ORIGINAL RESEARCH PAPER

Radiodiagnosis

# PRIMARY CRANIOSYNOSTOSIS: STUDY OF TWO CASES AND REVIEW OF LITERATURE

**KEY WORDS:**
Craniosynostosis, classification, imaging, diagnosis

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**ABSTRACT**

Study of two rare cases of craniosynostosis and to diagnose and classify them on the basis of their imaging and clinical features.

## INTRODUCTION

Craniosynostosis, also known as craniostenosis/sutural synostosis/cranial dysostosis. The craniosynostoses are a heterogeneous group of disorders characterized by abnormal head shape occuring as a result of premature fusion of suture/s. The overall prevalence of craniosynostosis has been estimated at between 1 : 2100 to 1: 2500 births (1-3). Craniosynostosis can be sporadic/isolated or can be found with other syndromes. Sporadic (nonsyndromic) craniosynostoses are more common than syndrome-associated cases, accounting for 75 - 80% of all cases (1,4). Between 85-90% of these involve only a single suture, whereas 5-15% are multisuture synostoses. Sex varies with craniostenosis type. Both scaphocephaly and trigonocephaly have a moderate male predominance (M:F = 3.1:1 and M:F = 2:1, respectively)(1). Most craniosynostoses—even syndromic ones—are not detected during pregnancy. Affected infants generally present during the first year of life. The commonest presentation is abnormal head shape with craniofacial asymmetry. Etiologically, craniosynostosis may be characterized as primary (intrinsic defect in suture) or secondary (premature closure of normal sutures because of another medical condition)(5). Secondary craniosynostosis occurs in relation to a variety of causes: endocrine disorders, hematologic disorders causing bone marrow hyperplasia, inadequate brain growth.

**Nonsyndromic Craniosynostoses** (NCSs) The genetic etiology of the nonsyndromic craniosynostosis is still very poorly understood, to date, EFNA4 is the only gene that when mutated causes only nonsyndromic craniosynostosis (6).The genetic component is believed to be suture specific. For example, genome-wide association studies have identified strong and reproducible associations between sagittal NCS and *BMP2* and *BBS9,* whereas gene mutations are relatively rare in metopic NCS. Coronal NCS has a stronger genetic component compared with other forms. The genetic basis of lambdoid NCS—the rarest type—is unknown (1).

**Syndromic Craniosynostoses** account for just 25-30% of all cranial synostoses. Mendelian and chromosomal alterations are important causative mechanisms of this group of craniosynostosis. Linkage analysis in familial cases and molecular analysis of chromosomal alterations have led to the identification of seven genes that when mutated are associated with syndromic craniosynostosis: FGFR1, FGFR2, FGFR3, TWIST1, EFNB1, MSX2 and RAB23 (7). Compared to nonsyndromic counterparts, syndromic craniosynostoses are much more likely to be associated with additional craniofacial or skeletal anomalies, such as limb abnormalities, dysmorphic facial features, and skull deformity. In addition, brain malformations are common, and developmental delay is more frequent. In contrast to nonsyndromic craniosynostoses (where sagittal suture is most often affected), bicoronal synostosis is the most common pattern in these patients. Mutations in the *FGFR2* gene account for several of the most severe syndromic craniosynostoses, including Apert, Pfeiffer and Crouzon syndromes.

### Case Study

**Case 1 :** A 4 month old male baby came for routine work up with complaints of syndactyly and developmental delay. Clinically mid face hypoplasia and syndactyly of both hands and feet were seen. On radiography, only two rows of phalanges were noted in the digits of both feet with diffuse soft tissue thickening. Hand radiograph showed indistinct rows of phalanges of 2nd to 5th digits with distal clumping and soft tissue fusion (mitten glove deformity). On Computed Tomography, findings were brachycephaly with fusion of bilateral coronal sutures without any brain parenchymal abnormality. No systemic abnormality was detected at the time of preliminary screening.


**Image Showing Hypertelorism In Child With Brachycephaly And Mid Face Hypoplasia, Skull 3d -vrt Image Shows Fusion Of Bilateral Coronal Sutures, Image Showing Syndactyly Of Hand ('mitten Glove' Deformity) With Corresponding Radiograph, Image Showing Syndactyly Of Feet With Corresponding Radiograph.**

**Case 2 :** A new born female delivered by caesarian section came for routine work up of abnormally large head. On physical examination altered craniofacial configuration, hypertelorism, exophthalmos and mid face hypoplasia were noted. Skull radiograph showed trilobe shaped skull with increased anteroposterior diameter. Computed Tomography demonstrated abnormal configuration of the calvarium, with "cloverleaf" appearance. Abnormal fusion of posterior sagittal, coronal and lambdoid sutures were observed. Bulging of the middle cranial fossa and mild descent of posterior fossa structures into foramen magnum were noted. Limbs and intra-abdominal imaging was unremarkable.

