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Research Article

Molecular Mechanisms, Clinical Approach to Diagnosis and Competent Care of Craniosynostosis

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Abstract

Craniosynostosis is defined as a partial or complete premature fusion of one or multiple cranial sutures resulting in distortion of skull shape and craniofacial dysmorphism. It is a heterogeneous condition with non-genetic and genetic etiology. The prevalence of craniosynostosis is 1 in 2000 and 1 in 2500 live births and is the second most common craniofacial anomaly after cleft lip/palate. Understanding the pathogenesis of craniosynostosis is very important. Knowledge of perinatal presentation of syndromic and non-syndromic craniosynostosis helps in appropriate genetic evaluation. Neurological abnormalities can be prevented/improved by early diagnosis and treatment for those who require surgical intervention.

Keywords: Clinical Approach; Craniosynostosis; Syndromes

Introduction

The cranial bones are tethered together by cranial sutures. The metopic suture closes at the age of nine months and for the remaining sutures, closure occurs in the third decade. The fusion of all sutures is from back to front and from lateral to medial except for the metopic suture which fuses from front to back [1]. Premature fusion of cranial sutures (Craniosynostosis) leads to a lack of growth at synostotic sutures with overgrowth of unfused sutures resulting in abnormality in the shape of the skull [2]. The term craniosynostosis was coined by Virchow. Different shapes of the head based on the suture involved in synostosis are listed in table 1. Sagittal synostosis is the most common isolated craniosynostosis accounting for 60-70% followed by metopic synostosis (25-30%), unilateral coronal synostoses (15-20%), bicoronal synostosis (7-10%). Lambdoid synostosis accounts for 3-5% [3,4]. Saggital synostosis is predominantly seen in males and coronal synostosis is predominantly seen in females. Metopic and lambdoid synostosis has no gender predominance. There is no predilection for any specific geographic region or ethnicity.

Type of Synostosis		Shape of the head
Saggitals ynostosis	Complete fusion	Dolichocephaly/Scaphocephaly
Metopic synostosis	Complete fusion	Anterior Trigonocephaly
Coronal synostosis	Unilateral	Anterior Plagiocephaly
	Bilateral	Brachycephaly
Lambdoid synostosis	Unilateral	Posterior Plagiocephaly
	Bilateral	Turricephaly
Posterior third of the sagittal suture and both the lambdoid sutures		Posterior trigonocephaly
Bilateral synostosis of both coronal and both lambdoid sutures		Oxycephaly
Synostosis of all major sutures		Cloverleaf skull

Table 1: Different shapes of the head based on the suture/sutures involved in synostosis [3].

Genetic basis and pathophysiology

Genetic etiology can be identified in 30-60% of cases with craniosynostosis. In 25-30% of cases, craniosynostosis presents as a feature of a genetic syndrome. More than 200 syndromes have been identified to be associated with craniosynostosis.

Isolated non-syndromic craniosynostosis is usually sporadic with multifactorial etiology exceptions being sagittal craniosynostosis with genetic heterogeneity of familial cases with autosomal dominant inheritance, especially in 2-5% of infants with sagittal synostosis and 10 -15% of infants with coronal synostosis, copy number variations in few cases with isolated single suture craniosynostosis. In syndromic craniosynostosis, gain-of-function mutations, mutations causing haploinsufficiency, and dosage reduction contribute to the phenotype. Understanding the molecular mechanism of craniosynostosis is important. Transcription factors play an important role in the development of the cranium. Osteoblast development is by RUNX2, inhibition of chondrocyte proliferation is by TGFβ (Transforming Growth Factor beta) and inhibition of calvarial osteoblast differentiation is by MSX2. Signaling pathways involved in craniosynostosis are FGF/FGFR and related signaling, Twist1 and related signaling, TGF signaling pathway, BMP signaling pathway, Wnt signaling pathway, Hedgehog signaling, RA, and POR signaling. FGF/FGFR signaling interacts with PI3K/Akt, RAS/MAPK, and PLCγ signaling pathways and plays an important role in the embryonic development of the cranium. Depicts the pathways and the genes involved in the pathogenesis of craniosynostosis. The genes and type of mutations involved in common craniosynostosis syndromes are listed in table 2 [5], and the genes/pathways involved in syndromes where craniosynostosis is an associated finding are listed in table 3. Chromosomal abnormalities account for the syndromic forms of craniosynostosis in 10-15% of cases [6]. Copy number variants encompassing the genes important for cranial development were reported in a few cases with isolated single-suture craniosynostosis [7]. Chromosomal aberrations and small exonic deletions/duplications were also reported in the literature [8,9].

