# CRANIOSYNOSTOSIS

**Abstract**

Because of a lack of growth perpendicular to the fused suture and compensatory regrowth at the non-fused sutures, cranial sutures that fuse prematurely cause distortion of the skull's shape. It can be categorised as solitary, syndromic, or non-syndromic. The worst types of cranial deformities and total cranial development restriction brought on by craniosynostosis can lead to elevated intracranial pressure. When craniosynostosis is detected, it is treated surgically.

**Keywords:** craniosynostosis, fusion, isolated, restriction, surgical

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## I. CRANIOSYNOSTOSIS

Our bones support our bodies and contribute to our shape. An adult's body contains 206 bones. The 22 bones thatmake up the human skull are comprised of 8 cranial bones and 14 facial bones.[1] The occipital bone, temporal bones, parietal bones, sphenoid, ethmoid, and frontal bones make up the brain case, or neurocranium. The calvaria,also known as the cranial vault, skull vault, or skullcap, makes up the human body. It consists of 15 sutures, of which 3 (coronal, sagittal, and lambdoid) are single sutures and the remaining 7 (squamous, spheno-frontal, spheno-squamous, spheno-parietal, parieto-mastoid, and occipito-mastoid) are paired ones.[2]

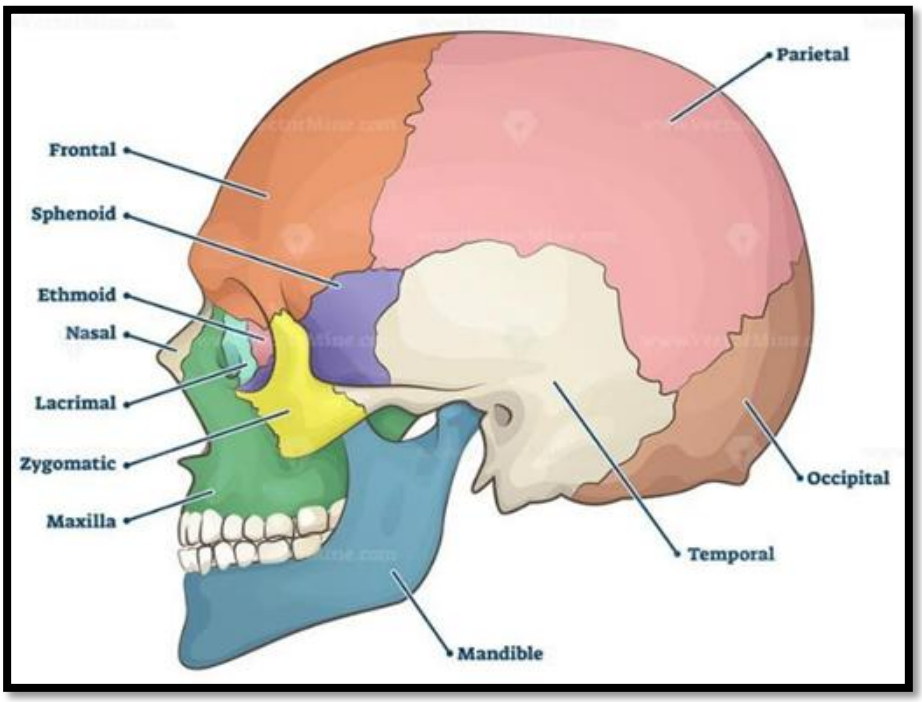


**Figure 1: Cranium and its parts**

One of the most prominent craniofacial anomalies is cranial synostosis (most prevalent after orofacial clefts). The word is made up of three words: "carnio," which means "cranium," "syn," which means "together," and "ostosis," which means "connected to bone." With a prevalence rate of 1 in 2250 live births, it is pervasive worldwide.[4]

The most commonly used **Clinical Genetic Classification of craniosynostosis** is:

When a person has a craniosynostosis alone, it is referred to as a non-syndromic or isolated variant. When a group of anomalies, such as the Apert, Carpenter, or Crouzon syndromes, are present, it is referred to as a syndromic variant.[5] When an illness is sporadic, the affected person's family members do not exhibit any symptoms. 92% of occurrences of craniosynostosis are sporadic. The disease is typically solitary and non-syndromic in most cases. Increased intracranial pressure, visual or hearing impairment, sleep issues, choanal atresia, or psychomotor delay along with intellectual incapacity are sequelae of craniosynostosis. Congenital heart disorders, deformities of the hands and feet, and a delay in reaching developmental milestones are all linked to the abnormality of the skull

**Table.1: Clinical Genetic Classification of Craniosynostosis**
**Reference: Mooney MP, Siegel MI (Eds.). (2002). Understanding Craniofacial Anomalies**

| Diagnostic Category | Name Of Disorder | Etiology |
|---|---|---|
| Isolated craniosynostosis | Morphologically described | Uterine constraint or FGFR3 mutation |
| Syndromic craniosynostosis | Antley-Bixler syndrome | Unknown |
| | Apert syndrome | Usually mutation in FGFR3 |
| | Baere- Stevenson syndrome | Mutation in FGFR2 or FGFR3 |
| | Baller- Gerold syndrome | Mutation in TWIST |
| | Carpenter syndrome | Unknown |
| | Craniofrontonasal dyspasia | Unknown gene at Xp22 |
| | Crouzon syndrome | Mutations in FGFR2 |
| | Crouzonomesodermoskeletal syndrome | Mutations in FGFR3 |
| | Jakson- Weiss syndrome | Mutation in FGFR2 |
| | Muenke syndrome | Mutation in FGFR3 |
| | Pfeiffer syndrome | Mutation in FGFR1 or FGFR2 |
| | Saethre- Chotzen syndrome | Mutation in TWIST |
| | Shprintzen- Goldberg syndrome | Mutation in FBN1 |

The incidence of non-syndromic cases in children is 1 in 5000 births for sagittal synostosis, 1 in 10,000 births for coronal synostosis, 1 in 7000–15,000 births for metopic synostosis, and less than 1 in 10,000 births for lambdoidal synostosis, according to the International Society for Pediatric Neurosurgery.[6] (Figure 2) According to estimates, 1 in 2,500 Indians experience craniosynostosis.7 A typical case of craniosynostosis is typically identified within the first year of life with te aid of concomitant clinical symptoms.