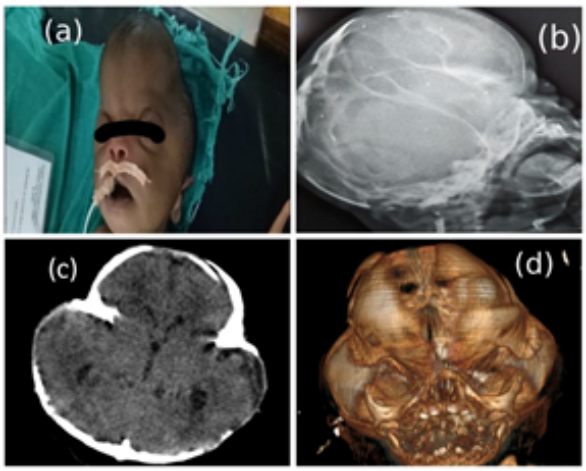


**Image Showing Altered Craniofacial Configuration, Hypertelorism, Exophthalmos And Mid Face Hypoplasia. Skull Radiograph Shows Abnormal "towering Calvaria" And Prominent Markings On Inner Table (copper Beaten Skull ). Axial Ct Image Showing Abnormal Fusion Of Posterior Sagittal, Coronal And Lambdoid Sutures . Skull 3d-vrt Image Showing Trilobed Configuration Of The Calvaria, With "cloverleaf" Appearance.**

## DISCUSSION

Craniosynostosis is premature fusion of cranial suture/s. It can be primary (developmental disorder) or secondary (to another known abnormality). It can be "simple" involving one suture or "compound" where two or more sutures are involved.

In the embryonic developmental process, mesenchymal tissue forms the cranial vault. It is first arranged as a capsular membrane around developing brain. Gradually, the outer mesenchymal layer is formed through the process of intramembranous ossification (8-12). This intramembranous bone growth depends mainly on the direction of the forces that are defined by the growth of the brain. In the developmental period, the brain is surrounded by dural fibers, which are closely related and strongly attached to the sutural system. Calvarial sutures are formed during the embryonic development at the sites of approximation of the membranous bones and later represent the major sites of bone expansion. This process is a combination of i) deposition of osteoid at the sutural margins, ii) surface apposition and remodeling of the bone, and iii) centrifugal displacement by the expanding brain (11-17). The fusion of the sutures is mainly regulated by the dura mater, which interacts with the overlying tissues of the cranial vault. The dura mater provides many important regulators of growth, such as intercellular signals (fibroblast growth factor [FGF] and transforming growth factor beta [TGF-β]), mechanical signals, and cells which undergo transformation and migrate to the sutures. This complex signaling cascade can be disrupted by a large number of genetic mutations, leading to an abnormal development of the cranial sutures (16-21). Finally, this may result in a premature fusion of one or more sutures, which is called craniosynostosis.

Radiographs are sufficient to identify simple single-suture craniosynostoses. Although the diagnosis of cranial synostosis can be made clinically or on plain film radiographs, thin-section CT scans with multiplanar reconstruction and 3D shaded surface display (SSD) are invaluable for detailed evaluation and preoperative planning. Radiography of limbs can provide additional information.

Based on imaging findings sagittal synostosis is the most common (40–55%), followed by coronal (20–25%), metopic (5–15%), multiple suture synostosis (5–15%) and lambdoid (0–5%)( 22). According to the suture involved, clinical and imaging appearance varies and different technical terms are used to describe them : Sagittal suture fusion results in a boat-shaped deformity of the skull, termed ***Scaphocephaly*** or dolichocephaly with growth restriction in width and compensatory excessive growth in calvarial length in the anterior to posterior direction. This growth pattern leads to varying degrees of frontal bossing and occipital coning (28-30). Unicoronal synostosis is involved in nearly 25% of nonsyndromic cases (29). It results in ***Anterior plagiocephaly*** where forehead is flattened on the affected side and higher supraorbital margins form a characteristic sign on radiographs, known as the "Harlequin" sign. On the opposite side, the forehead is pushed forward. Additional findings include flat cheeks on the side of synostosis and nasal septum deviation towards the normal side. It is more common in girls than in boys (M:F::2:1)(31,32,33,34-36). ***Posterior plagiocephaly*** is a unilateral lambdoid synostosis. Frontal and occipital bossing can develop contralateral to the affected side. The ipsilateral ear and mastoid can be displaced downward and also displaced in the anteroposterior direction. Clinically, the shape of the head from above can resemble a trapezoid (37,38,39). Posterior plagiocephaly should be differentiated from ***positional plagiocephaly***, which is more common. The latter is caused by repeated pressure to the same area before or after birth. The ipsilateral ear and forehead are usually displaced anteriorly, giving the head a parallelogram shape. The ipsilateral occipital flattening can be accompanied by a contralateral occipital bossing. Also there may be ipsilateral frontal bossing and contralateral frontal flattening. The male-to-female ratio is 3:1. The effects of positional plagiocephaly are primarily cosmetic and do not require surgical intervention (37,39). Incidence of positional plagiocephaly has risen over recent years due to the "back to sleep" campaign to reduce the incidence of sudden infant death syndrome (SIDS). The presence of torticollis, prematurity, and gross motor delay can also predispose an infant to positional plagiocephaly (34,37,39,40). ***Brachycephaly*** is a bilateral coronal synostosis. As a result of the fused coronal suture, the skull is short. The forehead and occipital part are flattened and the frontal bone is prominent and elongated in a vertical direction. The orbits are abnormally separated (hypertelorism) and the Harlequin malformation of the orbits is seen on radiographs (41). ***Turricephaly*** or "towering" skull is a more extreme deformity caused by bicoronal or bilambdoid synostosis. In contrast to brachycephaly, turricephaly causes skull lengthening in a cranial to caudal dimension (42). ***Trigonocephaly*** is caused by synostosis of the metopic suture. The forehead appears wedge-shaped or triangular with bifrontal narrowing and parieto-occipital broadening . This also produces an appearance of hypotelorism and a low nasal dorsum with epicanthal folds (42). ***Oxycephaly*** results most commonly from a combination of severe sagittal and coronal synostoses. This condition may result in microcephaly with raised intracranial pressure and neurologic impairment (43). ***Kleeblattschädel*** ("cloverleaf" skull) is a consequence of combined sagittal, coronal, lambdoid synostoses. The cloverleaf skull is associated with towering skull with bulging temporal regions and proptotic eyes (44,45).

