

Case Series: Variable Genetic Expressivity In Crouzon Syndrome- A Comparative Report Of Three Cases

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ABSTRACT: *Despite the intense research, the clinical manifestation of syndromic craniosynostosis patients remains an enigma. Human skull is made up of various bone joints connected by sutures. The sutures fuse in later life after the complete growth of the brain. If any of these sutures close early, it may encumber the normal growth of the brain. In craniosynostosis there are disturbances in the growth of the skull which are caused by premature synostosis at one or more cranial sutures, resulting in typical deformities of the vault called as dyscrania. Crouzon syndrome is an emblematic example of craniosynostosis. Cranial malformations in crouzon syndrome depend on the order and rate of progression of sutural synostosis. Thus, physical appearance varies from patient to patient. In this article we intend to compare two patients with crouzon syndrome and a clinically non syndromic patient with beaten metal appearance radiographically. The idea behind this is that each syndromic patient is distinctive and a separate approach for treatment of such patients is desired.*

Key words: *Craniofacial, Crouzon, premature, synostosis*

1. INTRODUCTION

The skull is comprised of several bones that are interconnected by sutures. These sutures allow the skull to expand and develop in synchrony with the growth of the brain. If one or more sutures close prematurely, especially before the complete growth of the brain, the developing brain may exert pressure on the skull and may grow in the direction of the other open sutures. This can result in an abnormally shaped head and in severe cases, can in turn, also exert pressure on the growing brain. Premature synostosis, predominantly involves the

sagittal and coronal suture. Lambdoidal sutures are seldom involved. The order and rate of suture fusion determines the degree of deformity and disability^[1,2]. Various sutures may be prematurely synostosed, and multiple sutural involvement is found eventually in most cases. Premature sutural fusion may occur alone or in conjunction with other anomalies, making up various syndromes.^[3] In this article we report two cases of Crouzon syndrome and a case of non-syndromic patient with radiographically beaten-metal appearance. Crouzon syndrome is rare, seen 1 in 60,000 persons. The differential diagnosis of Crouzon syndrome includes simple craniosynostosis as well as the Apert, Pfeiffer and Saethre-Chotzen syndromes. Unlike the other forms, Crouzon syndrome presents with no digital abnormalities.^[4]

Case Report-I

A 22-year-old male patient reported to the dental department for routine dental check-up. Extra oral examination revealed protruding eyes and enlarged calvarium. History from the parents revealed that these features started developing since he was young, and the severity has gradually increased. The mother had experienced an uneventful pregnancy and delivery. Patient had normal IQ level and has completed his schooling. Patient's brother had mild exophthalmos. No other family member had similar appearance. Patient gave no history of hearing impairment. His speech was slurred and visual acuity was decreased. General examination revealed normal stature, moderate build and nourishment. Ocular examination showed exophthalmos, strabismus and hypertelorism. There was asymmetric enlargement of skull with irregularly shaped vault, increased vertical height and boat shaped head (scaphocephaly). Supraorbital ridges were prominent. The mandible was relatively large with retruded maxilla resulting in midfacial deficiency and nose was widened. The lips were incompetent and lower lip was thick and everted (Fig1). Intraorally, palate was deep and narrow. There was anterior edge to edge bite with posterior open bite in premolar region. A remarkable finding was fusion of right mandibular incisors, over-retained multiple deciduous teeth and impacted right and left maxillary canines and right mandibular canine. (Fig2). There were no signs of any syndactyly, but nails were hypoplastic with koilonychia. Postero-anterior view of the skull revealed obliteration of sagittal and coronal suture lines with obvious bony continuity. A mild beaten metal appearance was seen in skull due to compression of the developing brain on the fused bone. (Fig3) Lateral skull view did not reveal any beaten-metal appearance and showed widened sella tursica. Frontal bone was prominent with deficient maxilla. Panoramic radiograph confirmed the presence of missing teeth in the jaw bones. The condyles were widened with anterior bony projections. (Fig4) IOPA radiograph showed a macrodont in right mandibular incisor region suggestive of fusion. (Fig5) A thyroid function test was advised for the patient, T3, T4 and TSH values were within the normal range. Patient was referred for dental restorations; he did not go for any further investigations or treatment regarding the syndrome due to financial constraints.