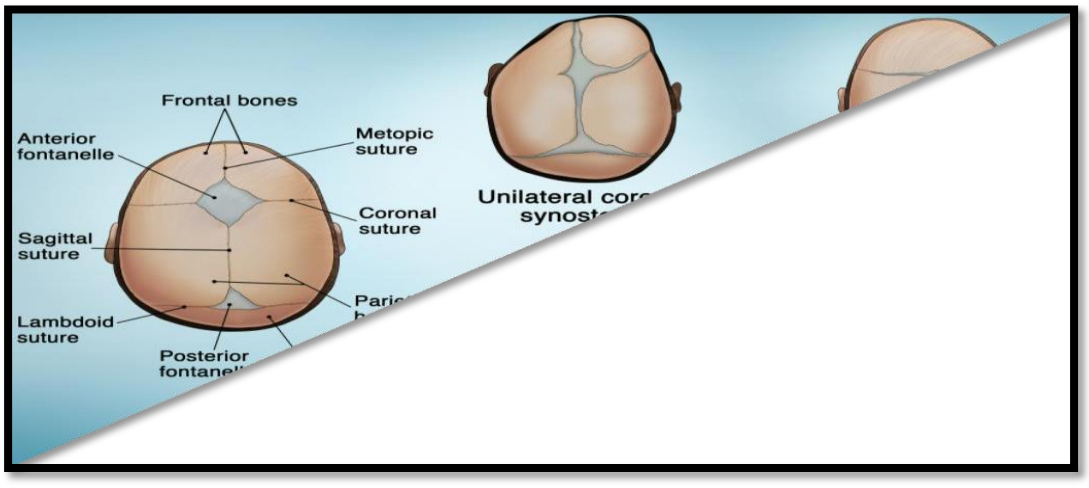


**Figure 2: Single suture craniosynostosis**

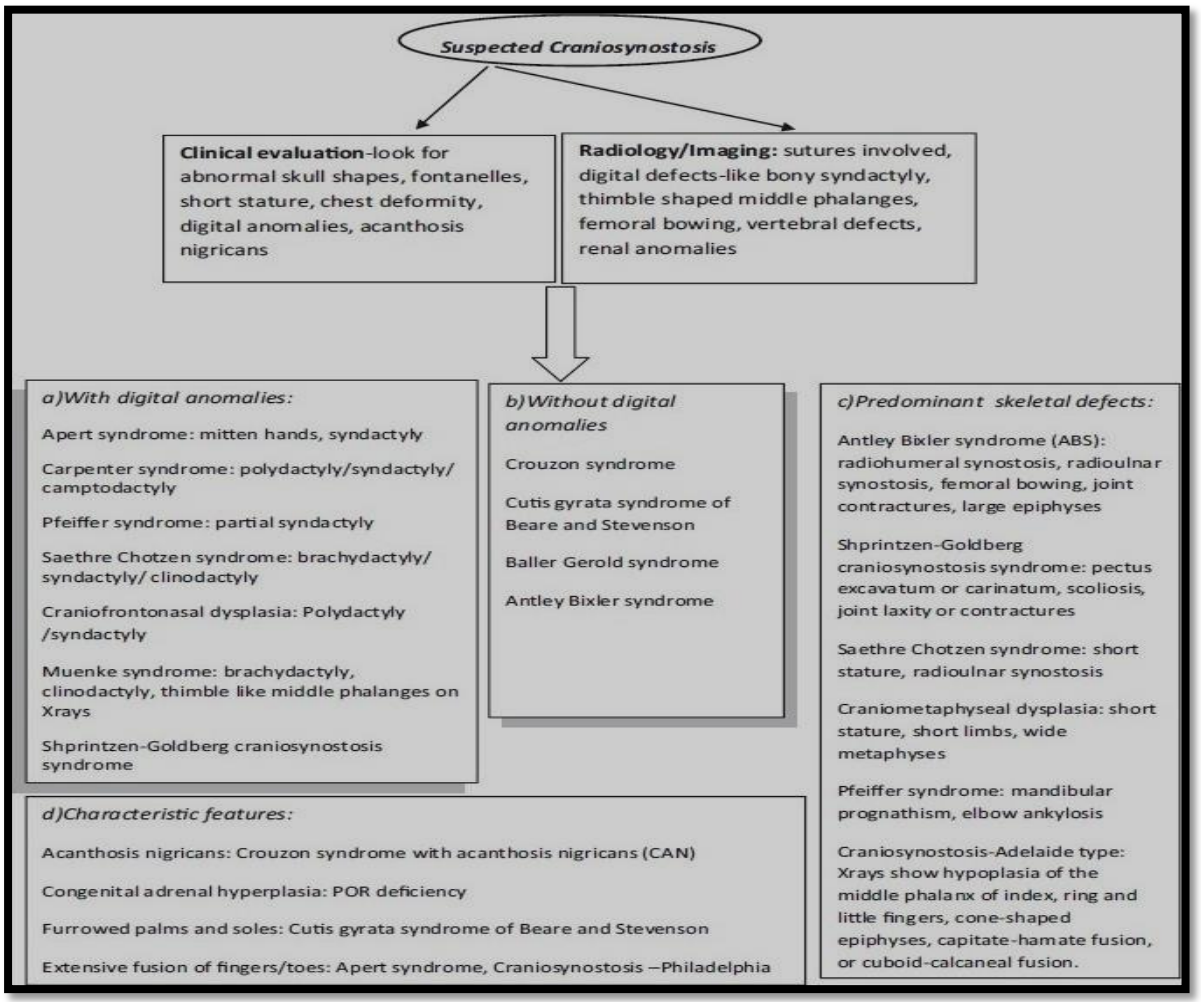


**Figure.3: Approach to clinical diagnosis of craniosynostosis syndromes[8]**

The knowledge of the genes responsible for craniosynostosis has greatly increased. FGFR, TWIST, MSX2, and EFNB1 gene mutations are the several types of genetic changes that have so far been linked to craniosynostosis. The treatment of craniosynostosis is a heterogeneous procedure, with cases of the syndromic forms requiring immediate interventions while the less severe, non-syndromic forms being treated electively due to the heterogeneous nature of the underlying causes and clinical features.[9.]

When treating severe instances, emphasis is placed on maintaining the airway, providing feeding, providing eye protection, and maintaining normal intracranial pressure. The choice of treatment method and degree of surgery, as and when required, is based on the patient's age at the time of presentation and clinical features. The first line of treatment for craniosynostosis should be conservative, especially for patients with positional plagiocephaly and mild unilateral synostosis. The goal of surgical treatment in all cases of craniosynostosis is to create enough cranial space for optimal brain development and an appearance that is acceptable cosmetically.10

 

## II. DEVELOPMENT AND GROWTH OF SKULL IN CRANIOSYNOSTOSIS

Understanding the various morphological changes that organ systems go through as they develop can help clinicians diagnose and treat the dysmorphology that is present in many congenital anomaly syndromes. Human craniofacial morphologies can vary widely and are generally considered to be normal. This variety is caused by genetic and epigenetic mechanisms, such as adaptation to harsh environments. Certain morphologies make people more prone to and at risk for developing craniofacial abnormalities. [11]

