

Imaging diagnosis of Crouzon syndrome in two cases confirmed on genetic studies - with a brief review

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Abstract

Crouzon syndrome is the most common form of craniofacial dysostosis, characterised by a classical triad of abnormal skull shape, abnormal facies, and exophthalmos. The clinically overt dental abnormalities in these patients, distracts clinicians from the developmental neurological defects and therefore this entity remains relatively under - highlighted in radiology literature. We report and highlight the role of imaging in diagnosis of Crouzon syndrome in two patients, and discuss the relevant differential diagnosis. Moreover, our report is among the few Indian studies in which Crouzon syndrome was confirmed by genetic studies. The classical clinical triad of Crouzon syndrome was observed in both patients. The skull radiographs and cranial CT with 3D reconstruction VRT (Volume rendered technique), revealed characteristic radiological features. Genetic studies reconfirmed the clinical and radiological diagnosis of Crouzon syndrome, in both patients.

Key words: Crouzon Syndrome; dental abnormalities; Imaging; Skull radiographs; Cranial CT; Volume rendered technique; Genetic studies

Introduction

Crouzon syndrome, is a rare genetic disorder characterized by a triad of skull deformities (due to premature closure of cranial sutures: craniosynostosis), midface hypoplasia, and ocular abnormalities usually manifesting as exophthalmos.^[1-3] Clinically overt dental abnormalities in these patients, usually lead them to dental consultations, and therefore this entity is more frequently reported in dental sciences literature.^[2,4,5] We report and highlight the role of imaging in diagnosis of Crouzon syndrome in two patients and discuss the relevant differential diagnosis. The

classical clinical triad of Crouzon syndrome was observed in both patients. The skull radiographs and cranial computed tomography (CT) with 3D volume rendered technique (VRT) revealed characteristic features of raised intracranial pressure and premature synostosis of cranial sutures. Genetic studies reconfirmed the clinical and radiological diagnosis of Crouzon syndrome, in both the patients. Our report is among the few Indian studies in which Crouzon syndrome was confirmed by genetic studies. Early clinical and radiological diagnosis can prevent the development

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of debilitating mental retardation, visual defects, auditory compromise, and airway obstruction in these patients.^[5,6]

Case Report: Patient 1

A 2-year-old boy was brought with complaints of abnormal facies and abnormal skull shape since birth. On clinical examination, plagiocephaly, hypertelorism, depressed nasal bridge and exophthalmos were observed [Figure 1]. However, dentition appeared normal. The only elder sibling and parents were normal. Lateral skull radiograph revealed shallow orbits, depressed nasal bridge, copper beaten skull, asymmetrical calvarial thickening, and absence of coronal sutures [Figure 2]. The clinical and radiographic appearances suggested craniosynostosis. Radiographs of limbs and spine were normal. Cranial CT, with 3D reconstruction (VRT) was performed for evaluation of brain parenchyma, calvarial bones, and skull sutures. The study revealed normal brain parenchyma. The cranial vault showed complete fusion of coronal sutures with normal lambdoid sutures and asymmetrical regions of thinning and thickening in the calvarial bones [Figure 3]. The 3D VRT CT images revealed complete fusion of sagittal and coronal sutures, with normal lambdoid suture [Figure 4]. The clinical and imaging observations were consistent with craniosynostosis in Crouzon syndrome. The diagnosis of Crouzon syndrome was further confirmed on genomic DNA, using Sanger sequencing (ABI Prism), which showed heterozygous mutation in Exon 8 (c. 1025 > A, p. Cys342Tyr) of Fibroblast Growth Factor Receptor 2 gene (FGFR 2), located on Chromosome 10. Following the genetic diagnosis, multistep surgical correction procedures for

the craniofacial deformity were advised for the patient. However, the parents refused the same and left the hospital against medical advice.

Case Report: Patient 2

The second patient, a 1-year-old first born girl, also presented with abnormal facies, abnormal skull shape, and proptosis since birth. On clinical examination, plagiocephaly, hypertelorism and exophthalmos were seen, with normal dentition. The parents appeared normal. Anteroposterior skull radiograph revealed hypertelorism with copper beaten skull and conspicuous absence of coronal and lambdoid sutures [Figure 5]. The clinical and radiographic features suggested craniosynostosis. The radiographs of the limbs and spine were normal. Cranial CT, with 3D volume rendered reconstruction, was performed which revealed normal brain parenchyma, complete fusion of coronal and lambdoid sutures, with only the sagittal suture appearing normal [Figure 6]. The clinical and imaging observations were consistent with Crouzon syndrome. Genetic tests showed heterozygous mutation in Exon 8 (c. 1025 > A, p. Cys342Tyr) of FGFR 2 gene, on Chromosome 10. However, despite adequate counseling, the parents of this child also rejected multistage surgical treatment.