Case report-II

A 45-year-old female patient reported to the dental department with a complaint of deposits on teeth since 4-5 years. Due to her peculiar facial appearance a comprehensive, focussed history of a development anomaly was taken. Patient experienced repeated episodes of severe headaches and had hearing deficit. Her speech was normal. She gave no history of similar facial appearance of parents or siblings. On general examination patient was relatively tall. Ophthalmic examination disclosed exophthalmos, strabismus and hypertelorism. She had triangular shaped cranial vault, frontal bossing with prominent supra-orbital ridges. There was mid-face deficiency with a relatively large mandible. Patient's lips were competent with a narrow, parrot beak nose. (Fig6) Palate was deep and narrow with prominent lateral palatal swellings giving an impression of pseudo cleft. A sub mucosal cleft was palpable at junction

of hard and soft palate. Patient was free from any digital abnormalities. The left maxillary canine was congenitally missing and right maxillary canine was palatally erupted (Fig7).She had no clinical signs of mental deficiency. Postero-anterior view showed a beaten metal appearance and wide orbits mesio-distally.(Fig8) Lateral skullview showed beaten metal appearance, wide sella tursica and reduced diploe space.(Fig9) Panoramic view depicted narrow condyles with anterior bony projection.(Fig10) A provisional diagnosis of Crouzon syndrome was given. Thyroid function tests were normal. Since patient was not willing for any treatment for Crouzon syndrome, therefore she was sent for oral prophylaxis.

Case report III

A 15 year old female patient reported to the dental department with a complaint of non-eruption of teeth. Patient's parents disclosed normal developmental milestones. The medical history was non-contributory. Patient was born to non-consanguineous parents. Patient was born to normal pregnancy and delivery. There was no relevant family history. General examination revealed a swelling in the thyroid region. There was no abnormality of clavicles. Patient had normal extra oral findings. Intraoral examination disclosed missing permanent maxillary right and left, canines, premolars and second molar. Mandibular arch also revealed missing left permanent lateral incisor, right and left canines, premolar and second molar. The right permanent lateral incisor was in infraocclusion. Over retained primary teeth were present.(Fig11) A tentative diagnosis of hypothyroidism was considered. Thyroid function tests were normal, serum calcium, phosphorous and alkaline phosphatase levels were normal. An ultrasound of swelling in thyroid region revealed that the swelling was not of thyroid origin. Orthodontic correction was planned for the patient. Pre-treatment panoramic radiographs confirmed the presence of impacted teeth in the jaw bones. Postero-anterior view and lateral cephalogram revealed beaten metal appearance (Fig12). The skull morphology grossly appeared normal. A radiographic differential diagnosis of Crouzon syndrome and hypophosphatasia was considered. Hypophosphatasia was ruled out as alkaline phosphatase levels were within normal limits. No classical clinical findings of Crouzon syndrome were present.

Fig. 1 Extra oral photograph of patient 1.



Fig. 2: Intraoral photograph of patient 1 depicting multiple retained deciduous teeth.



Fig. 3; Posteroanterior view of patient 1 revealing a mild beaten metal appearance.



Fig. 4: Panoramic radiograph showing the presence of missing teeth.



Fig. 5: Intraoral Periapical radiograph showing fused mandibular incisor.



Fig. 6: Extra oral photograph of patient 2.



Fig. 7: Intraoral Photograph showing the presence of missing left maxillary canine.



Fig. 8: Postero-Anterior view demonstrating beaten metal appearance in patient 2



Fig. 9: Lateral Skull view showing the presence of wide Sella Turcica in patient 2.



Fig. 10 : Panoramic view demonstrating narrow condyles.



Fig. 11: Intraoral photograph of patient 3 showing the presence of over retained deciduous teeth.



Fig. 12: Posteroanterior view of patient 3 showing the presence of beaten metal appearance.



