Craniosynostosis (generic term)

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Abstract
Craniosynostosis consists of premature fusion of one or more cranial sutures, resulting in an abnormal head shape. It can be divided in several subgroups; the major different types are primary vs secondary craniosynostosis and isolated vs syndromic craniosynostosis. The overall incidence for all forms of craniosynostosis is 1/2,000-1/2,500 live-born children. Most cases are evident during the neonatal period. Occasionally, it may be detected prenatally by ultrasound examination or not noted until late in infancy. A primary defect in the mesenchymal layer ossification in the cranial bones is accepted to play a role in the etiology of primary craniosynostosis. Many of the syndromic forms (Apert, Carpenter, Crouzon, Muenke types) are related to mutations in one of the FGFR *genes. Mutations in the* TWIST *gene have been identified in Saethre-Chotzen syndrome. Mutations in* MSX2 *are causative in Boston-type craniosynostosis. Autosomal dominant inheritance has been identified in by far the most syndromic forms of craniosynostoses. The percentage of patients showing a spontaneous new mutations is high. Germ line mosaicism is also known to occur and should be discussed with the family. Usually no mendelian pattern of inheritance can be identified in nonsyndromic forms. Craniosynostoses are very heterogeneous traits. All are characterized by skull deformities, with face and often limb involvement in the syndromic forms. Children with syndromic forms (eg, Apert syndrome) can be affected by a variable degree of developmental delay. No medical treatment exists to stop an early ossification of a cranial suture. Infants with a craniosynostosis may require a series of surgical procedures.*

Keywords
Craniostenosis, brachycephaly, plagiocephaly, trigonocephaly, *FGFR* genes, *TWIST* gene, *MSX2* gene

Disease name/synonyms
Craniosynostosis/craniostenosis

Definition/diagnostic criteria
Craniosynostosis consists of premature fusion of one cranial suture (*Simple craniosynostosis)* or more cranial sutures (*Complex or compound craniosynostosis*), resulting in an abnormal head shape. Most cases are evident during the neonatal period. Craniosynostoses can be divided in several subgroups; the major different types are primary vs secondary craniosynostosis and isolated vs syndromic craniosynostosis.

Primary craniosynostosis
A craniosynostosis may result from a primary defect of ossification. Primary craniosynostosis

shows a skull deformity due to an impaired skull growth perpendicular to the affected suture, causing increased growth along the same direction that the suture follows. The isolated form occurs in individuals without other anomalies.

Secondary craniosynostosis

Craniosynostosis may also results from a failure of brain growth, and occur in an otherwise normal neurocranium. There is no abnormality in the ossification. Patients with this form usually are microcephalic, may or may not show symptoms in other body areas, and often have a developmental delay due to the primarily impaired brain growth. Sometimes the external shape of the neurocranium is influenced by external forces such as prolonged sleeping of the child on the back, which may cause flattening of the occiput and early closure of the lambdoid sutures. Even more rarely other disorders can cause a craniosynostosis such as several metabolic disorders.

Syndromic craniosynostosis

Craniosynostoses that are associated with other body deformities are called syndromic craniosynostoses. There are many dozens of different types, the major ones being Apert syndrome, Carpenter syndrome, Crouzon syndrome, Muenke syndrome, and Saethre-Chotzen syndrome. Many of these show the combination of craniosynostoses with limb anomalies, and are also referred to as acrocephalosyndactylies.

Diagnostic methods

A craniosynostosis is usually noted in the newborn period. Occasionally, it may be detected prenatally by ultrasound examination or not noted until late in infancy.
Careful clinical examination alone can often but not always allow establishing a diagnosis, due to the abnormal shape of the neurocranium, secondary facial features such as proptosis, and abnormal skull growth. Identification of the affected suture(s) is possible by plain skull radiographs. Computing tomography (CT) scanning is useful in delineating associated abnormalities of the face and central nervous system, and may be used to perform 3D analysis of the face as well (Darling et al, 1994). Magnetic resonance imaging (MRI) can provide improved definition of intracranial soft tissue structures compared with CT (Hayward et al, 1992).

Differential diagnosis

Primary craniosynostosis needs to be distinguished from secondary craniosynostosis. In primary craniosynostosis, abnormal biology of the suture causes premature suture closure; in the secondary craniosynostosis, the suture biology is normal, but abnormal internal or external forces result in premature suture closure.
In individuals with primary craniosynostosis it is important to determine which cranial sutures are involved and whether the craniosynostosis is an isolated finding or part of a syndrome.

