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CRANIOSYNOSTOSIS

KEYWORDS: To analyses,understand and treat craniosynostosis.

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ABSTRACT *AIM:- To study about craniosynostosis.*

OBJECTIVE:- The purpose of the study is to analyse published studies in order to provide a summary about craniosynostosis.

BACKGROUND:- Craniosynostosis (sometimes called craniostenosis) is a disorder in which there is early fusion ofthe sutures of the skull in childhood. It produces an abnormally shaped head and appearance of the face. When there is no other involvement besides the skull growth plates, the condition is termed Non-Syndromic Craniosynostosis.Treating craniosynostosis usually involves surgery to separate the fused bones. If there's nounderlying brain abnormality, the surgery allows your baby's brain adequate space to grow and develop

Introduction

Of the human skull's many functions; it's largest component, the cranium, which comprises the dome-shaped vault and the cranial base, protects and insulates the brain. Growth and development of the skull vault and cential nervous system are closely interrelated. The skull is dependent on the forces of brain growth to expand, and conversely, the brain requires the skull to accommodate growth, particularly during its most rapid growth phase; within the pre- and post-natal period.Abnormalities of skull growth can result in significant distortions to its shape. Due to the close relationship between skull and facial bone growth, visible deformities of the face may also ensue. This combination of features is often referred to as craniofacial anomalies or craniofacial disorders. [1]

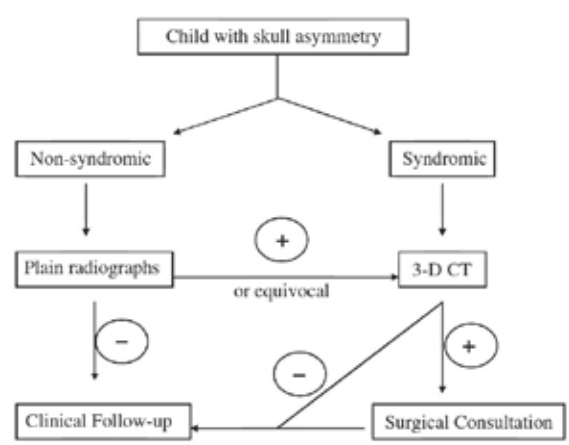
During infancy and childhood, the skull vault (calvaria) expands to accommodate the growing brain. This growth occurs predominantly at the narrow seams of undifferentiated mesenchyme, termed cranial sutures, which lie between different bones. The paired frontal and parietal bones are separated in the midline by the metopic and sagittal sutures, respectively; the frontal and parietal bones are separated by coronal sutures; and the parietal bones are separated from the single occipital bone by lambdoid sutures.

Clinical overview

The aims of clinical assessment are to determine whether craniosynostosis is present; whether there are additional features suggesting an associated syndrome and to assess whether urgent or elective management is required. Craniosynostosis is very heterogeneous in its causes and presentation, and correspondingly in its management. Most isolated non-syndromic cases present electively, but a minority of syndromic cases present acutely and require immediate intervention. Classifications of craniosynostosis based on the combination of sutures closed, associated features suggesting a syndrome, and identifiable aetiological factors (for example, intrauterine constraint,teratogenic exposure and genetic abnormalities) all have validity, and should be considered in combination.[2]

The clinical examination should follow a set pattern to avoid overlooking clues. Our own routine is to start with the hands and feet looking for congenital anomalies, for example, a broad radially deviated thumb or big toe in Pfeiffer syndrome ,more extensive syndactyly in Apert syndrome and longitudinally split nails in craniofrontonasal syndrome.Examine the face for dysmorphic features, including hyper-or hypotelorism, exorbitism, midface hypoplasia, asymmetry and ear size, position and shape. The combination of exorbitism, flattened malar region and beaked nose signals a 'crouzonoid' appearance ,likely to be associated with FGFR2 mutation. If there is hypertelorism, view the nose from above looking for a shallow groove, which suggests craniofrontonasal syndrome .Ptosis, low frontal hairline and small ears with prominent horizontal crura are features of Saethre-Chotzen syndrome .