Fig. 13:A Comparative sketch showing the posteroanterior view of 3 patients

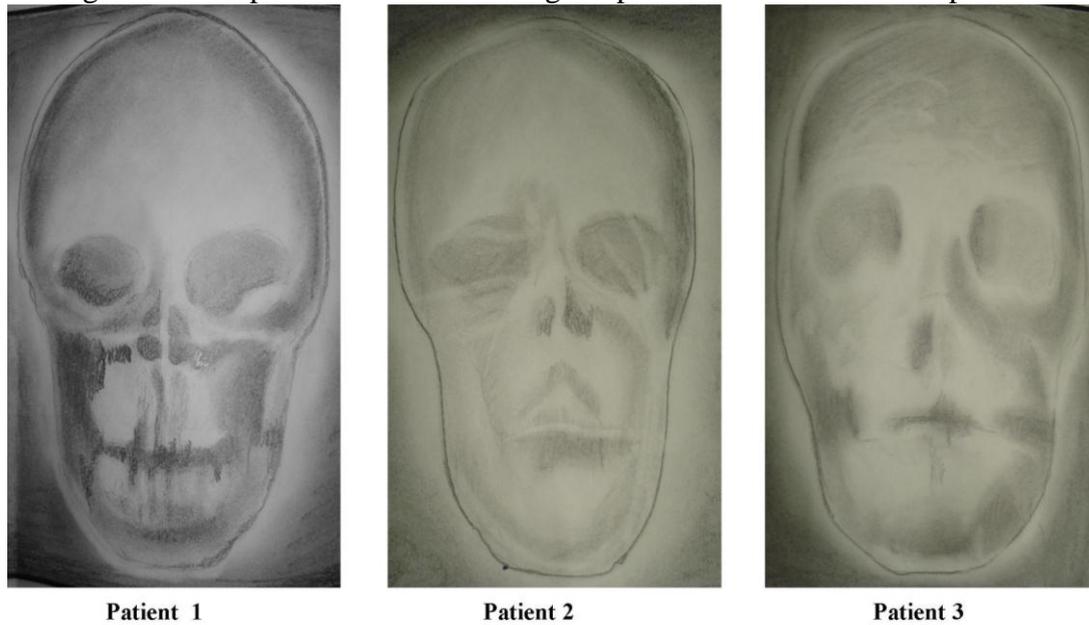


TABLE 1: Comparative evaluation of three cases of crouzon's syndrome

S.no	COMPARISON	PATIENT 1	PATIENT 2	PATIENT 3
1	Age	22/M	45/F	22/F
2	Skull	Irregularly shaped vault, normal vertical height / scaphocephaly (boat shaped head),	Triangular shaped vault, frontal bossing, prominent supraorbital ridges/ trigonocephaly, increased vertical height	No craniofacial abnormality seen clinically
3	Hereditary pattern	Hereditary pattern – 1 st brother had mild crouzon syndrome	No inheritance	No inheritance
4	Eye	Hypertelorism, supraorbital ridges	Mild hypertelorism	No abnormality detected
5	Symptom	No Headache	Headache present	No Headache
6	Sight	Blurred vision	Vision normal	Vision normal
7	Hearing	No hearing deficit	Hearing deficit	No hearing deficit
8	Nose	Wide lower part of nose	Parrot beak nose, narrow nose	Normal nose
9	Lips	Incompetent lips	Competent lips	Competent lips
10	Nails	Spoon shaped (koilonychias)	Normal	Normal
11	Mid face	Mild mid face deformity	Moderate mid face deformity	No mid face deformity

12	Palate	V- shaped maxillary arch and narrow maxilla	Deep and narrow palate, submucosal cleft present	Palate normal
13	Occlusion	Anterior edge to edge bite, open bite in premolar region	Anterior cross bite with posterior open bite	Multiple unerupted teeth and over retained deciduous teeth with Angles class I molar relation
14	Any dental anomaly	Fusion of right side permanent central and lateral incisor, over retained deciduous maxillary right side canine and deciduous mandibular right side canine and molars	Enamel hypoplasia was present, congenitally missing left side maxillary canine and palatally erupted right side canine.	Moderate fluorosis, with delayed eruption of permanent teeth.
15	Radiographic appearance	Mild Copper beaten appearance	Moderate Copper beaten appearance	Classical Copper beaten appearance