Etiology

A primary defect in the mesenchymal layer ossification in the cranial bones is accepted to play a role in the etiology of primary craniosynostosis.
Many of the syndromic forms (Apert, Carpenter, Crouzon, Muenke types) are related to mutations in one of the *FGFR* genes (Wilkie et al, 1995; Jabs et al, 1994; Malcolm and Reardon, 1996. Mutations in the *TWIST* gene have been identified in Saethre-Chotzen syndrome (El Ghouzzi et al, 1997; Howard et al, 1997). Mutations in *MSX2* are causative in Boston-type craniosynostosis (Jabs et al, 1993).
Several conditions are associated with secondary synostosis. Examples for this are: Metabolic disorders leading to premature fusion; Hyperthyroidism; Hypophosphatasia; Idiopathic hypercalcaemia; Vitamin D deficiency; Congenital haemolytic icterus; Positional molding; Severe constraint *in utero*; Retarded brain growth as a primary abnormality.

Clinical description

Craniosynostoses are very heterogeneous traits. All are characterized by skull deformities, with face and often limb involvement in the syndromic forms. When one or more sutures fuse prematurely, skull growth can be restricted perpendicular to the suture. If multiple sutures fuse while the brain is still increasing in size, intracranial pressure can increase.
The sagittal suture alone is most commonly involved. A sagittal suture stenosis leads to an increased anteroposterior (AP) diameter of the skull and decreased biparietal diameter. Bilateral synostosis of the coronal sutures is characterized by a skull with a small AP diameter (brachycephaly), often with a decrease in the depth of the orbits and hypoplasia of the maxillae. Unilateral closure of the coronal sutures leads to flattening of the orbit on the involved side. Unilateral closure of a lambdoid suture produces flattening the back of the head on the involved side (plagiocephaly). An isolated synostosis of a metopic suture creates a triangular forehead (trigonocephaly) with hypotelorism. Closure of multiple sutures

frequently produces a skull that is brachycephalic; in such cases, prominent digital markings occur in the cranium. The Kleeblattschadel, or cloverleaf skull, also results from premature synostosis of multiple sutures. Although a Kleeblattschädel can occur in an isolated form, it is usually accompanied by other symptoms (hypoplasia of the midportion of the face, limb defects, hydrocephaly, mental retardation), which may be indicative of syndromes like thanatophoric dysplasia, Pfeiffer syndrome, and Apert syndrome.

Some of the children with syndromic forms of craniosynostosis (eg, Apert syndrome) can be affected by a variable degree of developmental delay (Renier et al, 1996).

Epidemiology

The overall incidence for all forms of craniosynostosis is 1/2,000-1/2,500 live-born children. Of affected individuals, 2-8% have a primary craniosynostosis. Approximately 80-90% cases involve isolated defects, while the remaining cases form part of a recognized syndrome. In isolated cases, the sagittal suture is affected most often (55%), followed by the coronal (20%), lambdoid (5%), and metopic (5%) sutures .

Generally, craniosynostosis is equally distributed in both sexes. A slight male predominance is observed in cases of sagittal synostosis (3.5:1) (Lajeunie et al, 1996) and metopic synostosis (3.3:1) (Lajeunie et al, 1998). A female predominance (2:1) is noted in cases of coronal synostosis (Lajeunie et al, 1995).

Genetic counseling

It is paramount for adequate genetic counseling to make a distinction between isolated and syndromic forms of craniosynostosis. Adequate evaluation for additional symptoms has to be performed in each child with a craniosynostosis.

Autosomal dominant inheritance has been identified in by far the most syndromic forms of craniosynostoses (Lajeunie et al, 1995; Lajeunie et al, 1996). The percentage of patients showing a spontaneous new mutations is high. However, germ line mosaicism is also known to occur and should be discussed with the family.

Usually no mendelian pattern of inheritance can be identified in nonsyndromic forms of craniosynostosis, although rarely the isolated craniosynostosis is familial, following an autosomal dominant pattern of inheritance with reduced penetrance. The recurrence risk in such cases is dependent on the nature of the suture involved.

Antenatal diagnosis

Prenatal testing is available for pregnancies with an increased risk if the molecular defect has been identified in the family (such as an earlier affected child or an affected parent). Fetal DNA obtained through chorionic villus sampling (CVS) at about 10-12 weeks' gestation (preferably) or amniocentesis at 16-18 weeks' gestation can be analyzed for the known disease causing mutation.

In a pregnancy not previously identified to be at risk for craniosynostosis in which an abnormal skull shape is detected on prenatal ultrasound examination, prenatal testing is often not well possible, unless other symptoms indicate a well known syndromic form such as the limb anomalies in Apert syndrome.

Management including treatment

No medical treatment exists to stop an early ossification of a cranial suture. Reasons to perform surgical interventions can be increased intracranial pressure, decrease of skull growth below the 3rd centile, expressed facial deformity (which can give cosmetic reasons for interventions), and (rarely) progressive exophthalmos threatening the eyes. Not all children with a craniosynostosis need surgical interventions. The results are best when surgery is performed between the age of 4 and 8 months, although there may be reasons to postpone surgery till a later age (Di Rocco et al, 1992). Infants with a craniosynostosis may require a series of surgical procedures (Whitaker et al, 1987; Marchac et al, 1994; Renier et al, 2000).

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