Diagnostic approach



Computed tomography (CT) scanning and three dimensional reconstruction using both bone and soft tissue windows is the investigation of choice.6 This should clearly reveal the patency, or closure, of each individual suture .CTof the brain should also be performed seeking associated anatomical abnormalities (for example, ventriculomegaly and agenesis of corpus callosum) and to check the fluid spaces

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for evidence of craniocerebral disproportion. CT venography is required in complex cases where abnormal venous drainage is suspected. Skull radiographs are of limited use as their sensitivity for detecting sutural patency is significantly less than CT. They are most useful when screening cases of plagiocephaly when the clinical findings are not conclusive. Magnetic resonance imaging (MRI), although ideal for the brain, is less good at visualising the sutures of the brain.

MOLECULAR AND GENETIC BASIS OF DISEASE

In a recent analysis of a 10-year prospective cohort of craniosynostosis presenting to our unit, a genetic diagnosis was achieved in 21% of cases, comprising 86% single gene disorders and 15% chromosome abnormalities (one patient had both).7 The genes most frequently mutated were FGFR2 (32% of all genetic cases), FGFR3 (25%), TWIST1 (19%) and EFNB1 (7%). Figure 2 illustrates the domain structures of proteins encoded by these four genes, together with the clinical presentation and molecular distribution of mutations in the cohort survey, illustrating the relative prevalence of the major mutations causing craniosynostosis. Much rarer, but well established associations of gene mutations and craniosynostosis are for FGFR1 (mild Pfeiffer syndrome), POR (Antley-Bixler syndrome) and RAB23 (Carpenter syndrome); further information about these genes is provided below. Single-gene mutation associations that are based on only a handful of cases are not further discussed; these include mutations in EFNA4 (non-syndromic coronal synostosis),8 ESCO2 (Roberts syndrome), GLI3 (Greig syndrome), JAG1 (Alagille syndrome), KRAS (Noonan syndrome), RECQL4 (Baller Gerold syndrome) and TGFBR1 or TGFBR2 (Loeys-Dietz syndrome). Mutation in MSX2, the first genetic cause of craniosynostosis to be molecularly determined,9 is exceptionally rare, having been reported to date only in the original family, but several duplications including MSX2 have been associated with craniosynostosis.

FGFR2 (fibroblast growth factor receptor type 2)

The FGFR2 gene encodes a transmembrane receptor tyrosine kinase comprising an extracellular ligand-binding region (immunoglobulin-like domains IgI, IgII and IgIII), a single pass transmembrane region (TM) and split tyrosine kinase domain (TK1 and TK2). Heterozygous mutations of FGFR2 cause three classical craniosynostosis syndromes, those of Apert, Crouzon and Pfeiffer. All exhibit a characteristic crouzonoid facial appearance. Less commonly, mutations may present with non-syndromic synostosis, Beare-Stevenson syndrome (multisuture synostosis associated with cutis gyrata). Mutations in FGFR2 and FGFR3 tend to encode highly localised, recurrent missense substitutions encoding proteins with gain-of-function properties. The cellular consequences of mutation are complex, including enhancement of proliferation, differentiation and apoptosis of osteoblasts bordering the cranial suture mesenchyme; premature differentiation is probably the most important factor leading to craniosynostosis.11,12 Apert syndrome is characterised by bicoronal synostosis and bilateral symmetrical complex syndactyly of the hands and feet. Other frequent complications include cleft palate (44%) and learning disability, requiring special needs education (44%).13 Over 98% of cases are caused by specific missense mutations of FGFR2, either Ser252Trp (66%) or Pro253Arg (32%), in the linker between the IgII and IgIII domains the former substitution is associated with a higher frequency of cleft palate, but milder syndactyly.13 These substitutions specifically increase the affinity and broaden the specificity of FGF-ligand binding, explaining the exquisite genotypepheno-type correlation.Nearly all Apert syndrome mutations arise de novo, and have been shown to originate exclusively from the father. These mutations provide a paradigm for paternal age effect mutations that are enriched in sperm owing to a paradoxical selective advantage to mutant spermatogonial cells in the testis.

