial anomalies and ASD-features, (r = 0.68; $p = 0.54$), ADHD (r = 0.02; $p = 0.91$), ODD (r = -0.27; $p = 0.07$), or CD (r = -0.17; $p = 0.20$). Findings are presented in Table 1.

	Total sample	IQ ≥ 85			IQ < 85		
	frequency & percentage	frequency & percentage			frequency & percentage		
		combined	EA +	EA -	combined	EA +	EA -
ASD-features (SCQ>15)	12/82 (15%)	4/62 (6%)	3/17 (18%)	1/45 (2%)	8/20 (40%)	3/9 (33%)	5/11 (45%)
ADHD (DSM-IV criteria)	8/57 (14%)	5/46 (11%)	2/12 (17%)	3/34 (9%)	3/11 (27%)	1/5 (20%)	2/6 (33%)
ODD (DSM-IV criteria)	11/57 (19%)	5/46 (11%)	0/12 (0%)	5/34 (15%)	6/11 (55%)	1/5 (20%)	5/6 (83%)
CD (DSM-IV criteria)	2/57 (4%)	1/46 (2%)	0/12 (0%)	1/34 (3%)	1/11 (9%)	0/5 (0%)	1/6 (17%)
Psychopathology (deviant scores on the DISC-IV-P and/or the SCQ)	18/57 (32%)	11/46 (24%)	3/12 (25%)	8/34 (24%)	7/11 (64%)	2/5 (40%)	5/6 (83%)
Deviant scores on psychopathology and/or IQ below 85	22/57 (39%)						

EA = Extracranial Anomalies

Table I. Frequency and prevalence of deviant scores on psychopathology in trigonocephalic patients.

DISCUSSION

Intelligence and trigonocephaly

The prevalence of ID (12%) in our study group of trigonocephalic patients was significantly higher than in the general population. More specifically, the results from this study indicate that trigonocephalic patients are 4 times more likely to be intellectually disabled than individuals without trigonocephaly. Previous publications on intelligence levels in trigonocephaly patients have reported on similar prevalences of ID (between 6% and 13%).[6,36] Furthermore, our findings showed that especially patients with extracranial anomalies are at increased risk for ID. Intellectual disability was present in 27% of the patients with extacranial anomalies versus 5% in patients without extracranial anomalies. In their review of 273 trigonocepaly patients Lajeune et al. (1998) also reported a higher likelihood of ID in patients with extracranial anomalies, 34% versus 0.5% in trigonocephalic patients without extracranial anomalies.[22]

Psychopathology in trigonocephaly

The present study aimed to determine the risk of ASD-features, ADHD, ODD and CD in patients with trigonocephaly, while taking intelligence into account. Because low IQ was found to be associated with ASD-features, ADHD and ODD, we stratified the sample into two groups; IQ < 85 and IQ ≥ 85. Our findings indicate a 64% versus 24% prevalence of psychopathology (ASD-problems, ADHD, ODD or CD) in patients with IQ < 85 and IQ ≥ 85, respectively. Thus, the risk of psycho-pathology was relatively high in patients with IQ < 85. Among trigonocephalic patients with IQ levels ≥ 85, prevalences of ASD-problems, ADHD, ODD, and CD were not very different from reported prevalences in the general population.[1,7,12,13,25,27,31] However, based on our findings, we cannot draw any conclusions about the absence or presence of differences in the risk of psychopathology between children with craniofacial abnormalities and children in the general population. Yet, given the association between low IQ and increased risk of psychopathology, our findings suggest that the relatively high prevalence of ASD-features, ADHD, and ODD in patients with trigonocephaly seem to be mainly attributable to the increased likelihood of low intelligence levels in this group.

Extracranial anomalies in trigonocephaly

Thirty percent of the patients (n = 26) in our sample presented with extracranial anomalies. Our findings indicate that, when IQ was taken into account, there was no significant correlation between the presence of extracranial anomalies and psychopathology (ASD-features, ADHD, ODD, and CD). However, the presence of extracranial anomalies was associated with lower intelligence levels. Literature shows that intelligence have been associated with increased levels of psychopathology.[3,8,11,15,19,28,39] Probably, the increased risk of ID in patients with extracranial anomalies might reflect brain pathology. While this might, at a cognitive level, result in low intelligence levels, it might be associated with psychopathology at a behavioral level.

Brain pathology and trigonocephaly

High intracranial pressure has been proposed as the cause of development of psychopathology and cognitive deficits in patients with trigonocephaly.[2,29,30] Remarkably, all patients included in the present sample had been treated with a fronto-supra-orbital remodellation and advancement operation to avoid the development of high intracranial pressure. Our finding of an increased likelihood of ID in these patients suggests that there may be more, or other pathways causing cognitive dysfunction in these patients than the formally suggested "high intracranial pressure pathway". One alternative explanation for the increased incidence of ID in patients with trigonocephaly is offered by Speltz et al. (2004), who proposed the "secondary cerebral deformation hypothesis".[38] In this hypothesis, growing cortical and even subcortical brain tissue is believed to be compressed or "redirected" within a skull that has limited capacity to accommodate such growth, resulting in neurodevelopmental disorders. However, Bottero et al (1998) found that trigonocephaly patients with extracranial anomalies, who have an increased likelihood of developing neurodevelopmental problems, did not have a more severe degree of frontal stenosis compared to patients without extracranial anomalies.[5] This makes the "secondary cerebral deformating hypothesis" less likely. A second alternative is proposed by Kjaer (1995), who suggested that the central nervous system and craniofacial skeleton are developmentally interconnected.[20] Indeed, the fibroblastic growth factor receptors, which play a role in the development of both the skull[14,16] and the underlying brain, have been found to play a role in craniosynostosis.[4,26,37,46] This makes a hypothesis on interconnected

development causing both craniosynostosis and neurodevelopmental problems plausible. Future research might address the mechanism(s) behind the increased likelihood of neurodevelopmental problems in patients with trigonocephaly.

Limitation of study

Although the sample size of this study was relatively high compared to previous studies, our subgroup analysis seemed to have suffered from low power due to the small number of patients in each subgroup. Furthermore, we did not compare trigonocephalic patients to matched controls. In order to address the significance of differences in psychopathology between patients with trigonocephaly and children from the general population, we recommend future research in this area and the use of a matched reference group.

CONCLUSION

Based on the findings of the present study, the relatively high prevalence of ASD-features, ADHD, and ODD in patients with trigonocephaly, seems to be mainly attributable to the increased likelihood of low intelligence levels in this group.

