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Case Report

A unique presentation of Crouzon-like syndrome: Complex craniosynostosis in the absence of genetic mutations or familial predisposition – A case report

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ABSTRACT

Background: Crouzon syndrome is a rare genetic disorder characterized by premature fusion of skull sutures during skull development, resulting in various craniofacial abnormalities and complex craniosynostosis is a condition in which more than one such sutures of the skull fuse prematurely.

Case Description: Herein, we present a case of a 5-year-old male diagnosed with Crouzon-like syndrome and complex craniosynostosis involving multiple cranial sutures, including metopic, sagittal, coronal (right and left), and lambdoid sutures, and without any identifiable mutations on karyotyping. The patient underwent successful surgical intervention with a satisfactory outcome, highlighting the importance of early diagnosis and intervention to prevent or minimize associated neurological manifestations and craniofacial abnormalities.

Conclusion: Our case report underscores the involvement of multiple cranial sutures in complex craniosynostosis and the absence of identifiable mutations or family history of similar craniofacial abnormalities, providing important insights into the diagnosis and management of this condition.

Keywords: Complex craniosynostosis, Cranial reconstruction, Crouzon syndrome, Genetic disorders, Neurology, Pediatric neurology

INTRODUCTION

Craniosynostosis refers to the condition where one or more sutures close prematurely. Premature closure of sutures can restrict or impede the growth of the brain within the affected area of the skull, while growth continues in areas where sutures remain open. If multiple sutures close prematurely, it can result in an atypical skull shape, even though the brain reaches its typical size. However, when restricted suture closure limits the brain's space to grow, it can cause increased pressure within the skull, leading to various neurological manifestations.[15] The condition affects approximately 3.1–6.4/10,000 live births worldwide.[13] It can be classified into different types based on the specific suture involved, including sagittal, metopic, lambdoid, and coronal (including the bi-coronal subtype).[6,15] Complex craniosynostosis occurs when multiple sutures are affected. In addition, there are approximately 50 distinct types of syndromic craniosynostosis, which involve

other parts of the body as well. Some commonly known syndromes include Crouzon syndrome (CS) (Craniofacial dysostosis), Apert syndrome (Acrocephalosyndactyly), and Pfeiffer syndrome (Brachysyndactyly).[6]

Complex craniosynostosis can give rise to a range of symptoms and complications, including but not limited to severe visual acuity impairment, speech and cognitive developmental delay, stunted height growth, and low weight gain. Other symptoms may include hypertelorism, proptosis, bilateral optic nerve compression, and irritability.[9]

Untreated craniosynostosis can result in facial abnormalities, sensory, respiratory, and neurological impairments, ocular anomalies, and psychological disruptions. Effective management of craniosynostosis requires early detection, skilled surgical interventions, postoperative care, and appropriate follow-up.[9]

In our case, the patient presented with a fusion of all the five sutures usually involved in complex craniosynostosis, that is, metopic, bi-coronal, sagittal, and lambdoid, leading to severe symptoms and complications; additionally, the patient has a normal male karyotype and showed no known mutations in polymerase chain reaction (PCR) or craniofacial deformities in the family history. In the subsequent section, we will discuss the case in detail.

CASE PRESENTATION

A 5-year-old male child was admitted to the hospital with notable craniofacial abnormalities, including a decreased anteroposterior length of the skull, prominent bulging of the eye, and congenital blindness. The child's medical history revealed a neonatal jaundice episode shortly after birth, requiring an 8-day incubation period. Despite being born with a weight of 3.4 kg, the child exhibited failure to thrive and bilateral vision loss since birth. Additional physical examination findings included low-set ears and laryngomalacia.

At three months of age, the patient experienced a severe episode of bronchopneumonia, which was successfully treated with tazobactam+ceftriaxone, amikacin, and amoxicillin+clavulonic acid. At the age of 2.5 years, the patient had a history of febrile seizures preceded by an aura characterized by highly irritable and inconsolable crying, along with having a mild craniofacial deformity. It was at this age that the patient was suspected to have craniosynostosis, as suggested at a local hospital in their hometown. However, the patient first presented to our hospital at the age of 5 years with the complaint of skull deformity, reduced vision, and failure to achieve cognitive milestones, and it was then that surgical intervention was performed on the patient.

In addition to cognitive impairment and irritability, the patient exhibited significantly reduced visual acuity and proptosis in both eyes. The physical examination also revealed abnormal dentition, narrow orbits, maxillary hypoplasia, brachycephaly, plagiocephaly, trigonocephaly, turricephaly, and hypertelorism. These findings were attributed to premature fusion of the sagittal, metopic, bi-coronal, and lambdoid sutures, as confirmed by 3D computed tomography (CT) reconstruction [Figure 1]. A magnetic resonance imaging (MRI) scan demonstrated scalloping of the inner table and tonsillar herniation approximately 5 mm below the McRae's line, along with bilateral intracanalicular compression of the optic nerves [Figure 2]. Karyotyping results indicated a normal male karyotype with PCR showing negative results for known FGFR-2 gene mutations, and the family history did not reveal any craniofacial deformities.