Pfeiffer syndrome is usually characterised by broad, radially deviated thumbs and/or big toes, sometimes with cutaneous syndactyly, and includes individuals previously classified with a 'Jackson-Weiss' phenotype. The craniofacial severity is variable, an important subgroup presenting with severe multisuture synostosis ('Kleeblatscha¨del'), which is very challenging to manage and associated with significant mortality. FGFR2 mutations in Pfeiffer syndrome overlap those in Crouzon syndrome, but the majority of severe cases are caused by a small subset of substitutions encoding Trp290Cys, Tyr340Cys, Cys342Arg or Ser351Cys.17 Crouzon syndrome is usually the mildest of the FGFR2-associated disorders and the clinical diagnosis is suggested by the combination of crouzonoid facies and absence of major abnormalities of the hands and feet. Although bicoronal synostosis is most common, Crouzon syndrome can present with late-onset pansynostosis.It is important to be aware of this possibility in a child with a crouzonoid appearance, because apparently mild distortion of the skull shape may maskthepresenceofraisedICP.Theassociationofcrouzonoidfacies with acanthosis nigricans is caused by a specific FGFR3 mutation. The distribution of mutations causing Pfeiffer and Crouzon syndromes in FGFR2 overlaps considerably. Most mutations (94%) occur in the third extracellular immunoglobulin-like domain encoded by exons IIIa or IIIc, where they cause constitutive activation by covalent cross-linking of receptor monomers. The remainder of the mutations are scattered in seven other exons of the gene, including several mutations in the tyrosine kinase domain.20 Abnormal splicing of the IIIc exon tends to be associated with more severe limb abnormalities, so these mutations generally present with Pfeiffer or occasionally even Apert syndrome (Alu element insertions).

FGFR3 (fibroblast growth factor receptor type 3)

FGFR3 encodes a protein that has a domain structure closely resembling its paralogue FGFR2 . Although FGFR3 mutations are commonly associated with bone dysplasia (hypochondroplasia-achondroplasia-thanatophoric dysplasia series), two heterozygous mutations cause specific craniosynostosis syndromes, Muenke syndrome and Crouzon syndrome with acanthosis nigricans. Muenke syndrome, defined by identification of the Pro250Arg substitution, is individually the most common genetic abnormality found in craniosynostosis, comprising B5% of all cases.The associated phenotype is not distinctive and was not properly delineated until the mutation was described in 1996. Patients usually present with either unicoronal or bicoronal synostosis, but at least 20% of mutation carriers do not have clinically significant craniosynostosis. The facial appearance ranges from normal to a dysmorphic appearance easily mistakable for Saethre-Chotzen syndrome. Minor digital abnormalities (especially brachydactyly) are not characteristic and there should be a low threshold for requesting the genetic test to establish the diagnosis. An important complication is low frequency hearing loss, requiring the fitting of hearing aids in B20% of patients.The Pro250Arg substitution is the exact equivalent to the Apert Pro253Arg substitution in FGFR2, and also causes ligand-dependent gain-of-function.However the reasons for the specific association of this mutation with craniosynostosis are not fully understood. Crouzon syndrome with acantho-

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sis nigricans is characterised by the Ala391Glu substitution. The acanthosis nigricans, which develops during childhood, is usually not apparent at presentation, so specific testing should be requested in the diagnostic workup of Crouzon syndrome. A positive result should prompt a careful neurosurgical assessment as hydrocephalus is a frequent association. [3]

TYPES OF CRANIOSYNOSTOSIS

Table 1 Characteristics of various types of craniosynostosis

Type	Head shape	Clinical features
Sagittal 	Scaphocephaly or dolichocephaly	Frontal bossing, elongated cranium (boat-shaped), prominent occiput, palpable keel ridge, normal head circumference, reduced biparietal diameter (skull longer in anteroposterior diameter), reversed slope of cranium Anterior fontanelle may be patent or not
Coronal 	Unilateral plagiocephaly	Marked craniofacial asymmetry: flattened forehead on affected side, flat cheeks, nose deviation to normal side, higher supraorbital margin leads to harlequin sign on radiographs and outward rotation of orbit
	Bilateral; brachycephaly, acrocephaly	Vertical, broad, flattened forehead, possible hypoplasia of midface and progressive proptosis, choanal atresia, high-arched palate, and poor dental occlusion Skull shorter in anteroposterior diameter, biparietal diameter increased A ridge possibly detected via palpation over coronal suture Nasolacrimal duct possibly narrowed, visual acuity possibly decreased
Metopic 	Trigonocephaly	Pointed or triangular forehead and prominent midline ridge, lateral supraorbital recession, fontanelle usually absent, hypotelorism
Multiple	Oxycephaly	Tower skull with shallow orbits

