ABSTRACT

Crouzon's syndrome is a rare autosomal dominant skeletal disorder caused by multiple mutations in the fibroblast growth factor receptor 2 (FGFR2) gene. It is characterized by premature closure of the cranial sutures, midface hypoplasia, orbital deformities, and other associated abnormalities. The diagnosis is based on clinical findings and radiological examination. Early recognition and specific therapeutic intervention are essential to guide the growth and development of the craniofacial region. We report a rare case of Crouzon's syndrome in a 4-year-old girl with characteristic features of cranial deformity, maxillary hypoplasia, cleft palate, and exophthalmos.

Key words: Cleft palate; Craniofacial dysostosis; Exophthalmos

Introduction

Craniosynostosis syndromes are characterized by premature closure of one or more cranial sutures and produce the characteristic craniofacial and other associated abnormalities. Crouzon's syndrome (CS) is one of the craniosynostosis syndromes, which is caused by a mutation in the fibroblast growth factor receptor 2 gene (FGFR2). It accounts for approximately 4.8% of all cases of craniosynostosis, with the prevalence of approximately 1 per 25,000 live births worldwide. Crouzon's syndrome is commonly inherited as an autosomal dominant trait, with complete penetrance and variable expressivity, but 30 to 60% of cases are sporadic and represent fresh mutations. The sporadic cases are postulated to be associated with advanced paternal age, and some investigators have found that this mutation is more common in the sperm of older men. Due to variability of phenotypic expression, some patients exhibit complete phenotypic penetrance, whereas other family members may appear normal and still carry a Crouzon mutation.

Crouzon's syndrome is characterized by premature closure of the cranial sutures, midface hypoplasia, orbital deformities, and other occasional associated abnormalities. The abnormal skull shape is usually noted in the newborn period although, occasionally, it may be detected either prenatally or not until later in infancy. The appearance of an infant with CS can vary in severity depending on the order and rate of the fusion of the sutures. Despite tremendous advances in the establishment of inheritance mode of this condition and its prevention and treatment, it remains a significant cause of morbidity worldwide. It is important to be aware of CS so as to impart better care. Genetic testing and individual study of each patient with suspected CS are essential for early diagnosis and management,
and to differentiate the condition from other syndromic and non-syndromic craniosynostosis. This report is of CS in a 4-year-old girl who presented with characteristic features of cranial deformity, maxillary hypoplasia, exophthalmos, and cleft palate.

**Case report**

A 4-year-old girl of normal intelligence presented to the Department of Oral Medicine, Diagnosis and Radiology, Vydehi Institute of Dental Science and Research Center, Bangalore, India, in February 2010 with difficulty in speech and swallowing due to a cleft in the roof of the mouth. She was referred by a general physician for dental evaluation. She was the only child of clinically healthy parents of non-consanguineous marriage. At the time of her birth, her father was 35 years old and her mother was 23 years old. History from her parents revealed that her facial features were different from other children of her age. They had noticed the cleft in the roof of the mouth at birth and gradual bulging of her eyes after the age of 1 year. There was no family history of similar symptoms or any other congenital abnormality. Her developmental milestones were normal, but she appeared smaller than other children of her age.

At clinical examination (Fig 1) she was found to have an irregularly shaped cranial vault, with the right side of the head being more prominent, mild brachycephaly, a flat occiput, and a flat forehead with low-set frontal hairline. Ridging of the skull was palpable in the regions of the right coronal suture, lambdoid sutures, and anterior to the vertex. There appeared to be facial flattening with maxillary hypoplasia and a relatively large mandible. The upper lip was small with an everted lower lip. The lips were potentially competent. Ophthalmologic evaluation revealed shallow orbits, hypertelorism, bilateral proptosis, mild exotropia, and bilateral chronic papillary edema with partial optic atrophy. Her nasal bridge was depressed with left septal deviation. Her nose was slightly pointed and had mild rhinitis. Low-set ears without hearing loss were noted. Her hands and feet appeared normal and no other abnormality was present.

At intraoral examination, U-shaped dental arches with a high-arched palate and complete cleft of soft palate was noted (Fig 2). Her oral hygiene was fairly good. Early childhood caries with root stumps of incisors and decayed molars were present. There was no evidence of temporomandibular dysfunction. Orthopantomographic view confirmed the clinical findings. Radiographic lateral skull view demonstrated a retruded maxilla with a relatively large mandible and copper beaten appearance of the skull (Fig 3).