REFERENCES

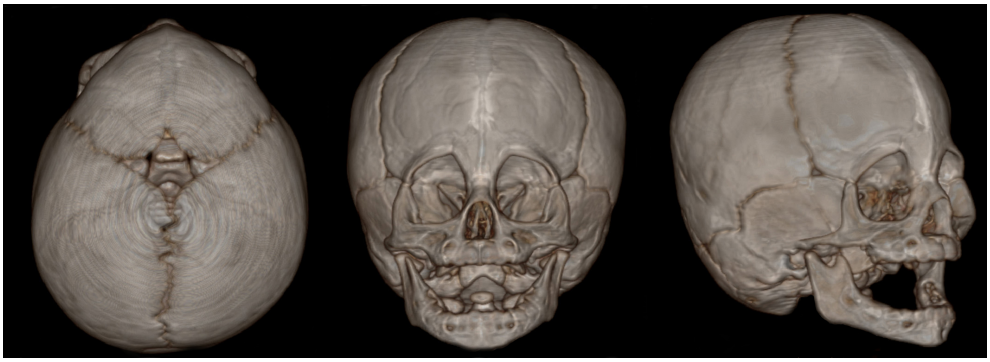
1. Angold A, Costello EJ: Toward establishing an empirical basis for the diagnosis of oppositional defiant disorder. J Am Acad Child Adolesc Psychiatry 35:1205-1212, 1996
2. Arnaud E, Renier D, Marchac D: Prognosis for mental function in scaphocephaly. J Neurosurg 83:476-479, 1995
3. Baker BL, Blacher J, Crnic KA, et al: Behavior problems and parenting stress in families of three-year-old children with and without developmental delays. Am J Ment Retard 107:433-444, 2002
4. Belluardo N, Wu G, Mudo G, et al: Comparative localization of fibroblast growth factor receptor-1, -2, and -3 mRNAs in the rat brain: in situ hybridization analysis. J Comp Neurol 379:226-246, 1997
5. Bottero L, Lajeunie E, Arnaud E, et al: Functional outcome after surgery for trigonocephaly. Plast Reconstr Surg 102:952-958; discussion 959-960, 1998
6. Bottero L, Lajeunie E, Arnaud E, et al: [Mental prognosis of trigonocephaly and therapeutic implications]. Ann Chir Plast Esthet 42:296-304, 1997
7. Chandler S, Charman T, Baird G, et al: Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. J Am Acad Child Adolesc Psychiatry 46:1324-1332, 2007
8. Dekker MC, Koot HM, van der Ende J, et al: Emotional and behavioral problems in children and adolescents with and without intellectual disability. J Child Psychol Psychiatry 43:1087-1098, 2002
9. Dykens EM: Psychopathology in children with intellectual disability. J Child Psychol Psychiatry 41:407-417, 2000
10. Ferdinand R, van der Ende J, Mesman J: Diagnostic Interview Schedule for Children. Rotterdam: Sophia Kinderziekenhuis (Sophia Childrens Hospital), 1998
11. Fergusson DM, Horwood LJ: Early disruptive behavior, IQ, and later school achievement and delinquent behavior. J Abnorm Child Psychol 23:183-199, 1995
12. Ford T, Goodman R, Meltzer H: The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. J Am Acad Child Adolesc Psychiatry 42:1203-1211, 2003

13. Froehlich TE, Lanphear BP, Epstein JN, et al: Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. Arch Pediatr Adolesc Med 161:857-864, 2007
14. Gripp KW, Zackai EH, Stolle CA: Mutations in the human TWIST gene. Hum Mutat 15:479, 2000
15. Hinshaw SP: Externalizing behavior problems and academic underachievement in childhood and adolescence: causal relationships and underlying mechanisms. Psychol Bull 111:127-155, 1992
16. Kan SH, Elanko N, Johnson D, et al: Genomic screening of fibroblast growthfactor receptor 2 reveals a wide spectrum of mutations in patients with syndromic craniosynostosis. Am J Hum Genet 70:472-486, 2002
17. Kaufman AS, Kaufman J, Mclean J: WISC-III Short Forms: Psychometric Properties vs. Clinical Relecance vs. Practical Utility. , in Anual meating of the Mid-South Educational Research Association., 1994
18. Kelleher MO, Murray DJ, McGillivary A, et al: Behavioral, developmental, and educational problems in children with nonsyndromic trigonocephaly. J Neurosurg 105:382-384, 2006
19. King BH, State MW, Shah B, et al: Mental retardation: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry 36:1656-1663, 1997
20. Kjaer I: Human prenatal craniofacial development related to brain development under normal and pathologic conditions. Acta Odontol Scand 53:135-143, 1995
21. Kort W, Schittekatte M, Dekker PH, et al: WISC-III NL. Handleiding. Nederlandse bewerking. . London: The Psychological Corperation, 2005
22. Lajeunie E, Le Merrer M, Marchac D, et al: Syndromal and nonsyndromal primary trigonocephaly: analysis of a series of 237 patients. Am J Med Genet 75:211-215, 1998
23. Lord C, Rutter M, Le Couteur A: Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659-685, 1994
24. Mullen EM: Mullen Scales of Early Learning (AGS ed.). Circle Pines, MN: American Guidance Service Inc., 1995

25. Mulligan A, Richardson T, Anney RJ, et al: The Social Communication Questionnaire in a sample of the general population of school-going children. Ir J Med Sci, 2008
26. Oh LY, Denninger A, Colvin JS, et al: Fibroblast growth factor receptor 3 signaling regulates the onset of oligodendrocyte terminal differentiation. J Neurosci 23:883-894, 2003
27. Polanczyk G, Rohde LA: Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 20:386-392, 2007
28. Rapport MD, Scanlan SW, Denney CB: Attention-deficit/hyperactivity disorder and scholastic achievement: a model of dual developmental pathways. J Child Psychol Psychiatry 40:1169-1183, 1999
29. Renier D, Marchac D: Craniofacial surgery for craniosynostosis: functional and morphological results. Ann Acad Med Singapore 17:415-426, 1988
30. Renier D, Sainte-Rose C, Marchac D, et al: Intracranial pressure in craniostenosis. J Neurosurg 57:370-377, 1982
31. Roeyers H, Warreyn P, Raymaekers R: vragenlijst sociale communicatie (SCQ) Destelbergen: uitgave SIG, 2002
32. Rutter M, Bailey A, Lord C: The Social Communication Questionnaire manual. Los Angeles: Western Psychological Services, 2003
33. Shaffer D, Fisher P, Lucas CP, et al: NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39:28-38, 2000
34. Shimoji T, Shimabukuro S, Sugama S, et al: Mild trigonocephaly with clinical symptoms: analysis of surgical results in 65 patients. Childs Nerv Syst 18:215-224, 2002
35. Shimoji T, Tomiyama N: Mild trigonocephaly and intracranial pressure: report of 56 patients. Childs Nerv Syst 20:749-756, 2004
36. Sidoti EJ, Jr., Marsh JL, Marty-Grames L, et al: Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 97:276-281, 1996
37. Sleptsova-Friedrich I, Li Y, Emelyanov A, et al: fgfr3 and regionalization of anterior neural tube in zebrafish. Mech Dev 102:213-217, 2001