Discussion

Crouzon syndrome, a rare disorder, is estimated to occur in 1 in 25000 live births worldwide and accounts for 4.8% of all craniosynostosis.^[4,7] It was first described by



Figure 1: Clinical photograph of first patient, showing abnormal shape of head and depressed nasal bridge

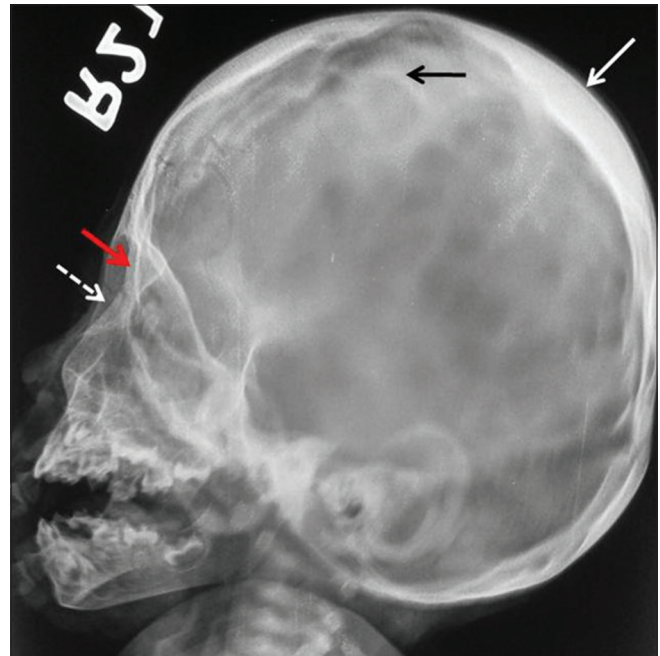


Figure 2: Lateral skull radiograph of first patient shows asymmetrical calvarial thickening (solid white arrow), copper beaten skull (black arrow), shallow orbits (red arrow), and depressed nasal bridge (dotted white arrow)

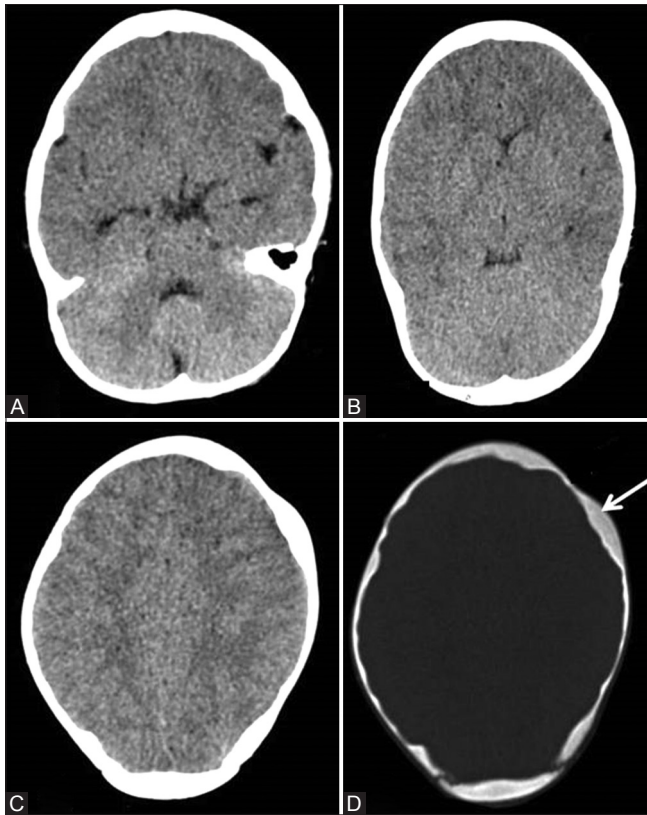


Figure 3 (A-D): CT head (first patient): brain window (A-C), shows normal brain parenchyma, bone window (D), shows asymmetrical calvarial thickening (white arrow)

a French neurosurgeon Louis Edouard Octave Crouzon in 1912, as a hereditary craniosynostosis syndrome, with a triad of skull deformities, facial anomalies, and exophthalmos.^[1] Additionally, cleft lip, cleft palate, and bifid uvula are known associations.^[2,3,6,8] It is an autosomal dominant disorder with complete penetration but variable expressivity. It arises due to mutation in *FGFR2*, which is mapped to chromosome locus 10q25--10q26, causing skull bones to fuse prematurely. Locus heterogeneity with mutation in *FGFR3* genes results in Crouzon syndrome with acanthosis nigricans.^[1,4] The growth of the skull and brain are impaired in a direction perpendicular to the fused sutures, giving rise to the craniofacial abnormalities.^[9,10]

