Craniosynostosis Syndromes

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KEYWORDS

• Craniofacial dysostosis • Craniosynostosis syndromes • Crouzon • Apert • Pfeiffer • Muenke

KEY POINTS

- Craniosynostosis syndromes have wide phenotypic variability. Understanding of the underlying genetic causes continues to develop.
- Children with these syndromes are best managed at a multidisciplinary craniofacial center.
- Early management focuses on airway protection, preservation of vision and hearing, and feeding.
- Timing of craniofacial reconstruction is driven by growth and development of the area of interest.
- In the past, intellectual disability was assumed. However, many patients with craniofacial dysostosis syndromes live rich lives and have normal or even exceptional intellect provided they are raised in a nurturing, stimulating environment.

Craniosynostosis is premature fusion of cranial sutures, and it occurs in 1:2000 to 1:2500 live births.[1,2] Most cases are nonsyndromic. Craniosynostosis syndromes, more than 150 of which have been identified, affect 1:25,000 to 1:100,000 infants.[2,3] The most common are reviewed in this article.

Craniosynostosis syndromes are diagnosed based on clinical features. Abnormal head shape and midface deficiency with exorbitism are typical craniofacial expressions,[1,2,4–6] and syndromes with these traits may be called craniofacial dysostosis syndromes. Limb and visceral manifestations further delineate each syndrome.

Fibroblast growth factor receptor (*FGFR*) and *TWIST* mutations are the most commonly associated with craniosynostosis syndromes. Although genotype-phenotype correlations have been characterized, phenotypically similar patients may have genetically distinct syndromes and identical mutations have been found in patients with different clinical diagnoses.[2,7,8] Fibroblast growth factors participate in myriad processes including skeletogenesis and limb development. Gain-of-function mutations in *FGFR1*, *FGFR2*, and *FGFR3* cause the *FGFR*-related craniosynostosis syndromes, which include Crouzon, Apert, Pfeiffer, Beare-Stevenson, Jackson-Weiss, and Muenke syndromes as well as Crouzon syndrome with acanthosis nigricans and *FGFR2*-related isolated coronal synostosis. These syndromes account for approximately 17% of craniosynostosis cases.[9]

Crouzon syndrome

Genetics

- *FGFR2* mutations
- Autosomal dominant; complete penetrance, variable expressivity
  - Occasionally de novo
- 1.6:100,000; 4.5% of craniosynostosis cases[2,10]

Clinical features

Cardinal features:
- Craniosynostosis
- Midface/orbital hypoplasia
- Clinically normal hands/feet

Crouzon syndrome, like all craniofacial dysostosis syndromes, is classically characterized by premature fusion of the coronal and frontosphenoidal sutures and the sphenoethmoidal synchondrosis.[11] Fusion results in brachycephaly; midface deficiency; and a short, wide anterior cranial base. The forehead is prominent because of compensatory growth at unaffected sutures. Additional sutures may be involved and rarely there is no sutural involvement (Fig. 1).[6,12,13]

Exophthalmos is always present, largely because of orbital hypoplasia with retruded supraorbital, infraorbital, and lateral orbital rims. The widened cranial base can result in hypertelorism. Most patients have exotropia;[14] orbital dystopia and strabismus can be observed.[15] Approximately 20% of patients develop optic atrophy.[14]

Anteroposterior and vertical midface hypoplasia are consistent features. Dental crowding, crossbite, and apertognathia are typical. Cleft lip and palate are rare.[15]

The authors have nothing to disclose.

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Atlas Oral Maxillofacial Surg Clin N Am 22 (2014) 103–110
1061-3315/14/$ - see front matter
http://dx.doi.org/10.1016/j.cxom.2014.04.001

Fig. 1 Crouzon syndrome. Frontal views of a child with Crouzon syndrome. The only prior procedures performed were placement of PET and VP shunt. PET, pressure equalization tubes; VP, ventriculoperitoneal.

Other features
- Typically normal intellect
- Hydrocephalus (up to 30%); occasional nonprogressive ventriculomegaly[16,17]
- Hearing loss common[18]
- Classically normal limbs/axial skeleton (occasional mild anomalies)[19–23]
- Cardiovascular anomalies rare

Differential diagnosis

If choanal atresia is present, consider Crouzon syndrome with acanthosis nigricans. Apert, Pfeiffer, Jackson-Weiss, and Saethre-Chotzen syndromes are diagnostic considerations.[6]

Apert syndrome

Genetics

- *FGFR2* mutations
  - Specific mutations linked to clinical features (ie, severe craniofacial involvement)[24]
- Most are de novo
  - Sometimes autosomal dominant; complete penetrance.[2]
- 1:100,000; 4% to 5% of craniosynostosis cases[2,25,26]

Clinical features

Cardinal features:
- Craniosynostosis
- Midface/orbital hypoplasia
- Bilateral syndactyly of hands/feet (minimally second to fourth digits)

Craniofacial anomalies are generally more severe in Apert than in Crouzon syndrome.[13] Asymmetry frequently affects the cranial base, orbits, and midface.[15] Megalencephaly is common.[27]

Infants with Apert syndrome have bicoronal synostosis with a midline calvarial defect from glabella to the posterior fontanelle that predictably obliterates over time.[12,13] The anterior cranial base is short. Patients often have a flattened occiput and a wide, steep forehead. The skull is wide with temporal bulging; temporal fat pads are prominent (Fig. 2).[15,28]

The orbits are hypoplastic; exophthalmos and hypertelorism are always observed.[14] Supraorbital and infraorbital rims are retruded. The lateral orbital wall is ballooned; lateral orbital rim projection is near normal. Palpebral fissures are often downslanting.[15] Exotropia, refractive errors, and strabismus are common;[14] optic atrophy is seen more in Crouzon syndrome.[29,30] Eyebrows may be interrupted over a bony defect at the lateral supraorbital rim.[15]

The midface is retrusive. The nose is short with a depressed bridge and rounded tip.[15] Ears tend to be large and may be low set.[15,31]

Lips are hypotonic.[15] Lateral palatal swellings contain mucopolysaccharides and grow with age; the palate is highly arched.[32,33] The soft palate is often long and thick.[33] Cleft palate is seen more than in Crouzon syndrome or the general population. Delayed and ectopic dental eruption are common. Most patients have dental crowding, crossbite, and apertognathia (Fig. 3).[15,34,35]

Other manifestations
- Ventriculomegaly common; progressive hydrocephalus rare[16,36]
- Mental retardation more common than in Crouzon syndrome