38. Speltz ML, Kapp-Simon KA, Cunningham M, et al: Single-suture craniosynostosis: a review of neurobehavioral research and theory. J Pediatr Psychol 29:651-668, 2004
39. State MW, King BH, Dykens E: Mental retardation: a review of the past 10 years. Part II. J Am Acad Child Adolesc Psychiatry 36:1664-1671, 1997
40. Stinissen J, Willems PJ, Coetsier P, et al: Handleiding bij de Nederlandstalige bewerking van de Wechsler Adult Intelligence Scale (W.A.I.S.) (manual of the Dutch edition of the WAIS). Lisse, The Netherlands: Swets & Zeitlinger, 1970
41. Thompson AP: Test-retest evaluation of a four-subtest WAIS-R short form with young offenders. J Clin Psychol 51:410-414, 1995
42. Tsushima WT: Short form of the WPPSI and WPPSI-R. J Clin Psychol 50:877-880, 1994
43. van der Meulen J, van der Hulst R, van Adrichem L, et al: The increase of metopic synostosis: a pan-European observation. J Craniofac Surg 20:283-286, 2009
44. Wechsler D: Wechsler Adult Intelligence Scale (3rd. ed.). in. New York: New York: Psychological Corporation, 1997
45. Wechsler D: Wechsler Intelligence Scale for Children (3rd. ed.). in. New York: New York: Psychological Corporation, 1991
46. Wilke TA, Gubbels S, Schwartz J, et al: Expression of fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3) in the developing head and face. Dev Dyn 210:41-52, 1997
47. Willigen Mv: Mullen ontwikkelingstest 1-68 maanden (Dutch translation of the Mullen Scales of Early Learning). Groningen: Rijksuniversiteit Groningen, Vakgroep Orthopedagogiek., 2002

C H A P T E R E I G H T



General Discussion

The surprisingly high number of extra cranial abnormalities and behavioural problems seen in children with metopic synostosis sparked the initiative to embark onto this investigative journey. A wide variety of aspects were subsequently looked at, in an attempt to increase our understanding of this entity. The following characteristics of metopic synostosis were investigated:

- Epidemiology
- Etiology (molecular genetics)
- Surgical results
- Radiological findings
- Neurodevelopment

EPIDEMIOLOGY

Papers reporting on the workload of the average craniofacial unit usually showed the majority of single suture craniosynostosis cases being scaphocephalic, with trigonocephaly only taking third place (after plagiocephaly) in the prevalence ranking[1-3]. Reports from the '60's and '70's show prevalence numbers of no more than 10%[4-7], while publications from within the last decade mention a metopic prevalence of around 25% and more.[2, 8] Over recent years our unit noted a (both relative and absolute) increase in the number of metopic synostosis being treated in Rotterdam. When this anecdotal observation was ventilated amongst peers, the changing epidemiological spectre appeared to be a pan–European trend. This gave rise to the hypothesis that metopic synostosis was increasing in Europe not only in absolute numbers, but also relative to other forms of single suture synostosis.
All cases of craniosynostoses seen over a period of nine years from 1997-2006 in 7 different craniofacial units across Europe were collected. Out of a total of 3240 cases, 756 were metopics (23%) and 1344 were sagittals (41%).[9] Statistical analysis of the data collected confirmed a remarkable increase that occurred in 2000-2001, with significant increase of metopic synostosis cases in the second half of this period when compared to the first half ($p = 0.002$). Not only did metopic synostosis increase in absolute numbers, but also in relation to the (non-significant, $p > 0.05$) increase of sagittal synostosis in the same period. The hypothesis therefore was proven to be true.

ETIOLOGY

Reasons behind this increase remain unclear. It is plausible that factors known to have an influence on midline fusion disorders also are involved in the etiology of metopic synostosis. Folic acid for instance could very well play a role in its origin.[10, 11] It is however unlikely that this is the sole factor accounting for the increase seen, since the intake of folic acid by pregnant woman in the different European countries differs so much. In chapter 3 another angle on the etiology of this disorder was subsequently explored. Until now only sporadic evidence of genetic malformations in metopic synostosis has been found (only one case of trigonocephaly with a FGFR 1 mutation was ever reported in the literature).[12] Routine screening for a genetic etiology in children with craniosynostosis is reserved for syndromic cases and for children presenting with coronal synostosis. Most of these disorders are linked to anomalies of the genes coding for the Fibroblastic Growth Factor Receptors (FGFR) 1-3. [13]

The high rate of extracranial and neuropathological disorders seen in association with metopic synostosis in particular however resulted in the hypothesis that there is an underlying genetic cause. The role that fibroblastic growth factor receptors (FGFR) play in the development of both the skull and the underlying brain makes this a very tempting hypothesis. Raybaud et al. for instance discussed the link between FGFR and white matter development by L1 cell adhesion molecule, which plays a role in the latter while needing FGFR to operate in a proper way.[14] The finding of the worlds first described case of metopic synostosis with the FGFR 3 Pro250ARG mutation (which is typical for Muenke syndrome), combined with the same mutation in his mother, supports this hypothesis.

SURGICAL RESULTS

Bitemporal hollowing, so often seen in patients following a frontal cranioplasty, is widely regarded as being the most common aesthetic drawback of the fronto-supra-orbital advancement and remodellation technique. Closely followed by the frequently occurring residual hypotelorism, it has prompted many surgeons to adjust their techniques, with only variable success. Both findings fuel the perception that the growth of the periorbital region and the forehead as a whole continued to be restricted, even after correction.

On the other hand, autocorrection of hypotelorism has been reported. Some even suggested that trigoncephaly is a self-limiting disease, considering the scarceness of (residual) malformation in the adult general population. That this assumption however, is not always true, is proven by the mother and her child, seen in figures 1-3. The mother was never operated upon.

