A Review of Craniofacial Syndromes

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ABSTRACT

Craniosynostoses are a complex and heterogeneous group of conditions. The purpose of this review is to describe the entity of craniosynostosis and its associated genes along with the ophthalmic and systemic findings. Several genes such as *FGFR*s, *TWIST1*, and *MSX2* are involved in both syndromic and non-syndromic craniosynostosis.

Key Words: craniosynostosis, craniofacial syndromes, craniosynostosis genes

Introduction

Craniosynostosis is the premature closure of one or more skull sutures which results in deformities of the skull vault. The overall incidence is 1 in 2,000 to 2,500 live births[1] but multiple craniosynostosis is much less common than isolated craniosynostosis.

Closure of the sagittal sutures results in a long and narrow cranium (dolichocephaly). It occurs in 45–58% of all craniosynostoses, and is the most common of the isolated craniosynostoses.[2] Synostosis of coronal suture (anterior plagiocephaly) leads to a broad forehead with a recessed lateral and superior orbital rim. This occurs in 20–30% of all craniosynostoses. Metopic synostosis results in a triangular shaped forehead (trigonocephaly), with a prevalence of 6–7 in 100,000 live births, but in the past decade has increased as much as fourfold.[3] Lambdoid synostosis (posterior plagiocephaly) is posterior flattening of the ipsilateral parietooccipital region. It represents approximately about 1% of all craniosynostosis. Positional posterior plagiocephaly may also occur but is not genetic and rather more often due to oligohydramnios.

Features of Craniosynostosis

Ocular and Systemic Findings

The multiple craniosynostoses are more often associated with more exaggerated abnormalities of head shape, systemic syndromes, and also more severe ocular and systemic complications including findings such as skeletal, developmental, and other organ system abnormalities. Midface hypoplasia, shallow orbits, hypertelorism and ocular abnormalities may be seen in Pfieffer, Crouzon, and Apert syndromes (Table 1), cardiac defects in Saethre Chotzen (Table 2) and Carpenter syndromes (Table 3), and diaphragmatic hernia in Craniofrontonasal syndrome (Table 4). The Tables 1-4 outline the features of several of these disorders.[4-10]

Significant refractive error and strabismus are more likely to occur in coronal synostosis. Anomalous extraocular muscles with or without strabismus, cylinder in the axis of the orbital recession, a "Harlequin shaped orbit" on radiographic imaging, and amblyopia are all more common. One-fourth of the patients had a fixation preference, hyperopia in almost 30%, myopia in 5%, and astigmatism in 35%. Anisometropia was present in 20%. Half have strabismus, being exodeviation the most frequent.[11] Sagittal synostosis is the only isolated craniosynostosis that may result in increased intracranial pressure with papilledema. Metopic synostosis often results in pseudoesotropia. There are no ocular manifestations for lambdoidal synostosis.

Patients with complex multiple synostosis often have very anomalous extraocular muscles (e.g. absent, duplicated, proximally inserted). Patients typically have exorbitism due to shallow orbits and may manifest V or A pattern deviations with alternating hypertropia of the adducting eye in lateral gaze. The exorbitism can lead to corneal exposure which may be vision threatening. Both anterior segment and optic nerve malformations may also occur.

Molecular Genetics

Cranial suture development involves interaction of tissues of the cranial suture complex.[12] The sutures need to be in an unossified state for brain growth yet allow bone to be formed at the edges of the bone front. The cells in the middle of the mesenchymal tissue remain undifferentiated during development, while the cells near the two osteogenic bone fronts undergo intramembranous ossification.

Several genes such as *FGFR*s, *TWIST1*, and *MSX2* are involved in both syndromic and non-syndromic craniosynostosis. Most common is the *FGFR3* Pro250Arg mutation seen in 4–12% of isolated unilateral and 30–40% of isolated bilateral coronal synostosis cases.[13] Mutation in *ERF* can result in sagittal, lambdoid, and multisuture craniosynostosis in cases diagnosed as isolated or

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Table 1. *FGFR* genes with related syndrome and characteristics

FGFR1 (8p11.23)**,** ***FGFR2*** (10q26.13) **,** ***FGFR3*** (4p16.3)

Fibroblast growth factor receptor; autosomal dominant
Gain of function mutations: involved in RAS/MAP kinase, PI3/AKT, or PLCγ pathways
:increased *CBFA1* and *RUNX2* (master osteoblast regulator) expression
Paternal age effect on mutations found