Three-dimensional computed tomographic (CT) scans of the skull showed a hammered silver (beaten metal/copper beaten) appearance of the skull, which was more prominent in the occipital region. Early fusion of the coronal and lambdoid sutures, shallow and widely spaced orbits, hypoplastic maxilla and zygoma, and diffuse indentation of the skull (Figs 4 and 5) were seen. Computed tomographic scan of the brain demonstrated features suggestive of focal atrophy of the left cerebral hemisphere. Mild ventriculomegaly was seen on magnetic resonance imaging.

![Figure 1](image1.png)  (a) Frontal and (b) lateral views of craniofacial appearance of a girl with Crouzon's syndrome demonstrating hypertelorism, exorbitism, and midface hypoplasia

![Figure 2](image2.png)  Occlusal view showing cleft in the soft palate
(MRI) scan of the brain (Fig 6). Cardiovascular, respiratory, and abdominal examinations were normal. Routine hematological and biochemical tests were within normal limits.

Based on the above clinical and radiological findings and in the absence of hand and feet anomalies, a diagnosis of CS was made. Her parents were introduced to the nature of the child’s disease and the complications involved if left untreated. She underwent extraction of root pieces of the anterior teeth and restoration of grossly decayed teeth. Her cleft palate was repaired by a maxillofacial surgeon and she was referred to a team of surgeons for a series of staged surgical procedures.

**Discussion**

In 1912, a French neurologist, Octave Crouzon first described this syndrome in a mother and son with the characteristic triad of calvarial deformities, facial anomalies, and exophthalmos. Similar characteristic features of varying degrees were evident in this patient.

Crouzon’s syndrome is caused by mutation of the FGFR2 gene on chromosome 10q25-10q26. Mutation of the FGFR gene is also responsible for other craniosynostosis such as Apert’s, Pfeiffer’s, Jackson-Weiss’, and Saether-Chotzen’s syndromes. Rarely, acanthosis nigricans may coexist with

**Figure 3** Lateral skull radiograph demonstrating maxillary retrusion, mandibular prognathism, and copper beaten appearance of the skull

**Figure 4** Three-dimensional computed tomographic scans of the skull showing (a) shallow orbits, hypoplastic maxilla, and zygoma in frontal view, and (b) early fusion of coronal sutures (arrow) in axial view

**Figure 5** Three-dimensional computed tomographic scan of skull (posterior view) showing early fusion of the lambdoid sutures (black arrow) and characteristic digital impressions in the skull (white arrow)
CS and is caused by mutation in the transmembrane region of the \textit{FGFR3} gene (locus 4p16.3) \cite{9}.

Crouzon’s syndrome has no racial or sex predilections. However, when the craniosynostosis is of sagittal or metopic types, the predominance increases in boys, while coronal craniosynostosis is more common in girls \cite{10}, as observed in this patient. The condition is usually detected in the first year of life. However, there are also congenital premature forms in which the synostosis begins inside the uterus and is evident at birth with facial deformities \cite{10}. In patients with CS, the coronal sutures usually close first and eventually all cranial sutures close early. The coronal and sagittal sutures are most commonly involved. As the skull grows in planes perpendicular to the cranial sutures, premature suture closure causes skull growth to cease in the plane perpendicular to the closed suture and to proceed parallel to the suture. The skull shape becomes asymmetric, with the shape depending on the sutures involved. The characteristic cranial shapes are brachycephaly (disproportionate shortness of the head) as seen in this patient, scaphocephaly (boat-shaped head), trigonocephaly (triangle-shaped head) or, in severe disease, cloverleaf skull (kleeblattschadel) deformity \cite{11}.

The facial malformations consist of hypoplasia of the maxilla with mandibular prognathism, high-arched palate, bilateral palatal swelling, cleft palate in some patients, exaggerated facial angle, and the nose appears prominent and pointed (psittichorhina/beak-like nose) \cite{12}, recalling a ‘parrot beak’ due to the short and narrow maxilla. Conductive hearing loss and ear infections are common due to middle ear deformities. Upper airway obstruction may occur due to midfacial hypoplasia and a narrow epipharynx \cite{10}.

Ocular abnormalities such as bilateral ocular proptosis due to extremely shallow orbits and hypertelorism, were evident in this patient. Hypertelorism is thought to arise due to a decrease in the growth of sphenozygomatic and sphenotemporal sutures \cite{13}. Optic atrophy is frequently seen and has been reported in 30 to 80\% of patients \cite{14}. Other ocular abnormalities include divergent strabismus, conjunctivitis or exposure keratoconjunctivitis, as well as unexplained loss of visual accuracy.