Disorder	Gene	Pathway	Type of mutation	Pattern of inheritance
Pfeiffer syndrome	*FGFR1*	RAS/MAPK	Gain of function	AD
Apert syndrome Crouzon syndrome Pfeiffer syndrome Beare-Stevenson syndrome Jackson-Weiss Syndrome Antley-Bixler syndrome	*FGFR2*	RAS/MAPK	Gain of function	AD
Muenke syndrome Crouzon/acanthosis nigricans	*FGFR3*	RAS/MAPK	Gain of function	AD
Saethre-Chotzen syndrome	*TWIST1*	NOTCH	Partial loss of function	AD
ZIC1-craniosynostosis	*ZIC1*	WNT	Gain of function	AD
TCF12-related craniosynostosis	*TCF12*	NOTCH	Partial loss of function	AD
ERF-related craniosynostosis	*ERF*	RAS/MAPK	Partial loss of function	AD
Carpenter syndrome 1	*RAB23*	Sonic Hedgehog/ Indian Hegehog	Complete loss of function	AR
Carpenter syndrome 2	*MEGF8*	Indian Hedgehog	Partial loss of function	AR
Philadelphia craniosynostosis	*IHH*	Indian Hedgehog	Gain of function	AD
Boston craniosynostosis	*MSX2*	SMAD-depended BMP	Gain of function	AD
Craniosynostosis and dental anomalies	*IL11RA*	STAT3	Complete loss of function	AR

Table 2: The genes and type of mutations involved in common craniosynostosis syndromes.

AD: Autosomal Dominant; AR: Autosomal Recessive

Approach

History

History should include a family history of abnormal shape of the head, advanced parental age, in-vitro fertilization, exposure to teratogens during pregnancy [10], abnormal shape of head or mi-

Disorder	Gene/ Genes	Pathway	Pattern of inheritance
Dysmorphic Syndrome			
Antley-Bixler syndrome	*POR*	Retinoic acid	AR
Meier-Gorlin syndrome	*ORC1, ORC4, ORC6, CDT1 CDC6 CDC45* *DONSON*	Nonspecific	AR
Baller-Gerold syndrome RAPADILINO syndrome Rothmund-Thomson syndrome type 2	*RECQL4*	Nonspecific	AR
Shprintzen-Goldberg syndrome	*SKI*		AD
Bohring-Opitz syndrome	*ASXL1*	Multiple pathways	AD
3MC syndrome 2	*COLEC11*	Multiple pathways	AR
Cranioectodermal Dysplasia 2	*WDR35*	Indian Hedgehog	AR
Craniofrontonasal syndrome	*EFNB1*	NOTCH	XLD
Kabuki syndrome	*KMT2D/ KDM6A*	Nonspecific	AD/X-Linked
Skeletal dysplasias			
Osteoglophonic dysplasia	*FGFR1*	RAS/MAPK	AD
Bent bone dysplasia	*FGFR2*	RAS/MAPK	AD
Thanatophoric dysplasia II	*FGFR3*	RAS/MAPK	AD
Robert SC phocomelia syndrome	*ESCO2*	Nonspecific	AR

Table 3: The genes/pathways involved in syndromes with craniosynostosis as an associated finding.

AD: Autosomal Dominant; AR: Autosomal Recessive: XLD-X-Linked Dominant

crocephaly in ultrasound, single or multiple pregnancies, lie and presentation of fetus, oligohydramnios, hypoxic ischemia, and in addition history of hematological disorders like thalassemia and metabolic disorders like vitamin D resistant rickets, hypophosphatasia, hyperthyroidism, and mucopolysaccharidosis. Based on history we can differentiate between primary craniosynostosis from secondary craniosynostosis which is a consequence rather than a primary cause.

Clinical features

Craniosynostosis is classified based on the involvement of a single suture or multiple sutures. The abnormal shape of the head without other abnormalities is suggestive of non-syndromic craniosynostosis. Based on previous studies, cases with non-syndromic craniosynostosis usually have normal intelligence. Neurocognitive abnormalities were noted in children with raised intracranial pressure [11,12]. The presence of craniofacial dysmorphism with an abnormality of digits and toes is suggestive of syndromic craniosynostosis.