The formation of the cranial vault is a very protracted and intricate process that begins early in embryogenesis and culminates in maturity. the formation of the cranial vault is preceded by the formation of mesenchymal cells through epithelial-mesenchymal transformation (EMT) via the mesenchymatous or pre-condensation, and the development of the cranial bones starts with the condensation of mesenchymal cells during the embryonic phase,which lasts for the first eight weeks of pregnancy. [12]

The second stage is the foetal period, which lasts from the end of the embryonic phase until birth. It is during this time that the rudimentary membranous skull construction known as IM ossification starts to take shape through bone remodelling and displacement. Cranial sutures, which are regarded as growth sites, are also formed during the foetal phase. Table 2 lists the several characteristics connected to the cranial vault's development during the embryonic stage.

**Table.2: Stages of human embryonic developments**

| Weeks | Days | External Features |
|---|---|---|
| 1 | 1-7 | Fertilization |
| 2 | 8-14 | Primitive streak develops |
| 3 | 15-21 | Gastrulation commences and notochordal process forms |
| | | Primitive pit, neural plate, neural groove, neural folds formSomites begin to form |
| 4 | 22-28 | Neural folds fuse, otic pits form Cranial neuropore closes. Thd first four somites are beginning to be incorporate into the occipital segmentation. Oropharyngeal membrane ruptures, optic vesicles develop, optic pits begin to form |
| 5 | 29-35 | Caudal neuropore closes. Pharyngeal arches 3 and 4 form Otic vesicles form. The meninx primitive is first seen as the first signs of the cranial vault. Occipital sclerotomal mesenchyme concentrates around the notochord. |
| | | Cerebral hemispheres become visible |
| | | Sensory and parasympathetic cranial nerve ganglia begin to form |
| 6 | 36-42 | The skull has a membranous roof present |
| | | Cerebellum begins to form. Conversion of the ectomenix mesenchyme into cartilage starts on40-41 days. Pia mater is present around the brain. |
| 7 | 43-49 | Skeletal ossification begins. |
| | | The first indication of dura mater is found in the skull. Chondrification continues. |
| 8 | 50-56 | By the end of 2nd month (57 days) the endomeninx covers significant portion of the brain andhas develop into the arachnoid and the pia mater. Dural reflections begin to form |