GENETIC SYNDROME	SUTURES INVOLVED	OPHTHALMIC FINDINGS	OTHER FINDINGS
Pfeiffer Syndrome (*FGFR1,2*) MIM#: 101600	Coronal Some sagittal	Shallow orbits, proptosis, hypertelorism, downslanting palpebral fissures, strabismus, antimongoloid slants, ptosis some anterior segment anomaly including microcornea, corectopia, limbal scleralization, glaucoma atypical bilateral superior iris coloboma optic nerve anomaly	Midface hypoplasia, prominent jaw, broad great toes with partial syndactyly of the digits and broad and medially deviated thumbs May have hearing defects due to bony defects; airway malformations, especially trachea can cause respiratory problems Intellectual disability
Jackson-Weiss Syndrome (*FGFR1,2*) MIM#: 123150	Coronal Some sagittal	Shallow orbits, proptosis Some have strabismus, usually exotropia	Midface hypoplasia; some cutaneous syndactyly of of second and third toes, variable tarsal fusion; first metatarsals and proximal phalanges of the great toes broad and deviated medially Few with abnormal neurologic development; IQs normal range
Crouzon Syndrome (*FGFR2*) MIM#: 123500 (with acanthosis nigricans *FGFR3* MIM#: 612247)	Coronal Some sagittal and lambdoid	Shallow orbits, proptosis, hypertelorism, exposure keratitis Absent/anomalous LR, IR, SO , V pattern exotropia (IOOA) Optic disc anomaly Amblyopia (20%), optic atrophy (up to 7%), Ametropia (75% - hypermetropia 60% and myopia 20%), strabismus (40%)	Midface hypoplasia, parrot beaked nose, short upper lid, prominent jaw Lack of major abnormalities of hands and feet Intelligence generally normal (only 3% with marked mental deficiency)
Apert Syndrome (*FGFR2*) MIM#: 101200	Coronal	Shallow orbits, proptosis, hypertelorism, downslanting palpebral fissures Absence of SR, V pattern exotropia, DVD Keratoconus disc anomaly, glaucoma Albinoid fundus	Prominent forehead, midface hypoplasia, flat nasal bridge, beaked nose, cleft palate, low set ears Very distinctive syndactyly of fingers (mitten hands) and toes CNS abnormalities (megalencephaly); learning disabilities Respiratory, cardiovascular, genitourinary anomalies
Muenke Syndrome (*FGFR3*) MIM#: 602849	Coronal	Hypertelorism, downslanting palpebral fissures, nasolacrimal duct obstruction Ptosis (30%), amblyopia (18%), strabismus (60%), ametropia (30%), IOOA (45%), nystagmus (20%), optic nerve findings (25%)	Facial appearance from normal to dysmorphic, easily mistaken for Saethre-Chotzen Syndrome Midfacial hypoplasia, beak shaped nose; brachydactyly, clinodactyly, broad thimble like middle phalanges, broad toes, capitate-hamate fusions, calcaneocuboidal fusions 95% show mild-moderate low frequency senosorineural hearing loss Developmental delay Females severely affected than males

MIM- mendelian inheritance in man; DVD- dissociated vertical deviation; SR – superior rectus; IOOA – inferior oblique overaction; CNS – central nervous system

Table 2. *TWIST1* gene with related syndrome and characteristics

TWIST1 (7p21.1)

Autosomal Dominant
Involved in the induction of mesodermal tissues and cytokine expression through NF-kB signal pathway
Its haploinsufficiency (loss of function) results in over expression of *RUNX2* (master regulator of osteoblast differentiation) and *FGFR 1,2,3*

GENETIC SYNDROME	SUTURES INVOLVED	OPHTHALMIC FINDINGS	OTHER FINDINGS
Saethre Chotzen Syndrome MIM#: 101400	Coronal Some sagittal	Ptosis, hypertelorism, blepharophimosis, epicanthal folds, downslanting palpebral fissures, lower lid entropion, anomalies of brows Optic atrophy, rotary nystagmus, EOM agenesis, strabismus In 10 patients- ptosis (90%), amblyopia (70%), horizontal strabismus (70%), vertical strabismus (60%), NLDO (60%), astigmatism (50%), inferior oblique overaction (40%), hyperopia (40%), myopia (30%), nystagmus (30%), optic nerve findings (30%) →Patients with *TWIST* mutations may have more ophthalmic abnormalities compared with patients with *FGFR3* mutations	Short stature, low-set frontal hairline, beaked nose, subnormal ear length 2/3 cutaneous syndactyly and brachydactyly, clinodactyly, radioulnar stenosis, broad laterally deviated great toe with bifid distal phalanx Deafness, cardiac defects Some have mild to moderate mental retardation Tend to have intracranial hypertension due to early progressive multisutural fusion and normal mental development

MIM- mendelian inheritance in man ; EOM – extra ocular muscle; NLDO – nasolacrimal duct obstruction

Table 3. *RAB23* gene with related syndrome and characteristics

RAB23 (6p12.1- q12)

Autosomal recessive
Encodes a member of the RAB guanosine triphosphatase (GTPase) family of vesicle transport proteins and acts as a negative regulator of hedgehog (HH) signaling. Its haplo-insufficiency may be affecting HH signaling