The diagnostic radiographic features of Crouzon syndrome are premature craniosynostosis, with characteristic presence of craniofacial anomalies, with absence of digital and limb anomalies.^[1,5] Premature craniosynostosis usually involves either coronal or lambdoid and occasionally the sagittal sutures. The abnormal process may also extend to involve sutures at the skull base. The latter explains mid face hypoplasia and upper airway obstruction.^[1,3,4] Occasional spine deformities, such as craniovertebral junction abnormalities, butterfly vertebrae, and fused cervical vertebrae have been reported.^[1] Therefore, radiographs of limbs and spine are important, in addition to skull radiographs, for definitive diagnosis.

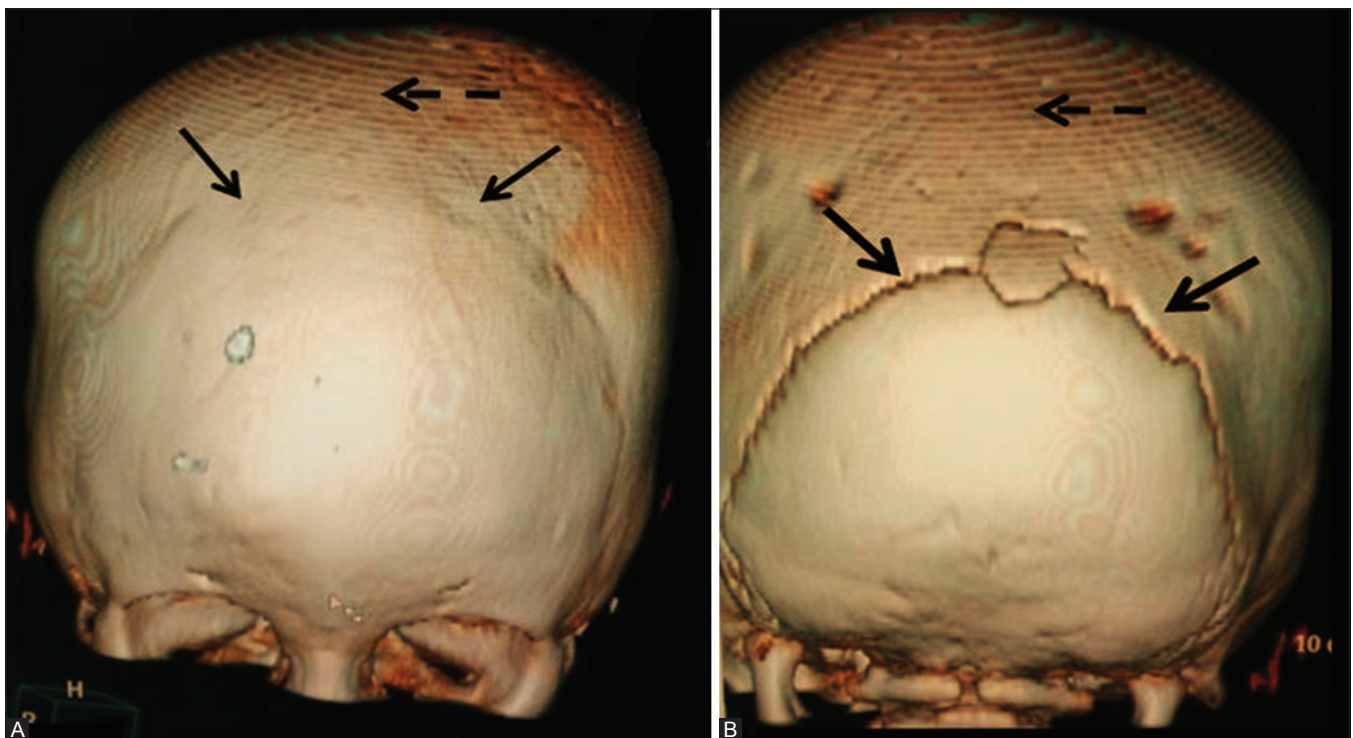


Figure 4 (A and B): Volume rendered 3D CT image (first patient): Anteroposterior view (A), shows complete loss of normal interdigitations in both coronal sutures (thin black arrows), indicating their fusion. Additionally, there is complete fusion of the anterior part of sagittal suture (dotted black arrow). Posteroanterior view (B), shows complete fusion of the posterior part of sagittal suture (dotted black arrow), however, lambdoid sutures are normal (thick black arrows)