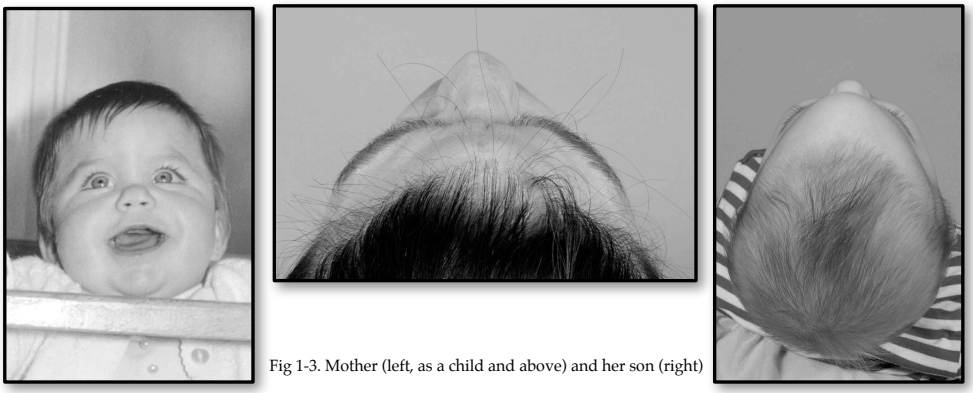


Fig 1-3. Mother (left, as a child and above) and her son (right)

The retrospective clinical study on the peri-orbital growth was aimed at finding the reason behind the bitemporal hollowing. It followed on from the hypothesis that the bitemporal hollowing is a result of restricted frontal bone growth.
The cephalometric analysis of the radiographs clarified the growth processes that occur after frontal cranioplasty in these patients. It was found that there were substantial growth restrictions in the temporal region, therefore providing support for the hypothesis. We also observed an increased interorbital growth rate, which is a likely reason why residual hypotelorism seen after cranioplasty is self-limiting and does not require adjustment of surgical techniques.
Other remarkable outcomes were the normal skull circumference growth patterns, both before as well as after surgery, the evolution of a slightly shorter skull over the years and the quicker normalisation of the inter-orbital distance in children operated after the age of one year compared to the ones operated before that age.

The next step was to investigate other possible causes for the bitemporal hollowing, like:

1. Temporal muscle atrophy
2. Superficial temporal fat pad atrophy
3. Surgical technique (and surgeons experience)
4. Severity of initial deformation
5. Skeletal growth
6. Limited expansion of the frontal lobes of the brain

The temporal muscle and the superficial temporal fat pad are mobilised during surgery in a sub-periosteal plane. Since the neurovascular input into these structures run along a different tissue plane, they are not disturbed by the surgery. Furthermore the muscles are kept incorporated in the skin/galeal flap, which results in an automatic anatomical repositioning after closure of the scalp. This was confirmed by physical examination where in 97% of all patients the muscle appeared to be in the proper position, even years after surgery. We concluded therefore that the influence of the muscle on the etiology of the temporal hollowing is limited.

Three other factors were analysed with the use of photographic material gathered during follow-up. By using a visual scale the presence and severity of temporal hollowing was quantified. The surgical technique (whether is was providing sufficient bone support in the temporal region) and the experience of the surgeon performing it did appear to be of influence, since temporal hollowing, once apparent immediately after surgery, did persist over the years. This was irrespective of the severity of the initial deformity.
The children included in this study group were matched with the subjects previously analysed in the above mentioned peri-orbital growth study, leaving a total of 33 children with both datasets. By comparing growth ratios based on radiographs with the photographic analysis, we could prove that limited osseous growth in the temporal region did correlate with a bad visual grading of temporal hollowing, thus providing further proof of a bony origin of this hollowing.
The last factor, the limited lateral drive of the frontal lobes of the brain as a cause of limited lateral growth of the forehead, is a very interesting one. It is well known that the main stimulator of skull growth is the expansion rate of the intracranial

volume. The skull stops growing when the intracranial volume is stabilised, as is seen in children with hydrocephalus who undergo ventricular drainage. If therefore the joint etiology of both skull and brain disorder is considered a serious option, it could then be argued that the hypoplastic malformation of the frontal lobes result in a reduced volumetric demand and thus a premature ossification of the metopic suture. The volumetric increase provided by the cranioplasty would rob the forehead of its drive to grow since there would be no more expansion needed for the frontal lobes, therefore slowing down the growth rate, resulting in bitemporal hollowing.

RADIOLOGICAL FINDINGS

Keeping this in mind, we hypothesised that there would be a significant amount of frontal lobe pathology in children with metopic synostosis. Analysis of intracranial deformities seen on CT scans of children with trigonocephaly could also shed some light on the remarkably high incidence of neurodevelopmental disorders, which is so typically associated with this type of craniosynostosis. We proceeded to investigate the intracranial abnormalities in preoperative CT scan of 78 children presenting with metopic synostosis to our craniofacial unit. A random control group of 12 posttraumatic children (with no trauma related intracranial abnormalities on their CT scans) was used for comparison.

In over half the children (60%) the frontal lobes where abnormally configured, which was in line with the hypothesised expectation. A total of 72% of children in our studied population presented with some form of intracranial abnormalities on their preoperative CT scan. Even though this seemed to support the theory of the (malformed) brain playing a substantial role in the etiology of metopic synostosis, there was no statistically significant relation between the severity of the preoperative frontal lobe agenesis and the severity of the initial skull malformation (the frontal angle or frontal stenosis, $p > 0{,}05$).

NEURODEVELOPMENT

The last chapter of this study focussed on the function of the brain in children with metopic synostosis in general, and that of the frontal lobes in particular. The assumption was made, that in the light of the studies mentioned above, frontal lobe function would be considerably compromised in a majority of these children. Several studies have claimed cognitive and psychiatric disorders in about 35% of cases. [15-17] These problems often become more apparent at school going age, when a sudden increase of social interaction is required. The behavioural problems appear to be present irrespective of corrective surgery. Validated tests were used and the results were corrected for low intelligence since intellectual disability (IQ lower than 70) in it self is associated with a high incidence of psychopathology, and thus could, as a consequence, negatively influence the outcome of this study.
A total of 39% of children presented with one or more clinical signs of neurodevelopmental disorders. The overall percentage of Attention Deficit Hyperactivity Disorder (ADHD) was 10%, against 3-5% in the normal population ($p<0,01$). The percentage of Autism Spectre Disorder (ASD) was 15%, while 1% is the norm ($p<0,01$). Oppositional Defiant Disorder (ODD) was present in 19% and Conduct Disorder (CD) in 4% of cases. Intellectual disability however, defined as IQ<70, was present significantly more often in these children with metopic synostosis than normal (in 12% of children, whereas 2,5% is normal).