Multisutural cranial synostosis is rare by itself and syndromic

in approximately 15% of cases (46). Over 100 syndromes associated with craniosynostosis have been delineated (47, 48), most of the common ones exhibit dominant inheritance.

***Crouzon Syndrome*** is most common of the craniosynostosis syndromes, occurring 1 in 25,000 live births (49). It follows an autosomal dominant inheritance pattern and mutations have been found in FGFR2 and FGFR3. Most commonly affected are the bilateral coronal sutures causing brachycephaly. Also seen is hypertelorism, shallow orbits resulting in exophthalmos, maxillary hypoplasia causing mandibular prognathism, high arched palate and low set ears associated with hearing impairment. Crouzon syndrome is also thought to convey an increased risk of raised intracranial pressure (50), due to the early closure of the sagittal and lambdoid sutures (51).

***Apert syndrome*** is the second most common, found in 1 in 100,000 newborns. Although it carries an autosomal dominant inheritance pattern, the majority are sporadic mutations in FGFR2.It also affects the coronal sutures bilaterally causing a brachycephaly (52) with hypertelorism, shallow orbits, exophthalmos and high arched palate. However, maxillary/midface hypoplasia is more severe than observed in Crouzon syndrome and can lead to life-threatening airway compromise. Also seen is an anterior open bite, downslanting palpebral fissures, a "parrot beak" nose and syndactyly of the second, third and fourth digits. These patients carry an increased incidence of delayed mental development, but many of these patients develop normal intelligence. Acne vulgaris is another characteristic feature seen during adolescence in over 70% of patients (53). Raised intracranial pressure also develop in most of the patients during first year of life in Apert syndrome (54).

***Pfeiffer Syndrome*** also occurs in 1 in 100,000 live births, most commonly due to FGFR2 and less commonly FGFR1 mutations (55). Cohen proposed a classification system (based upon their clinical findings and severity) Type I represents the classic Pfeiffer syndrome . Type II is more severe and is associated with a Kleeblattschädel (cloverleaf skull). Type III Pfeiffer syndrome is the most severely affected (56). The most common features include turribrachycephaly, midface hypoplasia, exorbitism, and the hallmark broad thumbs and great toes and variable soft tissue syndactyly. Other features include hypertelorism, strabismus, downslanting palpebral fissures and a beaked nasal deformity.

***Saethre- Chotzen*** Syndrome is found in 1 in 25,000 to 50,000 newborns and caused by mutations in TWIST1 gene (57,58,59). Heterogenous pattern of synostosis of bicoronal, unicoronal, sagittal, metopic or multisuture leading to a great variety of head shapes. Other features include, low frontal hairline, eyelid ptosis, facial asymmetry, syndactyly and ear deformities with a characteristic prominent crus helicis extending through the conchal bowl (59,60,61,62).

Another rare case of syndromic multisutural craniosynostosis is bilateral lambdoid and sagittal suture craniosynostosis, This type of craniosynostosis usually occurs as an isolated finding. Recent publications reported only Opitz syndrome with which it may be associated (63). Other rare syndromes with craniosynostosis are Thanatophoric dysplasia, Carpenter, Muenke etc.

## CONCLUSION

Craniosynostosis is premature fusion of cranial sutures and may be isolated or may present as a part of craniofacial syndrome. Here, the first case described above would be classified as Syndromic craniosynostosis - Apert syndrome. Second one was isolated case of *Kleeblattschädel* or cloverleaf skull without any other abnormality. It is a developmental craniofacial anomaly, resulting in impairment of brain development and abnormally shaped skull. ***Nonsyndromic Craniosynostoses*** are associated with increased risk for Psychiatric Disorders.

When left untreated, craniosynostosis can cause serious complications, such as developmental delay, facial abnormality, sensory, respiratory and neurological dysfunction, anomalies affecting the eye, and psychological disturbances. Thus, Imaging has a definite role in early diagnosis, prognosis and management including guiding surgical approaches and postoperative care.

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