Anteroposterior and lateral skull radiographs not only reveal abnormal skull shape but also show sclerosis and fusion of sutures. Sutural fusion manifests as partial or complete obliteration of the suture and fused sutures may appear “heaped up” with loss of normal interdigitations.^[11] Other radiographic features of craniofacial bones are hammered silver beaten/copper beaten skull vault, enlarged hypophyseal cavity, shallow

orbits, small paranasal sinuses, and hypoplastic maxilla.^[4,11,12] In both our patients, we observed copper beaten skull vault, asymmetrical regions of vault thickening, hypertelorism and depressed nasal bridge. However, limbs, digits and spine were normal; thus, other similar syndromes were definitively excluded.



Figure 5: Anteroposterior skull radiograph of second patient shows copper beaten skull (black arrow)

The widths of sagittal suture and coronal suture at birth, as estimated on CT, are known to be 5 mm and 2.5 mm respectively, and gradually reduce to approximately 1.5 mm and 0.8 mm by 1 year of age respectively and fuse at 40 to 60 years of age.^[13] In patients with craniosynostosis, the sutures are not visible. The prematurely fused sutures may be symmetrically or asymmetrically involved.^[14] In both our patients, there was symmetrical synostosis of the involved sutures. The role of cranial CT, with 3D VRT, in delineating the status of individual skull sutures, the occurrence and the extent of parasutural sclerosis and parasutural bony ridges in patients of craniosynostosis has been highlighted earlier only in a few studies.^[11,14] It is also known that increased bone deposition occurs at the perimeter of fused sutures.^[9] The same has been documented in our first patient, with increased bone deposition/sclerosis seen at the periphery of the fused left coronal suture. Information regarding suture status is a vital management data for planning reconstructive osteotomies in these patients. CT also plays a vital role in evaluation of postsurgical correction. Magnetic resonance imaging (MRI) is not routinely done, but in syndromic cases, it may be useful for documenting brain parenchymal abnormalities, overlooked on CT.^[15]