Since intellectual disability is associated with an increased risk of psychopathology, we proceeded to statistically correct for low IQ levels. By stratifying the sample in $IQ < 85$ and $IQ \geq 85$, our findings indicated a 64% versus 24% overall presence of psychopathology. Intelligence and ADHD were significantly correlated ($r = -0.36$; $p < 0.01$), as were IQ and ODD ($r = -0.34$; $p < 0.05$), indicating that low IQ is associated with a higher risk of both ADHD and ODD. On the contrary, IQ was not significantly correlated with CD ($r = -0.19$; $p = 0.18$).

Frequencies of the tested disorders were as follows:

	IQ < 85	IQ > 85	Normal
ADHD	27%	11%	2,2-8,7%
ASD	40%	4%	1,8-4,4%
ODD	55%	11%	2,3-4,9%
CD	9%	2%	1,5%

The increased incidence of frontal lobe function disorders in children with metopic synostosis provided further support to the theory that intrinsic brain development disorders play a role in the etiology of metopic synostosis. Currently there are no other studies published that can be used to compare our results.

FUTURE RESEARCH

The constricted growth rate of the forehead even after surgery, the genetic link between skull and brain pathology, the high rate of frontal lobe hypoplasia and the elevated incidence of cognitive and psychiatric disorders seen in children with metopic synostosis all seem to direct towards a multifactorial etiology of this disorder, which is linked to the development of the brain.

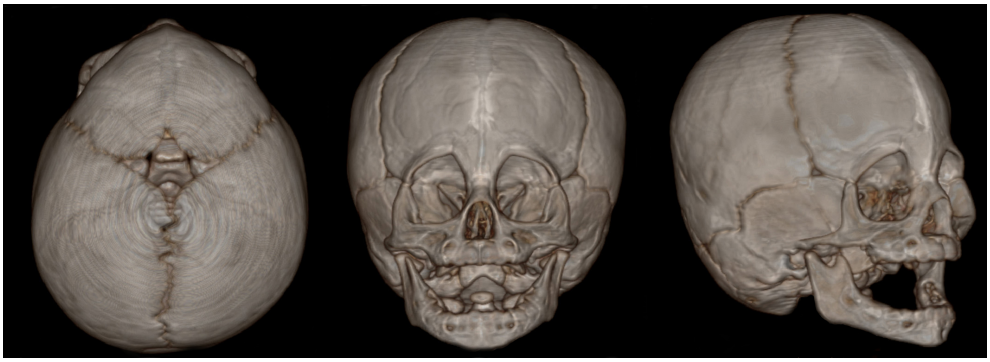
In order to further unravel the mysteries surrounding the etiology of metopic synostosis and its accompanying developmental disorders, future studies could for instance focus on the development of unoperated children with metopic synotosis, on joint molecular pathways driving neural crest cell development thus affecting bone as well as brain formation, or on the role of known factors of etiological influence, like Valproate, hypothyreoidism or possibly folic acid.

LITERATURE

1. Breugem CC, van RZBJ. Retrospective study of nonsyndromic craniosynostosis treated over a 10-year period. J Craniofac Surg 1999: 10: 140-3.
2. Kadri H, Mawla AA. Incidences of craniosynostosis in Syria. J Craniofac Surg 2004: 15: 703-4.
3. Marchac D, Renier D, Broumand S. Timing of treatment for craniosynostosis and facio-craniosynostosis: a 20-year experience. Br J Plast Surg 1994: 47: 211-22.
4. Anderson FM, Geiger L. Craniosynostosis: a Survey of 204 Cases. J Neurosurg 1965: 22: 229-40.
5. Hunter AG, Rudd NL. Craniosynostosis. I. Sagittal synostosis: its genetics and associated clinical findings in 214 patients who lacked involvement of the coronal suture(s). Teratology 1976: 14: 185-93.
6. Montaut J, Stricker M. Dysmorphies craniofaciales: les synostoses prématurées (craniostenoses et facio-craniostenoses). Paris: Masson, 1977.
7. Shillito J, Jr., Matson DD. Craniosynostosis: a review of 519 surgical patients. Pediatrics 1968: 41: 829-53.
8. Selber J, Reid RR, Chike-Obi CJ, et al. The changing epidemiologic spectrum of single-suture synostoses. Plast Reconstr Surg 2008: 122: 527-33.
9. van der Meulen J, van der Hulst R, van Adrichem L, et al. The increase of metopic synostosis: a pan-European observation. J Craniofac Surg 2009: 20: 283-6.
10. Chevrier C, Perret C, Bahuau M, et al. Fetal and maternal MTHFR C677T genotype, maternal folate intake and the risk of nonsyndromic oral clefts. Am J Med Genet A 2007: 143: 248-57.
11. Wilcox AJ, Lie RT, Solvoll K, et al. Folic acid supplements and risk of facial clefts: national population based case-control study. BMJ 2007: 334: 464.
12. Kress W, Petersen B, Collmann H, Grimm T. An unusual FGFR1 mutation (fibroblast growth factor receptor 1 mutation) in a girl with non-syndromic trigonocephaly. Cytogenet Cell Genet 2000: 91: 138-40.
13. Wilkie AO, Bochukova EG, Hansen RM, et al. Clinical dividends from the molecular genetic diagnosis of craniosynostosis. Am J Med Genet A 2007: 143A: 1941-9.
14. Raybaud C, Di Rocco C. Brain malformation in syndromic craniosynostoses, a primary disorder of white matter: a review. Childs Nerv Syst 2007: 23: 1379-88.

15. Kelleher MO, Murray DJ, McGillivary A, et al. Behavioral, developmental, and educational problems in children with nonsyndromic trigonocephaly. J Neurosurg 2006: 105: 382-4.
16. Bottero L, Lajeunie E, Arnaud E, Marchac D, Renier D. Functional outcome after surgery for trigonocephaly. Plast Reconstr Surg 1998: 102: 952-8; discussion 59-60.
17. Sidoti EJ, Jr., Marsh JL, Marty-Grames L, Noetzel MJ. Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 1996: 97: 276-81.

C H A P T E R N I N E



Summary

The diversity of the pathology seen in children with metopic synostosis has lead to this thesis. The research was planned with the intent to provide an insight into the current thoughts on this type of craniosynostosis and its treatment. Several aspects have thus been addressed in the previous chapters. They are summarised below:

CHAPTER 2 - INCREASED PREVALENCE IN EUROPE

In a Pan –European study data of 3240 cases were collected from 7 different cranio-facial units, seen over a period of 9 years (1997-2006). Statistical analysis of the data collected confirmed a remarkable increase of metopic synostosis occurring in 2000-2001, with significant increase in the second half of this period when compared to the first half. Reasons behind this increase remain unclear.