FGFR-associated syndromic craniosynostosis and its clinical features are listed in table 4. Clinical symptoms of synostosis are due to limited space for brain growth leading to increased intracranial tension and headache, intellectual abnormality, behavioral disturbances, deafness, visual defects, and dental anomalies. If synostosis develops in the earlier gestation it is associated with a severe phenotype [4]. Clinical features of non-FGFR-associated syndromic craniosynostosis are listed in table 5.

Prenatal diagnosis

The cranial sutures form around 16-18 weeks of gestation. Assessment of brain structure in ultrasound is based on the concept that sound waves penetrate the cranial sutures and fontanelle. In the presence of synostosis, sound waves do not penetrate the calvarium resulting in partial or complete acoustic shadowing of the underlying brain. Prenatal diagnosis may be challenging in cases with no family history or non-syndromic single-suture synostosis with mild or no skull deformity or in absence of associated anomalies [13]. Syndromic craniosynostosis has been diagnosed prenatally in a few cases but it would be challenging for diagnosing Pfei-

Syndrome	Craniofacial features	Extremities	Skin abnormalities	Visceral anomalies
Apert	Turribrachycephaly Midface retrusion Prominent eyes Downslanting palpebral fissures Dental abnormalities	Bony and soft tissue syndactyly of hands/feet or mitten hand	Hyperhidrosis Acneiform lesions	Normal to abnormal intellect Nonprogressive ventriculomegaly Agenesis corpus callosum Cardiac anomalies
Crouzon	Normal shape to cloverleaf skull Normal facial features/Significant proptosis, external strabismus, prognathism	Extremities are normal	Skin rugosity deep creases	Normal intellect Structural brain malformations are uncommon Chiari 1 malformation, Progressive hydrocephalus
Crouzon/ Acanthosis nigricans	Normal shape to cloverleaf skull Significant proptosis, external strabismus, prognathism.	Extremities are normal Acanthosis nigricans	Acanthosis nigricans	Normal intellect Structural brain malformations are uncommon Progressive hydrocephalus
Pfeiffer syndrome	Normal shape to cloverleaf skull Moderate to severe midface retrusion, prominent eyes	Thumb and great toe are broad, and medially deviated	Normal	Chiari 1 malformation, Progressive hydrocephalus
Beare-Stevenson cutis gyrata syndrome	Cloverleaf skull in most individuals Severe midface retrusion, proptosis	Normal	Cutis gyrata Acanthosis nigricans Hirsutism Skin tags	Intellect is abnormal Chiari 1 malformation, Progressive hydrocephalus
Jackson-Weiss Syndrome	Cloverleaf skull Proptosis and prognathism	Normal hands Broad and medially deviated great toe with 2nd, 3rd toe syndactyly Genu valgum	Normal	Normal intellect Structural brain malformations are uncommon
Antley-Bixler syndrome Type 1	Brachycephaly Midface hypoplasia Proptosis Dysplastic ears.	Radio-humeral synostosis, Femora bowing Arachnodactyly Camptodactyly	Normal	Hydrocephalous Cardiac anomalies
Muenke syndrome	Brachycephaly/anterior plagiocephaly Mild-to-severe midface retrusion, hypertelorism	Carpal and tarsal fusions	Normal	Normal intellect Structural brain malformations are uncommon
Osteoglophonic dysplasia	Cloverleaf skull	Platyspondyly, Short, bowed limbs Short, broad hands and feet	Pretibial dimples	Normal intellect Structural brain malformations are uncommon
Bent bone dysplasia	Brachycephaly	Bending of long bones Brachydactyly	Hirsutism	Normal intellect Structural brain malformations are uncommon
Thanatophoric dysplasia II	Cloverleaf skull	Short long bones with metaphyseal flaring Brachydactyly	Normal	Perinatal lethal

Table 4: Clinical features of *FGFR*-associated syndromic craniosynostosis.