[4]

Treatment for craniosynostosis (Surgical)

Goal of the surgery

The primary goal in surgical intervention is to allow normal cranial vault development to occur.This can be achieved by excision of the prematurely fused suture and correction of the associated skull deformities.If the synostosis goes uncorrected, the deformity will progressively worsen not only threatening the aesthetic aspect, but also the functional aspect.This is especially the case in the asymmetric conditions, such as unilateral coronal synostosis, with compromised function of the eyes and the jaw.In addition signs of compromised neurodevelopment have been seen amongst all the synostoses, although this may also be caused by primary maldevelopment of the brain and can thus not be prevented by surgical intervention.

Spring-mediated Cranioplasty

David et al. (2010) conducted a study to compare the outcomes of the first 75 cases of springassisted surgery (SAS) for the treatment of sagittal with a prospectively collected group of patients treated with cranial expansion (cranial vault remodeling [CVR]). All patients successfully underwent SAS without significant complications with a mean follow-up of 46 months. Perioperative variables including odds ratio, time, blood loss, transfusion requirements, intensive care unit and hospital stay lengths, and hospital costs differed significantly in favor of SAS. The mean cephalic index improved from 69 preoperatively to 75.4 after SAS, comparable with the change from 66 to 72.5 for CVR. This correction was maintained at 3- and 5-year follow-ups. Anterior frontal bossing was corrected on three-dimensional scan volume measurements. Taylor et al. (2011) retrospectively compared the safety and efficacy of spring-mediated cranioplasty (SMC) and minimally invasive strip craniectomy with parietal barrel staving (SCPB) analyzing the hospital records of the first 7 SMCs and the last 7 SCPBs. All 14 patients successfully underwent cranial vault remodeling with significant improvement in cephalic index. Demographics, length of stay in the intensive care unit, preoperative cephalic index , and postoperative cephalic index were similar between SMC and SCPB. Spring-mediated cranioplasty had statistically significantly shorter operative time, less estimated blood loss and shorter length of hospital stay as compared with SCPB. Complications included 1 spring dislodgment in an SMC that did not require additional management and 1 undercorrection in the SCPB group. The authors stated that spring-mediated cranioplasty has become the predominant means of treatment of scaphocephaly in patients younger than 9 months because of its improved morbidity profile. A retrospective study of 23 metopic synostosis patients operated with spring-assisted correction conducted by Maltese et al. (2007). The authors used a spring used together with a cranioplasty for the correction of both hypotelorism and orbital shape in trigonocephaly. Preoperative mean bony interorbital distance was 10.6 mm (range, 7.7 to 13.2 mm). It increased to 15.7 mm (range, 10.4 to 22 mm) at 1.5 months postoperatively and to 16.2 mm (range, 10.9 to 24.5 mm) 5 months postoperatively. Results as judged clinically ranged from little effect to a definitive overcorrection. The fronto-orbital axis was improved in every case. Average fronto-orbital axis was -4 degrees (range, -33 to 23 degrees) preopera-

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tively and 28 degrees (range, 11 to 46 degrees) post-operatively.[7]

Conclusion

Craniosynostosis is a condition in which one or more of the fibrous sutures in an infant skull prematurely fuses by turning into bone (ossification)[9],thereby changing the growth pattern of the skull.Because the skull cannot expand perpendicular to the fused suture, it compensates by growing more in the direction parallel to the closed sutures[10].Craniosynostosis occurs in one in 2000 births. Craniosynostosis is part of a syndrome in 15 to 40% of the patients, but it usually occurs as an isolated condition.[11] For treatment,The applicant process in cases ion of a statistical shape model as a tool for guiding the skull reshaping of craniosynostosis has proven successful, as shown in a first clinical evaluation.Statistical shape models are capable of providing objective, yet patient-specific criteria for the reshaping process. At the same time they accelerate the process of reshaping as they prevent mistakes or uncertainties followed by time consuming corrections.It will be examined whether the model can be applied for segmentation purposes as well, as this is the most time-consuming task in the model generation pipeline. In this work, the matching of the model was carried out on the basis of a few landmark measurements.[8]

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