CHAPTER 3 - GENETIC ETIOLOGY

Routine screening for a genetic etiology in children with craniosynostosis is reserved for syndromic cases and for children presenting with coronal synostosis. Most of these disorders are linked with anomalies of the genes coding for the Fibroblastic Growth Factor Receptors (FGFR) 1-3.

Over the last decennia, genetic studies have revealed only sporadic evidence of genetic malformations in metopic synostosis. We found the FGFR 3 Pro250ARG mutation, which is typical for Muenke syndrome, in a case of metopic synostosis. Up till now all of the cases of Muenke syndrome presented with uni- or bi-coronal synostosis. The same mutation was found in the boy's mother.

CHAPTER 4 - PERI-ORBITAL GROWTH AFTER SURGERY

In a clinical study we subsequently focused on the peri-orbital growth following cranioplasty in 92 cases of trigonocephaly. Cephalometric analysis was performed using specific landmarks, clarified in the drawing below (Fig 1.).

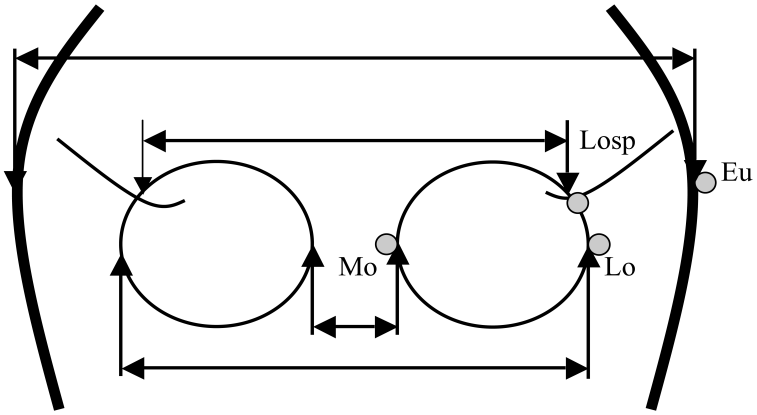


Fig I. Schematic drawing of periorbital region, with the location of the landmarks used (MO - medial orbital wall, LO - lateral orbital wall, LoSp - junction between the lateral orbital wall and the sphenoid wing, Eu - Eurion, the most widest point of the skull)

Since it was impossible to standardise the radiographs due to the young age of the children, we resolved to the use of growth ratios. Analysis of these ratios revealed a persistently higher medial orbital wall growth ratio (Mo-Mo) when compared to the fairly normal lateral orbital wall growth ratio (Lo-Lo) and lateral skull growth ratio (Eu-Eu), indicating an (limited) auto-correction of the hypotelorism in the years following the cranioplasty. When compared to growth ratios of the skull-width and the lateral orbital wall, the temporal landmark showed the slowest postoperative growth rate, which could account for the temporal hollowing so often seen after cranioplasty in this population.

CHAPTER 5 - THE ORIGIN OF TEMPORAL HOLLOWING

Following this paper we proceeded to investigate other potential etiological pathways possibly leading to temporal hollowing. Factors related to the soft tissue, like temporal muscle or superficial temporal fat pad atrophy, seemed an unlikely cause, since both layers are mobilised in a sub-periosteal plane during the operation and stay attached to the skin/galeal flap, thus preserving their vascularity.
Furthermore, in 97% of all patients the muscle appeared to be in the proper position even years after surgery.
The surgical technique and the experience of the surgeon performing it did appear to be of influence, since temporal hollowing, once apparent immediately after

surgery, did persist over the years. The amount of hollowing however was irrespective of the severity of the initial deformity.
By comparing growth ratios based on radiographs with the photographic analysis (in 33 cases), we could prove that limited osseous growth in the temporal region (LoSp) did correlate with a bad visual grading of temporal hollowing, thus providing further proof of a bony origin of this hollowing.

CHAPTER 6 - INTRACRANIAL DEFORMITIES

Since neurodevelopmental disorders are so typically associated with this type of craniosynostosis, preoperative CT scan of 78 children with metopic synostosis were screened and compared to a random control group of 12 posttraumatic children (with no trauma related intracranial abnormalities on their CT scans).
Intracranial evaluation (done by a paediatric radiologist) showed a total of 72% cases presenting with some form of intra cranial deformity. There were signs of elevated intracranial pressure (10%), ventricular dilitation (present in 40% versus 8% in the control group, $p = 0{,}03$) and frontal lobe hypoplasia in 60% of children. Mild frontal agenesis was seen in 56% and severe agenesis in 4%. Even though this seemed to support the theory of the (malformed) brain playing a substantial role in the etiology of metopic synostosis, there was no statistically significant relation between the severity of the preoperative frontal lobe agenesis and the severity of the initial skull malformation (the frontal angle or frontal stenosis, $p > 0{,}05$).

CHAPTER 7 - NEURODEVELOPMENTAL DISORDERS

The high incidence of behavioural problems seen in children with metopic synostosis appear to be present irrespective of corrective surgery. This study was conducted to investigate the type and incidence of behavioural problems related to frontal lobe dysfunction using validated tests. The results were corrected for low intelligence since intellectual disability (IQ lower than 70) in it self is associated with a high incidence of psychopathology, and thus could, as a consequence, negatively influence the outcome of this study.
A total of 39% out of 86 children presented with one or more clinical signs of neurodevelopmental disorders. By stratifying the sample in $IQ < 85$ and $IQ \geq 85$, our findings indicated a 64% versus 24% overall presence of psychopathology. Intelligence and ADHD were significantly correlated ($r = -0.36$; $p < 0.01$), as were IQ and ODD ($r = -0.34$; $p < 0.05$), indicating that low IQ is associated with a higher

risk of both ADHD and ODD. On the contrary, IQ was not significantly correlated with CD (r = -0.19; p = 0.18).

Frequencies of the tested disorders were as follows:

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CD	9%	2%	15%

The increased incidence of frontal lobe function disorders in children with metopic synostosis provided further support to the theory that intrinsic brain development disorders play a role in the etiology of metopic synostosis.