Disorder	Craniofacial features	Extremities	Skin abnormalities	Visceral anomalies
Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	Brachycephaly Midface hypoplasia Proptosis	Radio-humeral synostosis, Femora bowing Arachnodactyly Camptodactyly	Normal	Arnold chiari malformation Ambiguous genitalia
Meier-Gorlin syndrome	Microcephaly Small mouth with full lips micro-retrognathia	Absent/hypoplastic patellae Slender long bones	Thin skin with prominent vasculature over forehead, Icthyosis	Normal intellect Cardiac, urogenital anomalies
Baller-Gerold syndrome	Brachycephaly Prominent forehead Proptosis Short nose Narrow mouth	Hypo/aplasia of thumb and radius	Erythema of face and extremities Poikiloderma	Cardiiac anomalies
RAPADILINO syndrome	Long face Narrow palpebral fissures, Cararact Long slender nose Small chin	Hypo/aplasia of thumb and radius Absent or hypoplastic patella	Mottled or stippled pigmentation	-
Rothmund-Thomson syndrome type 2	Sparse scalp hair, eyelashes, eyebrows, abnormal teeth	Hypo/aplasia of thumb and radius Absent or hypoplastic patella	Erythema Poikiloderma Hyperkeratosis	Genitourinary anomalies
Shprintzen-Goldberg syndrome	Dolichocephaly Proptosis Hypertelorism Low-set ears Micro-retrognathia	Dolichostenomelia Arachnodactyly Camptodactyly	Normal	Chiari 1 malformation Cardiac anomalies
Bohring-Opitz syndrome	Trigonocephaly Prominent eyes Cleft lip/palate Micro-retrognathia	Flexion at the elbows with ulnar deviation Flexion of the wrists and metacarpophalangeal joints	Glabellar and eyelid nevus flammeus-fades with age	Severe intellectual disability
3MC syndrome 2	Hypertelorism, Blepharophimosis/Blepharoptosis, Arched eyebrows Cleft lip/ palate,	Radioulnar synostosis	Caudal appendage	Cardiac and genitiurinary anomalies
Cranioectodermal Dysplasia 2	Dolichocephaly Frontal bossing Low-set ears High forehead Telecanthus Full cheeks Everted lower lip	Brachydactyly Syndactyly Polydactyly	Sparse, thin hair	Nephronophthisis Liver disease
Craniofrontonasal syndrome	Brachcephaly Facial asymmetry Hypertelorism Bifid nose Wide mouth	Brachydactyly Syndactyly	Axillary pterygia	Intellect normal Genitourinary anomalies
Kabuki syndrome	Arched eyebrows Long palpebral fissures Eversion of the lateral third of the lower eyelid Short columella with depressed nasal tip	Brachydactyly Brachymesophalangy	Fetal fingertip pads	Mild-Moderate intellectual disability Cardiac, GIT, genitourinaty anomalies
Robert SC phocomelia syndrome	Brachycephaly Hypertelorism Prominent eyes Wide nasal bridge with hypoplastic nares	Wrist/ankle contractures Syndactyly Oligodactyly Brachydactyly	Midfacial capillary hemangioma Cafe au lait spots	Genitourinary anomalies

Table 5: Clinical features of non-*FGFR*-associated syndromic craniosynostosis.

ffer syndrome as it has variable expressivity and craniosynostosis may not be present but the other findings like broad thumbs and toes and vertebral abnormalities can be present. Abnormal shape of the skull, abnormal biparietal diameter, and ventriculomegaly are frequently associated with syndromic craniosynostosis [14].

Though three-dimensional ultrasonography is superior in diagnosing and differentiating craniosynostosis and overriding sutures, the operator's expertise and fetal position also contribute to the diagnosis. Fetal MRI is complementary to ultrasound in the evaluation of craniosynostosis as MRI gives a detailed anatomical picture of the base of the skull which can be distorted in some cases [15].

In cases where a previous child has craniosynostosis, confirmed on molecular genetic testing, prenatal testing is possible by either chorionic villus sampling or amniocentesis and mutation-specific testing.

Postnatal diagnosis

The diagnosis of craniosynostosis is based on clinical features. The presence of microcephaly with the abnormal shape of the head, small or absent fontanelle, nonmobility of skull bones in infants, and the presence of ridging are clinical clues to the presence of craniosynostosis. Posterior plagiocephaly due to craniosynostosis has to be differentiated from deformational or positional posterior plagiocephaly. In addition, digital anomalies of hands and feet, and visceral anomalies will give clues to syndromic craniosynostosis. It is extremely challenging to distinguish primary effects from secondary consequences of craniosynostosis.