2. DISCUSSION

In 1912, a French neurologist, Octave Crouzon presented his classical paper to medical society of the hospitals of Paris.^[5] It was a report on two patients, a 29 year old mother and her 3year old son, with strange malformations of the face and head, to which he gave the name “hereditary craniofacial dysostosis”. He listed the characteristic features namely, cranial malformation that is a combination both of a skull in the shape of a boat (scaphocephaly) and in shape of a wedge (trigonocephaly); malformation of the face resulting in arched nose resembling a parrot’s beak and marked protrusion of mandible beyond the maxilla (prognathism), bilateral exophthalmous with external strabismus and hereditary and familial occurrence of these malformations. Since then many reports of this strange malady have been documented. The phenotypic features of Crouzon syndrome maybe absent at birth and evolve gradually during the first fewyears of life.^[6,7]It is commonly inherited as an autosomal dominant trait, withcomplete penetrance and variable expressivity, but aboutone-third of the cases do arise spontaneously. Syndromic patients without any family history of the disorder are called as “sporadic craniofacial dysostosis”. The male-to female preponderance is 3:1.^[2]With the advent of molecular technology, the gene for theCrouzon syndrome could be localized to the FibroblastGrowth Factor Receptor II gene (FGFR2) at the chromosomal locus 10q 25.3-q26, and more than 30 different mutationswithin the gene have been documented in separate families.^[8] Premature fusion of the cranial sutures results in craniosynostosis, and this initiates changes in the brain and adjoining structures, such as chronic increase in intracranial pressure, reduced orbital volume, exophthalmos (proptosis), severe maxillary hypoplasia and occlusal derangement.^[5] Complications of Crouzons syndrome may include conjunctivitis or keratitis, luxation of the eye globes, exotropia, poor vision due to optic atrophy and corneal injury, blindness. Frequent headaches, seizures,

mental deficiency, increasing hydrocephaly, conductive hearing deficit, upper airway obstruction develop secondary to septal deviation, midnasal abnormalities, choanal abnormalities and nasopharyngeal narrowing, Others include nystagmus, iris coloboma, aniridia, anisocoria, corectopia, microcornea, megalocornea, keratoconus, cataract, ectopia lentis, blue sclera and glaucoma.^[3] Ultrasonic prenatal diagnosis of exophthalmos has been reported, which might give a clue regarding the forthcoming developing problems. In the present report we mentioned three cases which revealed considerable inter individual variation in craniofacial morphology. There is wide latitude of phenotypic variability. The variable expressivity of the syndrome may still cause problems concerning diagnosis and genetic counselling. The second case demonstrated marked degree of deformity. The third case clinically did not appear like crouzon syndrome. Sometimes a craniostenosis of minor degree can be diagnosed only by craniometry. The craniofacial abnormalities vary within wide limits. Syndromic craniosynostosis is presumed to be the result of both genetic and environmental interactions, however the impact of these specific components remain unknown. Early recognition is essential to guide growth and development of the face and cranium^[6,7] Management of such a problem requires multidisciplinary approach. Treatment includes measures to minimize intracranial pressure and secondary calvarial deformities.^{8,9,10} Orthodontic treatment with subsequent orthognathic surgical intervention has to be followed in managing the dentofacial deformity. Prognosis depends on severity of malformation. Innovations in craniofacial surgery have enabled patients to achieve their full potential by maximizing their opportunities for intellectual growth, physical competence and social acceptance. Patients usually have a normal lifespan.

3. CONCLUSION

The comparison of three above reported cases revealed that crouzon syndrome has wide array of clinical manifestations depending on the order and rate of progression of sutural synostosis. Any deviation in clinical manifestations poses a diagnostic challenge. Dentists should be vigilant and capable to identify varied clinical presentations of the craniosynostosis, thereby adopt a strategy for multidisciplinary treatment accordingly. A possibility of thyroid disorder should always be considered and ruled out prior to management.

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