Based on the involvement of multiple sutures in craniosynostosis, as well as the presence of shallow orbits, hypertelorism, proptosis, abnormal dentition, and midface retrusion, a diagnosis of "Crouzon-like syndrome with Complex Craniosynostosis" was made.

The patient underwent a surgical procedure that involved a bi-coronal skin incision, pericranial graft harvesting, bi-coronal bony flap raise, excision of the turricephalic bone, and pericranial duroplasty with rearrangement of bony fragments. During the postoperative period, the patient

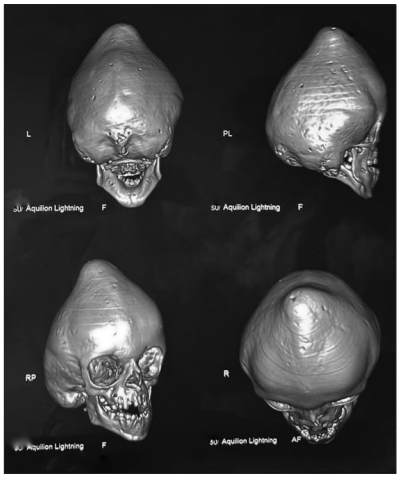

Figure 1: Preoperative three-dimensional computed tomography (3D-CT) reconstruction of head. This figure displays a 3D-CT reconstruction of the patient's skull bones before surgical intervention. The image reveals several craniofacial deformities, including brachycephaly, plagiocephaly, trigonocephaly, turricephaly, abnormal dentition, and hypertelorism, which are attributed to the fusion of the sagittal, metopic, bi-coronal, and lambdoid sutures.

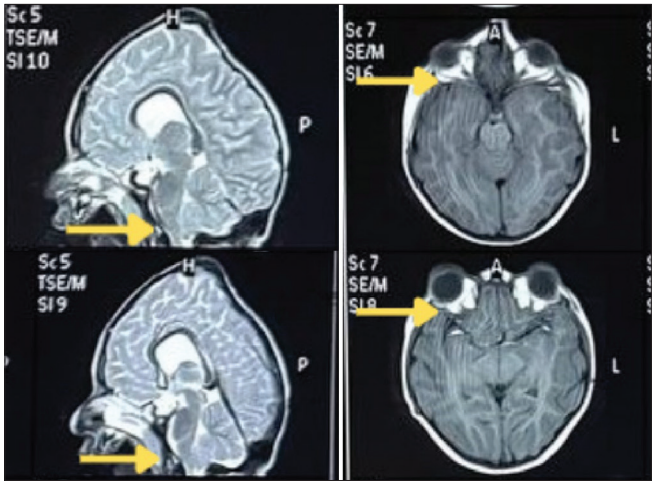

Figure 2: Magnetic resonance imaging (MRI) scans showing optic nerve compression and tonsillar herniation. This figure shows the MRI scans showing intracranial optic nerve compression and tonsillar herniation. The left column displays T2-weighted MRI images showing tonsillar herniation (marked by yellow arrows). The T1-weighted MRI images in the right column indicate shallow orbits and optic nerve compression (marked by yellow arrows).

experienced a convulsive episode characterized by clonic movement in the left hand, twitching in the left angle of the mouth, and, subsequently, the left leg. Levetiracetam was initiated for the management of suspected focal seizures.

DISCUSSION

Background

Craniosynostosis, characterized by the premature fusion of cranial sutures, exhibits varying incidence rates depending on the type of suture involved. Sagittal, coronal, metopic, and lambdoid sutures have approximate incidence rates of 60%, 25%, 15%, and 5%, respectively.[9] Complex craniosynostosis, a rare condition where more than one cranial suture fuses simultaneously, has an incidence rate of approximately 5%.[7] In cases of complex craniosynostosis, 36% involve the lambdoid suture, while the sagittal, coronal, and metopic sutures are affected in 31%, 18%, and 15% of cases, respectively. On average, complex craniosynostosis involves 2.9 sutures.[4]

Observations

Our patient presented with brachycephaly, turricephaly, midface retrusion, hypertelorism, shallow orbits, and bilateral intracanalicular optic nerve compression, leading to reduced cognitive ability and severely impaired vision. Surgical intervention was performed, involving a bi-coronal skin incision, pericranial graft harvesting, bi-coronal bony flap raise, excision of the turricephalic bone, and pericranial duroplasty with rearrangement of bony fragments. Levetiracetam was administered postoperatively to control suspected focal seizures.

The primary challenge encountered in this case pertained to the delayed presentation of the patient to our medical facility. At the time of initial evaluation, the patient exhibited advanced symptomatic craniosynostosis, necessitating surgical intervention. The surgical objective was to mitigate further impairment of the patient's visual acuity and facilitate optimal cognitive development, as both had been compromised due to the craniosynostosis condition.