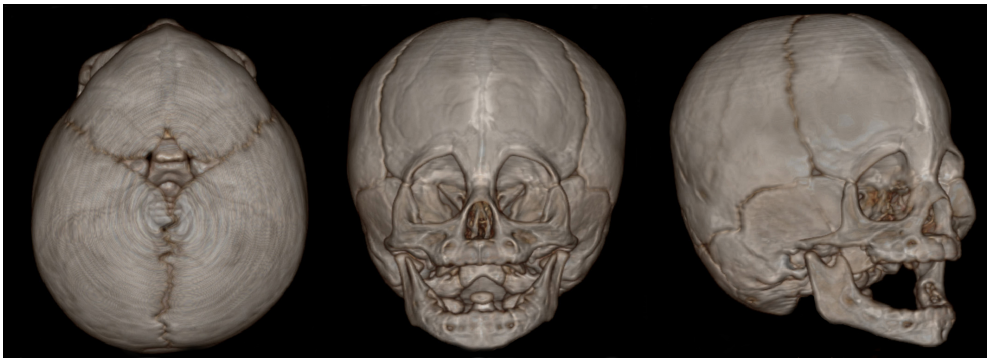
FUTURE RESEARCH

In order to further unravel the mysteries surrounding the etiology of metopic synostosis and its accompanying developmental disorders, future studies could for instance focus on the development of unoperated children with metopic synotosis, on joint molecular pathways driving neural crest cell development thus affecting bone as well as brain formation, or on the role of known factors of etiological influence, like Valproate, hypothyreoidism or possibly Folic Acid.

CONCLUSIONS

- Metopic synostosis is on the rise in several European Units.
- Genetic abnormalities have been shown to be linked to metopic synostosis.
- Relatively increased medial orbital wall growth rates reduce residual post-operative hypotelorism in metopic synostosis.
- The temporal area shows the least peri-orbital osseous growth rate after operation.
- Soft tissues play a limited role in the origin of temporal hollowing, which seems to be mainly the result of the above mentioned reduced osseous growth potential.
- There is a high number of intracranial abnormalities (72%) in these patients, with 60% of cases presenting with frontal hypoplasia.
- A substantial number of children (39%) with metopic synostosis appear to have neurodevelopmental disorders. However, this percentage is reduced down to levels close to normal after correcting for low intelligence.

C H A P T E R T E N



Samenvatting

De oorsprong van dit proefschrift ligt in de diversiteit van de pathologie die gezien wordt bij kinderen met een synostose van de voorhoofdsnaad. Het onderzoek beoogd een overzicht te geven van de verschillende aspecten van trigonocephalie. Verscheidenen daarvan zijn in de voorgaande hoofdstukken aan bod gekomen. Hieronder volgt een samenvatting van de bevindingen.

HOOFDSTUK 2 - TOEGENOMEN PREVALENTIE BINNEN EUROPA

In een pan–Europese studie werden data van 3240 gevallen van craniosynostose verzameld uit 7 verschillende craniofaciale klinieken. Het ging hierbij om kinderen gezien in de periode van 1997 tot 2006. Statistische analyse bevestigde een opmerkelijke toename van metopica synostose in 2000-2001, met een significante toename in de tweede helft van de bestudeerde periode in vergelijking met de eerste helft. De oorzaken daarvoor zijn tot nu toe onduidelijk gebleven.

HOOFDSTUK 3 - GENETISCHE ETIOLOGIE

Routinematige screening voor een genetische etiologie in kinderen met craniosynostose is voorbehouden aan syndromale gevallen of kinderen met een kroonnaad synostose. De meesten van deze afwijkingen zijn gerelateerd aan anomaliën van de genen die coderen voor de Fibroblastic Growth Factor Receptors (FGFR) 1-3.

Over de laatste decennia heeft genetisch onderzoek slechts sporadisch bewijs opgeleverd voor een genetische oorzaak van metopica synostose. Wij vonden de FGFR 3 Pro250ARG mutation, welke pathognomisch is voor het syndroom van Muenke syndrome, in een geval met metopic synostose. Tot nu toe zijn alle beschreven gevallen van het Muenke syndroom gerelateerd met een kroonnaad synostose. De moeder van onze casus bleek dezelfde afwijking te hebben.

HOOFSTUK 4 - PERI-ORBITALE GROEI NA CRANIOPLASTIEK

Een klinische studie richtte zich vervolgens op de peri-orbitale groei na corrigerende cranioplastiek bij 92 gevallen van trigonocephalie. Cephalometrische analyse werd gedaan met gebruik van specifiek meetpunten, aangeduid in onderstaand schema (Fig 1.).

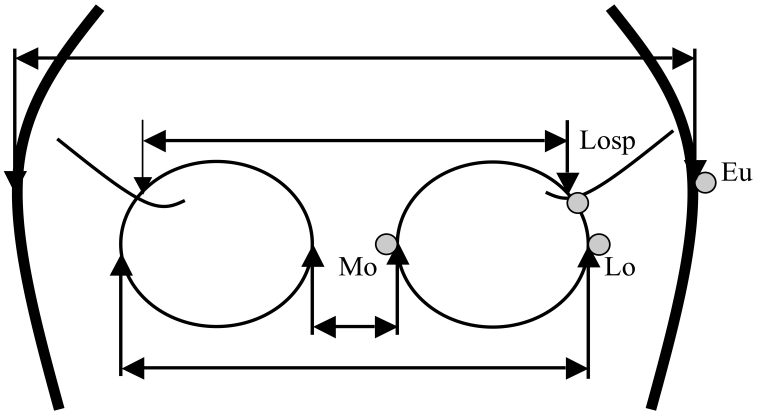


Fig I. Schematische tekening van de periorbitale regio, met de locatie van de gebruikte meetpunten (MO - mediale oogkaswand), (LO - laterale oogkaswand), (LoSp - kruispunt tussen laterale orbita wand and sphenoid vleugel), Eu - Eurion, (het meeste laterale punt van de schedel)

Omdat de röntgenopnamen op de jonge leeftijd van presentatie van deze kinderen niet gestandaardiseerd zijn, werd er geconverteerd naar het gebruik van groeiratio's. Analyse van deze ratios bracht aan het licht dat de groeiratio van de mediale oogkaswand na de operatie continu verhoogd is ten opzicht van die van de laterale oogkaswand. Dit wijst op een autocorrectie van het hypotelorisme. Bij vergelijking van de schedelbreedte, de laterale oogkaswand en de kruising van oogkanswand en sphenoid, blijkt dat deze laatste het langzaamste te groeien, hetgeen de temporale deuken op basis van onvoeldende botgroei in deze regio zou kunnen verklaren.

HOOFDSTUK 5 - DE ORIGO VAN TEMPORALE INDEUKINGEN

De temporale deuken kunnen door verschillende andere oorzaken veroorzaakt worden. Factoren gerelateerd aan de weke delen (zoals temporale vet pocket of temporalis spier) bleken onwaarschijnlijk gezien het subperiostale dissectievlak dat gebruikt wordt in de operatie. Zo bleek in 97% van de gevallen bij palpatie de temporalis spier voldoende hoog gepositioneerd te zijn.