**(Reference: Development and Growth of the Normal Cranial Vault by SW Jin, et al.)**

Sutures occur at the locations where the membranous bones approximate during embryonic development, acting as a flexible fibrous tissue between the surrounding bones. The crista galli, the cribriform plate, the smaller wings of the sphenoid, and the petrous temporal crests are the locations of prominent dural reflections, which are double folding of the meningeal dura attaching the base of the cranial vault. Partitions for the cerebral cavity beneath thecalvarium are made of dural reflections.[13]

These help identify the regions where bone growth slows down and the coronal, lambdoid, and sagittal sutures form along with falx cerebri and the tentorium cerebelli. Without these dural bands, the development of the brain would take place spherically. By 16 weeks, the sites of the reflecting bands in the dura had virtually been reachedby the radiating foci of ossification. Between the spreading islands of membranous bone, these latter sites continue to be connective tissue regions that have not ossified. Sutures are formed, and the skull bone grows quickly after that. At the edge of each bone field (the osteogenic front), osteoprogenitor cells proliferate and differentiate duringthis second stage of development.[14]

The neurocranium grows in the manner described below:

1. By bone filling of the proliferative connective tissue, the width of the parietal, lambdoid, parietosphenoidal, and parietotemporal sutures increases.
2. Sutures' lengthening, notably the coronal suture, due to the expansion of the cranial base.
3. The parietal, occipital, temporal, and sphenoid bones have grown in height.[15]

In craniosynostosis, premature suture fusion prevents bone development in that area. Loss of the sutural growth sites results in the inability to accommodate the neurocranium's rapid, expanding expansion. As a result, improper compensatory morphogenesis of the head results in craniofacial dysmorphology.

## III. ETIOLOGIES OF CRANIOSYNOSTOSIS

Syndromic craniosynostosis is thought to have a genetic basis for its origin. Coronal suture or multiple suture synostosis with symptoms of growth, developmental retardation, or other congenital defects is more likely to be caused by a combination of genetic and/or environmental factors. Isolated craniosynostosis, as opposed to syndromic craniosynostosis, is likely a complicated feature that results from a mix of polygenic influences and epigenetic factors, or the environmental variables.[16]

The autosomal dominant Crouzon, Apert, and Saethre Chotzen syndromes are the most prevalent craniosynostosis syndromes. These three disorders have separate traditional clinical descriptions. These disorders' phenotypic diversity reflects the phenotypic spectrum linked to fibroblast growth receptor 2 (FGFR2) mutations. Genetic heterogeneity can be shown in the nonsyndromic coronal craniosynostosis and nonsyndromic Pfeiffer, Jackson-Weiss, and Beare-Stevenson syndromes, which can be brought on by mutations in other members of the same receptor family. The transcription factor with DNA binding and helix-loop-helix domains that the TWIST gene codes for is the cause of the allelic Saethre-Chotzen and Robinow-Soaurf syndromes.

 

Craniosynostosis, Boston type, with a mutation in the MSX2 gene, which codes for a transcription factor with a homeobox domain, is one of the less frequent craniosynostosis syndromes.[17] In 2015, 57 human genes were identified for which mutations had been shown to be causally linked to craniosynostosis. Two major groupings can be made up of these genes. First, a set of 20 genes that typically cause diseases linked to craniosynostosis. In a small percentage of cases, a second group of genes that cause illnesses are likely causally linked to craniosynostosis. [18]

Studies on humans and animals indicate that environmental variables are less likely to be responsible for the development of craniosynostoses, which are frequently inherited in a Mendelian fashion. The majority of environmental influences most likely interact stochastically with genetic influences, other environmental exposures, and other environmental factors in real life. The following categories best describe the various environmental factors associated with craniosynostosis:

1. **Teratogens:** Teratogens are any environmental factors that cause structural changes after fertilisation. During the time of craniofacial organogenesis, maternal exposure to certain substances may cause deformities or disturbances. Prescription drugs, their metabolites, and dietary supplements are examples of teratogens. (b) Intoxicants; (c) recreational drugs; (d) hyperthermia.