Imaging techniques act as a guide to the clinical diagnosis, planning for surgery, and follow-up of the cases post-surgery. For isolated craniosynostosis, radiographs should be used for the initial assessment and a 3D CT skull is used only in those cases which need surgery. Ultrasound of the cranium is recommended for neonates and also for infants less than one year. Though the 3D-CT skull is the gold standard for diagnosis of craniosynostosis, it has high radiation exposure and needs anesthesia. So it has to be used with caution in cases with complex or syndromic craniosynostosis as required. Recently low-dose radiation 3D CT with good quality image has been proposed even for the diagnosis of syndromic craniosynostosis [16,17]. MRI has a limited role in the diagnosis of craniosynostosis but has a role in the diagnosis of intracranial anomalies before planning surgery for craniosynostosis. 3D MRI skull has been proposed by Eley KA., *et al.* [18] to improve the diagnostic accuracy of craniosynostosis.

Advances in technology have improved the management of craniosynostosis. Noninvasive three-dimensional stereophotogrammetry measures the cranial vault which is a critical step for surgical planning. Real-time intraoperative techniques like near-infrared spectroscopy will monitor hemodynamics in cerebral tissue. These technologies can be implemented into routine clinical practice if they are cost-effective [19].

Genetic evaluation

Genetic testing is based on clinical features, and type of synostosis. In cases with intellectual disability/autism either with single suture synostosis/nonsyndromic synostosis or syndromic craniosynostosis which is not fitting into any known craniosynostosis syndrome, the first tier of the test is a chromosomal microarray. The presence of deep-intronic variants, or even epigenetic influences could be the cause of synostosis in unresolved cases and we need to consider whole-genome sequencing, whole-genome bisulfite sequencing, and RNA sequencing. If the exact molecular diagnosis is established, definitive prenatal testing is possible in subsequent conceptions of the couple.

Management

A multidisciplinary approach in a stepwise manner is critical in determining the appropriate surgical procedure to correct calvarial and facial abnormalities. The main aim of surgery in nonsyndromic craniosynostosis is to restore the shape of the cranial vault and reduce intracranial pressure. In syndromic craniosynostosis, the aim is to restore the shape of the cranial vault, reduce intracranial pressure, correct midface retrusion, protect the orbits, and provide a patent nasopharyngeal airway [20]. Strip craniectomy/subtotal calvarectomy is done below the age of 3 months in cases with elevated intracranial pressure (ICP). Thus the early neonatal diagnosis of elevated ICP would reduce the complications. Further surgical techniques include posterior vault correction at the age of 6-8 months, fronto-orbital advancement at the age of 1-2 years, correction of midface hypoplasia at the age of 5-10 years, dental correction at 10-12 years, and orthognathic surgery at 15-20 years. These are done in a stepwise manner as required. Cases with complex and syndromic synostosis require multiple surger-

ies. The treatment of choice in cases with isolated craniosynostosis are strip craniectomy or cranial vault remodeling for sagittal synostosis, fronto-orbital advancement for coronal synostosis, fronto-orbital reconstruction for metopic synostosis, and posterior vault reconstruction for lambdoid synostosis [21]. Endoscopic suturectomy with postoperative helmet therapy is also a treatment of choice for single-suture synostosis [22]. Re-synostosis and a rise in intracranial pressure can occur despite early treatment of craniosynostosis. Prolonged follow-up is therefore needed after surgical correction [23]. The present insight in the treatment of craniosynostosis is targeted medical therapies which might augment the results of surgical intervention, prevent re-synostosis, enable the growth of the skull and development of the brain, and reverse neurocognitive abnormalities [24]. The prognosis of craniosynostosis depends on the clinical phenotype, number of sutures involved in craniosynostosis, degrees of involvement of the skull base sutures, and associated anomalies.

Conclusion

Craniosynostosis is a diagnostic and therapeutic challenge. Early management improves the quality of life specifically in non-syndromic craniosynostosis. Increased awareness of the molecular mechanisms causing craniosynostosis would help in the identification of target medical therapies to avoid surgical treatment. These therapies should be available for use in clinical practice with a safety profile, should be able to prevent premature bone fusion, and should be able to reduce reoperation rates.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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