De operatie techniek en de ervaring van de chirurg speelden ook een rol. Een deuk, eenmaal aanwezig na de operatie, bleek tot op late leeftijd te persisteren. De mate van postoperatieve indeuking was echter niet gerelateerd aan de ernst van de initiële afwijking. Door twee datasets te vergelijken (33 casus hadden een complete

set röntgenologisch en fotografische evaluatiedata) kon worden aangetoond dat specifiek de beperkte botgroei in de temporale regio correleerde met een slechte visuele score, daarmee verder bewijs leverend voor de ossale etiologie van deze deuken.

HOOFDSTUK 6 - INTRACRANIALE AFWIJKINGEN

Gezien de typische associatie tussen neurologische ontwikkelingsstoornissen en metopica synostose werden 78 preoperatieve CT scans aan een analyse onderworpen. Deze scans werden vergeleken met een controle groep van 12 kinderen die een schedel scan ondergingen in verband met een niet schedel gerelateerd letsel. Evaluatie door een gespecialiseerde kinderradioloog liet zien dat bij de overgrote meerderheid èèn of meerdere intracraniale afwijkingen aanwezig waren (72%). Het ging hierbij met name om tekenen van verhoogde intracraniale druk (10%), ventriculaire dilatatie (aanwezig in 40% tegen slechts 8% in de controle groep, $p = 0.03$) en frontale kwab hypoplasie (in 60%). Zesenvijftig van deze 60% betroffen milde afwijkingen, terwijl 4% van de kinderen een forse hypoplasie liet zien. Deze bevindingen lijken de relatie tussen het gemalformeerde brein en de premature schedelnaadsluiting te ondersteunen. Er bleek echter geen significante relatie te bestaan tussen de mate van frontaalkwab hypoplasie en de ernst van de initiële afwijking (de frontale stenose of hoek)($p > 0.05$).

HOOFDSTUK 7 - NEUROLOGISCHE ONTWIKKELINGSPROBLEMEN

De hoge incidentie van gedragsproblemen in deze patiënten populatie lijkt onafhankelijk van de correctieve ingreep aanwezig te zijn. Deze studie werd vervolgens uitgevoerd met gevalideerde tests om de aard en de mate van gedrags afwijkingen in kaart te brengen die specifiek gerelateerd zijn aan de frontale kwabben. De resultaten werden gecorrigeerd voor lage intelligentie (IQ lager dan 70), omdat lage intelligentie in zichzelf is geassocieerd met gedragsproblemen, hetgeen de uitkomsten van deze studie negatief zou kunnen beïnvloeden.

In totaal 39% van de 86 kinderen presenteerde zich met een of andere vorm van gedragsproblematiek. Na stratificatie van de onderzoeksgroep in $IQ < 85$ and $IQ \geq 85$ bleek een 64% versus 24% aanwezigheid van gedragsproblematiek binnen de groepen. Intelligentie en ADHD waren significant gecorreleerd ($r = -0.36$; $p < 0.01$), evenals IQ en ODD ($r = -0.34$; $p < 0.05$), beiden wijzend op een

relatie tussen laag IQ en een hoger risico op ADHD en ODD. IQ bleek niet significant gecorreleerd met CD (r = -0.19; p = 0.18).

Frequenties van de onderzochte gedragsproblemen waren als volgt:

	IQ < 85	IQ > 85	Normal
ADHD	27%	11%	2,2-8,7%
ASD	40%	4%	1,8-4,4%
ODD	55%	11%	2,3-4,9%
CD	9%	2%	15%

Ook deze verhoogde incidentie van frontaal kwab functie afwijkingen in de populatie kinderen met een metopica synostose is een verdere aanwijzing dat er een relatie bestaat tussen de intrinsieke ontwikkeling van het brein en die van de omliggende schedel.

TOEKOMSTIG ONDERZOEK

Om meer duidelijkheid te schapen in de etiologie van metopica synostose en de daaraan gerelateerde gedrags en ontwikkelinggsstoornissen, zou toekomstig onderzoek zich kunnen richten op de groep ongeopereerde kinderen met trigonocephalie om daarmee een antwoord te kunnen krijgen op de vraag of de huidige operatieve behandeling mogelijk een schadelijke invloed heeft op de ontwikkeling van het brein. Tevens zou het zinvol zijn om de gezamelijke moleculaire banen te onderzoeken die de neurale crest cel ontwikkeling aansturen, omdat deze op de ontwikkeling van zowel de schedel als het onderliggende brien van invloed zijn. Verder is de rol van externe factoren zoals Valproaat, hypothyroïdie of foliumzuur op de etiologie van deze aandoening is nog verre van duidelijk.

CONCLUSIES:

- De tot nu toe onverklaarbare toename van metopica synostose wordt in meerdere Europese craniofaciale centra geobserveerd.
- Er bestaat een relatie tussen een genetisch afwijking en metopica synostose.
- De relatieve toename van de groeisnelheid van de mediale orbitale oogkaswand geeft dat het hypotelorisme dat na de operatie nog aanwezig is in de loop der jaren vanzelf minder wordt.
- The temporale regio vertoond de minste expansieve groeipotentie van de gehele perioperatieve regio na operatie.
- Weke delen spelen een beperkte rol in de etiologie van postoperatieve temporale indeukingen. Deze lijken dan ook met name het gevolg te zijn van een verminderde groei van het bot in die regio.
- Er is een groot aantal trigonocephalie patiënten dat zich presenteert met een intracraniale afwijking (72%), terwijl 60% van hen een frontale hypoplasie heeft.
- Een substantieel aantal kinderen (39%) met metopica synostose heeft neurologische ontwikkelings stoornissen. Dit percentage wordt echter sterk gereduceerd tot vrijwel normaal als er gecorrigeerd wordt voor lage intelligentie.

Curriculum Vitae

The author of this thesis was born in Utrecht, The Netherlands, on 15 September 1966. After one year of dentistry he started his medical school in 1986 at the Rijks Universiteit Groningen, finishing in 1991. The following year was spend exploring the world, while taking the opportunity to visit 7 renowned Plastic Surgery units along the way.

In 1992 he proceeded with the final two years of medical school at the Erasmus University, only to leave for the U.K. as soon as he qualified as a doctor in 1995. There he worked in several surgical specialties before returning to Rotterdam to start as an AGNIO in 1996. His subsequent General Surgery training was done in the St. Elisabeth hospital in Tilburg under the enriching guidance of Prof. dr. J.A. Roukema, followed by his Plastic Surgery training with Prof. dr. S.E.R Hovius. During the last phase of his training he was given the opportunity to specialise in the field of craniofacial surgery under the supervision of M. Vaandrager. This lead to him joining the staff of the Plastic Surgery department in the Sophia Children's Hospital in 2003, a position he has held ever since.