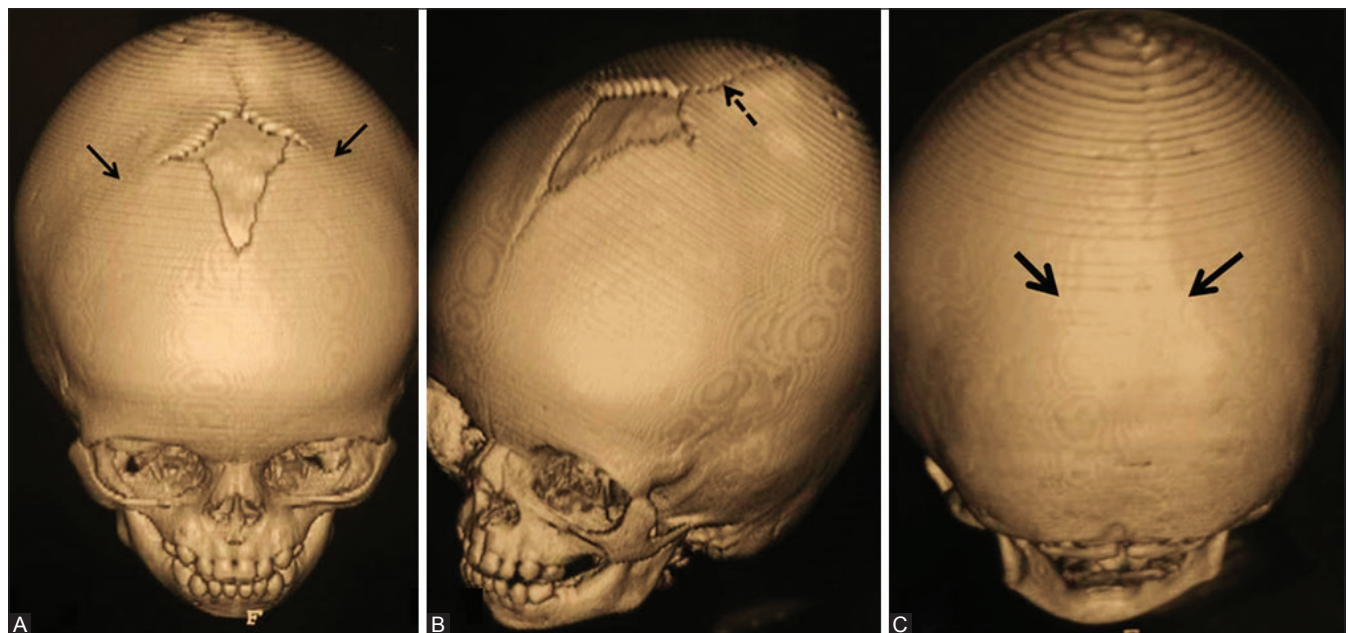


Figure 6 (A-C): Volume rendered 3D CT image (second patient): Anteroposterior view (A), shows complete fusion of both coronal sutures (thin black arrows). Oblique view (B) shows normal sagittal suture (dotted black arrow). Posteroanterior view (C), shows complete fusion of both lambdoid sutures (thick black arrows)

Table 1: Clinical and genetic features of Crouzon syndrome and other simulating diseases

Syndrome variety	Common clinical feature	Skin changes	Thumb abnormalities	Syndactyly	Polydactyly	Spine deformities	Genetic mutation
Crouzon syndrome		Absent	Absent	Absent	Absent	Present	FGFR2 (several mutations)
Crouzon syndrome with acanthosis nigricans		Hyperpigmentation and rugosities	Absent	Absent	Absent	Present	Ala391Glu mutation in FGFR3 gene
Carpenter syndrome	Craniofacial dysostosis	Absent	Absent	Absent	Pre-axial	Absent	RAB23/MEGF8 genes
Pfeiffer's syndrome		Absent	Broad thumb and great toe	Cutaneous syndactyly + osseous syndactyly	Absent	Absent	FGFR1 and FGFR2 genes
Jackson-Weiss syndrome		Absent	Broad great toe with varus deviation	Tarsal/metatarsal fusion	Absent	Absent	FGFR2 gene
Apert syndrome		Absent	Short and broad thumbs	Absent	Absent	Absent	FGFR2 gene

FGFR=Fibroblast growth factor receptor, Glu=Glutamic acid, Ala=Alanine, RAB23=Member of RAS oncogene family, MEGF8=Mouse epidermal growth factor

Recently, investigators from the United Kingdom have reported a novel gradient echo “black bone” MRI technique as an alternative to CT, for the identification of normal sutures and 3D delineation of prematurely fused sutures in patients of craniosynostosis.^[16] It is expected with wider availability of this technique, MRI will sooner rather than later, replace CT as the diagnostic and the postoperative evaluation modality.

The differential diagnosis of Crouzon syndrome includes Crouzon syndrome with acanthosis nigricans, Pfeiffer's syndrome, Apert syndrome, Saethre–Chotzen syndrome, Carpenter syndrome, and Jackson–Weiss syndrome.^[4,5,11,17,18] These syndromes show presence of limb and digital abnormalities, unlike Crouzon syndrome. Additionally, the clinical and genetic differential diagnosis of all these syndromes is summarized in Table 1.

Few investigators have published their experience on antenatal diagnosis of Crouzon syndrome and similar anomalies, using fetal ultrasound and MRI.^[19,20] However, the parents of both our patients did not have any antenatal records.

The treatment of Crouzon syndrome patients begins during the child's first year of life, with fronto-orbital advancement and cranial decompression, for prevention of raised intracranial pressure, which may lead to mental retardation and impaired vision.^[11] All surgical techniques are designed to increase cranial vault volume and reduce the raised intracranial pressure. “Ilizarov procedure,” recommended for Crouzon syndrome has been reported to produce complete correction of exophthalmos and cosmetic improvement of the middle third of face.^[21] “Distraction osteogenesis” is another surgical treatment for craniosynostosis. Postoperative skull radiographs and 3D CT are important to assess the accurate location of the distraction devices and the subsequent reduction in cranial markings, indicating a successful postprocedure reduction of intracranial pressure.^[21]

Conclusion

In patients with craniofacial dysostosis, Crouzon syndrome should be considered as an important radiological diagnosis, characterized by skull abnormalities, occasional spine deformities, and conspicuous absence of digital and limb anomalies. Cranial CT, with 3D VRT, plays an essential role in adequate assessment of sutures, thereby guiding appropriate and timely suture-related surgical procedures. Radiological examination contributes not only to definitive diagnosis, but also towards vital postoperative assessment of the surgical results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form (parents of) the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The (parents of) patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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