Association of acanthosis nigricans with CS is rare and is detected in childhood \cite{2}. Patients with acanthosis nigricans present with thick velvety brown-to-black hyperpigmented lesions involving the neck, armpit, groin, orbital area (predominantly the lower eyelid), and perioral areas \cite{15}.

Mental ability and psychomotor development is generally within the normal limits. However, increased intracranial pressure can lead to mental retardation \cite{10}. This patient had a normal intellect. Other less frequently associated characteristics are headache and convulsions.

Thorough clinical, radiological, and genetic analysis is required for early recognition and to diagnose CS. The radiographs revealed obliterated sutures, hypoplastic maxilla with shallow orbits, shortened cranial fossa, enlarged hypophyseal cavity, and small paranasal sinuses. Prominent cranial markings of the inner surface of the cranial vault may be seen as multiple radiolucencies appearing as depressions (so called digital impressions) resulting in the hammered silver (beaten metal/copper beaten) appearance. A copper beaten skull was seen radiographically in this patient, indicating internal remodelling of the calvaria due to an increase in intracranial pressure as a result of premature

![Figure 6](attachment://image.png)  
Magnetic resonance imaging scan of the brain showing mild ventriculomegaly
Crouzon’s syndrome

Cranial suture fusion. On spine radiography, abnormal cranio cervical junction, butterfly-shaped vertebrae, and fusion of the cervical vertebrae (C2-C3 and C5-C6) may be visible. Radiographic examination of the metacarpal bones and fingers may reveal slight achondroplasia. Ventriculomegaly is frequently noticed in central nervous system imaging, but is usually asymptomatic and does not require treatment. Occasionally, corpus callosum agenesis and optic atrophy are demonstrated by MRI. Threedimensional ultrasonography and MRI aid early detection and diagnosis of fetal malformation. Prenatal diagnostic testing for a known FGFR gene mutation is a reasonable option for couples at risk for having a child with CS due to germline mosaicism.

Crouzon's syndrome must be differentiated from simple craniosynostosis and other syndromic craniosynostosis. Once craniosynostosis is seen radiographically, it is important to determine whether it occurred because of abnormal biology of the cranial suture, possibly caused by an FGFR mutation (primary craniosynostosis) and would make CS a possibility. The features of Apert's syndrome are very similar to CS and are characterized by craniosynostosis, midface hypoplasia, and symmetric syndactyly of the hands and feet. Differential diagnosis is also made with the other syndromes associated with features of craniosynostosis such as Pfeiffer's syndrome, Saethre-Chotzen’s syndrome, and Jackson-Weiss' syndrome. All these syndromes involve craniofacial abnormalities as well as other abnormalities, including the hands and/or feet. Craniosynostosis may also be caused by abnormal external forces such as decreased brain growth or abnormal fetal head positioning (secondary craniosynostosis) and, in these patients, the abnormal head shape may correct itself with time.

The management of CS requires a multidisciplinary approach to prevent early fusion of craniofacial sutures and thus minimize intracranial pressure and secondary craniofacial deformities. The goal is to stage reconstruction to coincide with facial growth patterns, visceral function, and psychosocial development. Surgical treatment usually begins before the first year of life. Early release of the synostotic sutures of the skull allows adequate cranial volume for brain growth. Skull reshaping may need to be repeated as the child grows. Depending on the severity of the deformity, midfacial advancement and jaw surgery can be done to provide adequate orbital volume and to correct the occlusion for appropriate function. The prognosis depends on the severity of the malformation and the timing of intervention. Patients usually have a normal lifespan.

Conclusions

It is important to note that CS can present with a wide range of severity and no two individuals with the condition will necessarily have all the listed features of CS. The affected girl in this report presented with varying degrees of craniosynostosis, ocular proptosis, hypertelorism, hypoplastic maxilla, and cleft palate, which are strongly suggestive of CS. The diagnosis is usually based on clinical and radiographic findings of the craniofacial region. Molecular genetic testing for mutations in the FGFR2 gene may be useful adjuncts, particularly when prenatal detection in subsequent family members is desired.

Dental professionals should have sufficient knowledge of syndromes associated with dysmorphic faces to detect patients who are unaware of their condition so they may be identified and sent for early investigation and management as required to prevent complications due to late diagnosis.

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References

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