Another challenge in this case was the absence of a definitive cause. While autosomal dominant heredity accounts for the majority of craniosynostosis cases, approximately 25% are attributed to spontaneous mutations.[6] However, karyotyping results revealed a normal male karyotype, and the PCR results did not reveal any known mutations in the chromosomes. Mutations associated with craniosynostosis vary among different suture types, with multisuture, bi-coronal, and uni-coronal synostosis showing mutation rates of 11%, 37.5%, and 17.5%, respectively.[8]

Turricephaly, also known as oxycephaly, is associated with Arnold Chiari Type I malformation in approximately 75% of cases. However, no such malformation was detected in the patient under consideration.[2] Turricephaly is often linked with developmental problems such as poor IQ, linguistic delay, and motor delay.[12]

Clinical approach

In young patients presenting with cranial anomalies and exorbitism, CS should be considered as a crucial diagnosis. Maxillary hypoplasia in these patients can lead to functional difficulties such as increased intracranial pressure, corneal exposure, and obstructive sleep apnea.[2] In addition, the facial anomalies characteristic of CS can have profound psychological effects on the patients.

Detailed examination should include the following factors:

1. Cranial anomalies
2. Cardiac anomalies
3. Airway examination
4. Exposure keratopathy
5. Papilledema/optic atrophy.

Employing robust imaging techniques is imperative for accurately identifying and assessing the extent of anomalies to formulate an appropriate surgical and medical management plan.

Imaging

Three-dimensional ultrasonography during pregnancy can detect premature closure of skull sutures.[3] However, a head

CT scan remains the primary diagnostic tool to identify abnormalities such as the copper-beaten appearance of the skull, narrow orbits, maxillary hypoplasia, and premature fusion of sutures. MRI can be used to detect associated conditions such as hydrocephalus and Chiari malformations.[3]

Genetic testing

Genetic testing plays a significant role in diagnosing craniosynostosis, with a gain of function mutation observed in over half of the cases.[1] The FGFR-2 gene's IIIa and IIIc exons have been linked to nearly all cases of craniosynostosis. However, a negative genetic test does not exclude the possibility of CS. Extensive research has revealed over 60 mutations in the FGFR-2 gene.[16]

Management

Optimal management of patients with CS requires a multidisciplinary team consisting of a craniofacial surgeon, neurosurgeon, oculofacial plastic surgeon, head and neck surgeon, oral and maxillofacial surgeon, and pediatrician. Prompt diagnosis and management are crucial in preventing complications, the absence of which was one of the challenges that we faced. CS can be differentiated from other craniosynostoses by the presence of normal extremities, normal intellect, parrot beak nose, maxillary hypoplasia, and exorbitism;[14] thus, our patient had CS-phenotype, but the absence of mutations in the patient makes this case a rare presentation.

The management of CS involves acute and surgical measures. Acute management includes treating raised intracranial pressure, ventriculoperitoneal shunt placement for hydrocephalus, tarsorrhaphy for exposure keratopathy, and tracheostomy for severe maxillary or mandibular hypoplasia.

Surgical management aims to correct craniofacial anomalies, such as cranial vault remodeling, orbital rim and midface advancement, and mandibular advancement. The timing and order of surgical interventions depend on the degree and severity of craniofacial abnormalities.

Surgical management

Surgical management plays a critical role in the treatment of CS and complex craniosynostosis. In the presented case study, cranial vault remodeling and correction of facial abnormalities were the main surgical procedures.[14] The approach to surgical management depends on various factors, including the severity of anomalies, the patient's age, and overall medical condition. Staged or combined surgical approaches may be employed.[14] Staged surgery typically involves cranial vault remodeling in infancy, correction of facial and orbital anomalies at 5–7 years of age, and maxilla/mandible correction/advancement during the teenage years.[5] In this case, the surgical management was performed in a combined manner at the age of 5 years. Common surgical procedures include LeFort I, LeFort II, Monobloc, or combination surgeries.[14]

The surgical treatment of craniosynostosis is essential to achieve the best functional and esthetic results for the patient. McCarthy *et al*.'s procedure is a commonly used standard strategy.[11]

Modifications to procedures should be based on individual patient's functional and cosmetic requirements. A multidisciplinary team consisting of craniofacial surgeons, neurosurgeons, oculofacial plastic surgeons, head and neck surgeons, oral and maxillofacial surgeons, and pediatricians should be involved to ensure optimal patient care.[14]

While distraction osteogenesis is an alternative procedure for repairing craniosynostosis, external distraction device placement may cause patient discomfort and inconvenience.[10]

CONCLUSION

The patient's condition was characterized by late presentation to the clinic, early cranial suture fusion, and aberrant craniofacial development. Clinical examination, imaging, PCR, and karyotyping were used to make the diagnosis. The craniosynostosis was successfully repaired surgically. The patient's motor and linguistic abilities improved, as did the IQ and the overall quality of life with reduced irritability.

The report emphasizes the involvement of all five cranial sutures normally associated with complex craniosynostosis and the absence of genetic abnormalities or family history of similar craniofacial abnormalities.

Ethical approval

Not applicable

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

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