GENETIC SYNDROME	SUTURES INVOLVED	OPHTHALMIC FINDINGS	OTHER FINDINGS
Carpenter Syndrome MIM#: 201000	Sagittal Some coronal and lambdoid	Variety of ocular features with none being constant or characteristic; inner canthi widely spaced apart, epicanthal folds, nystagmus, foveal hypoplasia, posterior embryotoxon Microcornea, corneal opacity, mild optic atrophy, pseudopapilledema	Some short in stature, flat nasal bridge, low set ears, pre-auricular pits Preaxial polydactyly, some degree of syndactyly especially in toes; digits often short and may be missing phalanges Obesity, umbilical hernia, cryptorchidism Heart septal defects in 1/3 of patients; (ASD/VSD/PS/TOF/PDA) Brain defects - atrophy of cortex and cerebellar vermis; some degree of mental retardation Cystic hygroma, bowed femora, abnormal skull shape, complex heart defect, preaxial hexadactyly of feet

MIM- mendelian inheritance in man ; ASD – atrial septal defect; VSD – ventricular septal defect; PS – pulmonic stenosis; TOF- tetralogy of fallot; PDA – patent ductus arteriosus

syndromic.[14] Gain of function mutations in *ZIC1* are seen in coronal craniosynostosis and intellectual disability.[15] Rare mutations in *LRIT3*, *ALX4*, *IGFR1*, *EFNA4*, *RUNX2*, TCF12 and *FREM1* are seen in some non-syndromic cases.[16,17] A loci for isolated sagittal synostosis near *BMP2* and *BBS9* was also reported.[18] Decreased expression of *SFRP2* and other genes involved in osteoblastogenesis as negative regulators of the Wnt pathway are downregulated in fused sutures from non-syndromic craniosynostosis.[19]

Several genes including *BMP-4, BMP-7, FGF-9, MSX1* and *MSX2*, as well as *TWIST*, are expressed in the presumptive sutural mesenchyme, the underlying dura and the approaching bone fronts and are known to be involved in epithelio-mesenchymal signaling.[20] Gain of function or gene overexpression (such as *FGFR* and *MSX2* mutations) or loss of function/ haploinsufficiency (*TWIST* mutations) mutations in several genes may result in disruption of the signaling pathways resulting in sutural stenosis. The mutated genes and associated syndromes are included in Tables 1 to 4.

Only approximately 15% of cases of craniosynostosis are syndromic which includes the more than 180 known

Table 4. *EFNB1* gene with related syndrome and characteristics

EFNB1 (Xq12, Xq13)			
X linked dominant Role in control of bone remodeling Protein encoded is a type 1 membrane protein and a ligand of Eph-related receptor tyrosine kinases for cell recognition Its haploinsufficiency (loss of function) results in loss of binding to the Eph receptor Severe phenotype in affected heterozygote females compared with homozygous males may be due to random X-inactivation in heterozygote females leading to the mosaic state			
GENETIC SYNDROME	**SUTURES INVOLVED**	**OPHTHALMIC FINDINGS**	**OTHER FINDINGS**
Craniofrontonasal Syndrome MIM#: 304110	Coronal Some sagittal	Ptosis with upslanting palpebral fissures, hypertelorism Pterygium 45% prevalence of visual impairment including amblyopia, anisometropia, strabismus (90%) V-pattern (55%)	Midfacial hypoplasia, bifid nasal tip, broad nasal root, , mandibular prognathia, short neck, wiry hair Longitudinal nail splits, syndactyly, some have sloping shoulders, asymmetric nipples, and agenesis of corpus callosum Diaphragmatic hernia Intelligence usually unaffected

MIM- mendelian inheritance in man

craniosynostosis syndromes. Only 24% of the syndromes can be attributed to known genes so it is likely that there are more mutations and other genes involved. Majority of the cases are autosomal dominant and around 50% are spontaneous mutations. Eight percent of craniosynostosis are familial.[21] It is helpful to have knowledge on the function of these genes to understand the pathophysiology of craniosynostoses.

Several other genes involved in syndromic craniosynostosis are *MSX2* (Boston-Type Craniosynostosis), *POR* (Antley-Bixler), *GLI3* (Greig Syndrome), and *RECQL4* (Baller Gerold Syndrome).[22-26]

Clinical Testing

Multidisciplinary approach. Management requires a multidisciplinary approach because of various issues such as increased intracranial pressure, neurocognitive problems, hearing loss, speech and language issues, and ophthalmologic problems among others. The team may include craniofacial surgeons, ENT surgeons, ophthalmologists, pediatricians, craniofacial nurse specialists and allied medical health professionals.

Computed tomography scan of the brain to find other associated abnormalities and a 3-dimensional reconstruction using bone and soft tissue windows is ideal.

Genetic Testing

Genetic testing is suggested in all syndromic patients and in non-syndromic patients if there is coronal/ multisuture involvement. The mutation detection frequency is highest in Apert. Pfeiffer, Crouzon, and syndromic coronal craniosynostosis vary from 60 to 80%.[27] Therefore, directed testing is recommended. Diagnosis for multiple genes in parallel with Next Generation DNA sequencing is also possible. In cases that yield negative results, exome or whole genome sequencing may be done.[28]

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