2. **Maternal factors:** A higher frequency of craniosynostosis has been linked to a deficiency in several vitamins, such as folic acid. It is also believed that changes in maternal hormones are connected.

3. **Intrauterine factors:** A sutural deformity may result from an anomaly in the intrauterine environment, such as foetal mandibular restriction brought on by multiple pregnancies or oligohydramnios. Similar to this, disturbance brought on by the presence of amniotic bands around the growing foetus can cause craniosynostosis.[19]

## IV. SYNDROMES ASSOCIATED WITH CRANIOSYNOSTOSIS

The etiologies and pathogenetics of the craniosynostoses are diverse. Premature sutural fusion can occur on its own or in combination with other defects to form different syndromes. There are over 180 recognised syndromes. Although familial occurrences of solitary craniosynostosis are recognised, the majority of cases are sporadic. Rarely occurs familial lambdoid synostosis. Coronal series exhibit associated abnormalities more frequently than sagittal series. Leg deformities, ear anomalies, and cardiovascular malformations are the three types of anomalies that are most frequently linked to syndromic.[20]

| Syndrome | Essential Features | Inheritance |
|---|---|---|
| Apert, Apert-Crouzon | Craniosynostosis, severe syndactyly of hands and feet, down-turned mouth, hypertelorism | Autosomal dominant |
| Saethre-Chotzen | Craniosynostosis, facial asymmetry, low-hairline ptosis, deviated nasal septum, syndactyly of second and third fingers | Autosomal dominant |
| Pfeiffer, Noack | Craniosynostosis, malformed enlarged thumb and great toe, soft-tissue syndactyly of second and third digits, normal intelligence | Autosomal dominant |
| Crouzon, craniofacial dysostosis | Craniosynostosis, maxillary hypoplasia, shallow orbits with proptosis, bifid uvula or cleft palate | Autosomal dominant |
| Craniosynostosis, fibular aplasia, Lowry | Craniosynostosis and fibular aplasia | Autosomal recessive |
| Jackson-Weiss | Craniosynostosis with midface hypooplasia, mild syndactyly of feet, broad great toes | Autosomal dominant |
| Carpenter | Oxycephaly, mild syndactyly of fingers, preaxial polydactyly of feet, hypogenitalism, obesity, congenital heart disease | Autosomal recessive |

**Other miscellaneous syndromes associated with craniosynostosis are:**

1. Acrocephalospondylosyndactyly
2. Acrocraniofacial dysostosis
3. Antley-bixler syndrome
4. Armendares syndrome
5. Baller-gerold syndrome
6. Beare-stevenson cutis gyrata syndrome
7. Berant syndrome
8. Cap syndrome
9. Calabro syndrome
10. Christian syndrome
11. Cranioectodermal dysplasia
12. Craniofrontonasal syndrome
13. Crouzonodermoskeletal syndrome
14. Curry-jones syndrome
15. Fontaine-farriaux syndrome
16. Gómez–lópez-hernández syndrome
17. Hall syndrome
18. Herrmann syndrome
19. Holoprosencephaly/craniosynostosis syndrome
20. Hypomandibular faciocranial syndrome
21. Jackson-weiss syndrome
22. Jones craniosynostosis/dandy-walker syndrome
23. Kozlowski craniosynostosis syndrome

24. Lowry-maclean syndrome
25. Meier-gorlin (ear-patella-short stature) syndrome
26. Sakati syndrome
27. Scarf syndrome
28. Ventruto syndrome
29. Wisconsin syndrome

## V. CURRENT APPROACHES AND TREATMENT PHILOSOPHIES

The first surgical procedures to treat craniosynostosis were performed in the late 1800s, using methods including linear craniectomy and cranial vault fragmentation. Multiple further treatments were required as a result of the high rate of reossification and subpar aesthetic results of these early procedures. However, simple craniectomy is still used infrequently nowadays for temporary cranial decompression. Surgical remodelling of the damaged portion of the cranial vault and orbits has since replaced these early operations. In order to fully benefit from the skull's ability to regenerate at this age, surgery is typically done between 6 and 9 months of age.[21]

The pathologic suture was removed by strip craniectomy in the earliest attempts at surgical repair. Refusion, however, usually happened, negating any surgical advances. 22 Since then, more invasive techniques have developed, including reconstructing the entire calvarial vault in a single session. Such operations cut apart the bifrontal and biparieto-occipital fragments to enable radial osteotomies for recontouring, then wire or suture fixation to a condensed midline parietal segment. Prior to reattachment using just the underlying dura mater, each parietal bone is likewise separated and modified to promote lateral convexity. With this method, the synostotic limitation is not only removed, but transverse breadth is also increased, and calvarial shape is enhanced.[23]

Last but not least, an alternate, less invasive method for treating sagittal synostosis has recently been endoscopic extended strip craniectomy combined with postoperative moulding helmet therapy.[24]

Complications can accompany surgical treatment for craniosynostosis due to the comprehensive nature of treatments intended to rebuild the calvarial vault. Although various studies have claimed a mortality rate as high as 2.3%, the majority of worldwide data fall between 1.5 and 2%.

The majority of fatalities were related to hemorrhagic complications, but a number of additional causes, including as air emboli, cerebral edoema, and respiratory infections, have also been noted. Similar to haemorrhage, infection is a serious issue after calvarial remodelling. Following surgery, one may experience edoema, erythema, discomfort, or purulent leakage. Finally, it should be noted that neurologic consequences, such as cerebrospinal fluid leak and seizures brought on by intracerebral contusion or haemorrhage, are important factors to take into account. The calvaria enlarges during infancy and youth to make room for the developing brain. These cranial sutures—narrow seams of undifferentiated mesenchyme that connect several bones—are where this expansion takes place. 23

 

## VI. CONCLUSION

As a result of a combination of inadequate growth perpendicular to the fused suture and compensatory overgrowth at the non-fused sutures, one or more of the cranial sutures prematurely fuse, causing secondary distortion of the skull shape. According to estimates, craniosynostosis affects between 1 in 2100 and 1 in 2500 newborns worldwide.

There are two types of craniosynostosis: isolated or syndromic and non-syndromic. The disease is typically isolated and nonsyndromic, but in more severe cases, it may be worsened by elevated intracranial pressure, visual or hearing impairment, sleep difficulties, choanal atresia, or psychomotor delay in combination with intellectual disability.

In syndromic craniosynostoses, the deformation of the skull is accompanied by additional clinical symptoms, such as malformations of the hands and feet, skeletal and cardiac abnormalities, developmental delays, and others.

If neglected, craniosynostosis might aggravate cranial deformities and possibly hinder overall cranial growth, which would raise ICP. The malformation may cause psychosocial problems as the youngster develops and interacts with classmates.

Because untreated craniosynostosis carries hazards, it is typically surgically treated shortly after diagnosis. Acute and elective management are the two levels in the treatment of craniosynostosis. Acute management care is provided for newborns and infants with severe multisuture synostosis and is focused on maintaining the airway, assisting with feeding, protecting the eyes, and treating elevated ICP. Elective management is used to release and realign the bones. Its three main goals are to treat the malformation of the skull, stop it from getting worse, and lower the likelihood that ICP may rise in the future.

It is advised to follow up frequently throughout childhood, especially to keep an eye out for signs of an elevated ICP such headaches, behavioural changes, or a decline in academic ability.

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