Review Article

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Crouzons Syndrome: A Review of Literature and Case Report

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Abstract

Crouzon syndrome is an autosomal dominant disorder with complete penetrance and variable expressivity [1]. In 1912 a French neurologist, Octave Crouzon (1874-1938) first described a hereditary syndrome of craniofacial dysostosis in a mother and her daughter which included a triad-cranial deformities, facial anomalies and exophthalmos [2]. The genetic defect appears to emanate from the mutation of fibroblast growth factor receptor 2 (FGFR2) on chromosome locus 10q25-q26, resulting in early fusion of skull bones during fetal development. Crouzon syndrome, also called craniofacial dysostosis characterized midfacial hypoplasia and orbital defects. It accounts for 4.8% of all cases of craniosynostosis [3]. Normally, the sutures in the human skull fuse after the complete growth of the brain, but if any of these sutures close early then it may interfere with the growth of the brain. . Mental retardation is not a hallmark feature unless premature closure of the cranial suture lines impairs brain development [4]. The disease is characterized by premature synostosis of coronal and sagittal sutures which begins in the first year of life. Case report of a 7 year old boy is presented with characteristic features of Crouzon's syndrome with mental retardation.

Keywords: Crouzon's Syndrome; Fibroblast Growth Factor; Premature Synostosis; Hypertelorism; Exophthalmos; Midfacial Hypoplasia.

Introduction

Crouzon syndrome is a rare genetic disorder characterized by premature closure of cranial sutures, exophthalmos and mid facial hypoplasia. Crouzon syndrome occurs in approximately 1 in 25,000 births world wide and 16.5 per 1,000,000 live births in World [5]. It may be transmitted as an autosomal dominant genetic condition or appear as a mutation. No known race or sex predilection exists The majority of the patients with Crouzon syndrome have mutations in the extracellular immunoglobulin III domain of the Fibroblast Growth Receptors 2(FGFR2) gene [6]. The differential diagnosis of Crouzon syndrome includes Apert syndrome, Pfeiffer, Jackson-Weiss, Carpenter and Saethre-Chotzen syndrome. Crouzon syndrome is distinguishable from other craniosynostosis syndromes by lack of hand and/or foot abnormalities [7,8]. Multiple staged surgeries are the general treatment plan for patients with Crouzon syndrome. In this article, we present a case of Crouzon syndrome in a boy aged 7 years.

Case Report

A 7-year-old boy along with his parents reported to our department for treatment. The chief complaint being as presented by the mother was mental retardation and overcrowding of teeth. Since the child's appearance and head size was not normal, the family and medical history were taken in detail. It was diagnose as Crouzon's syndrome associated with mild to moderate mental retardation. Review of

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medical history was unremarkable, specifically, the mother reported normal labor and delivery. There were no anomalies in any siblings or near relatives reported. The child was not on any medications and denied any medical allergies. Further medical history revealed that the enlarged size of the head was noted by the mother ever since he was 6 months and the severity has gradually increased.

On Examination

On examination, enlarged cranial vault with frontal bossing, maxillary hypoplasia and a relative, mandibular prognathism was found. Ocular manifestations such as shallow orbits, hypertelorism, bilateral proptosis, exophthalmos and strabismus were present. Other facial features included short and incompetent upper lip, depressed nasal bridge and low-set ears but without any hearing loss. His hands and feet found to be normal. Past medical history from the parents revealed that the features started developing slowly after birth and was diagnosed as CS at the age of 9 months and the patient had undergone cranial surgery to relieve closed sutures of the skull at the same age.

In Figure 1 Frontal and lateral view face showing the frontal bossing, midface hypoplasia and a relatively large mandible, shallow orbits, hypertelorism, exophthalmos, short and incompetent upper lip, depressed nasal bridge, (Figure 2) lateral view of the face.

The prenatal, delivery and postnatal history was found to be insignificant. Family history revealed no abnormality. He is the first child of clinically healthy parents of non-consanguineous marriage. His developmental milestones were found to be normal. The patient was presented with normal intelligence and little speech difficulty. At the time of his birth, his father was 36 years old and his mother was 22-year-old.

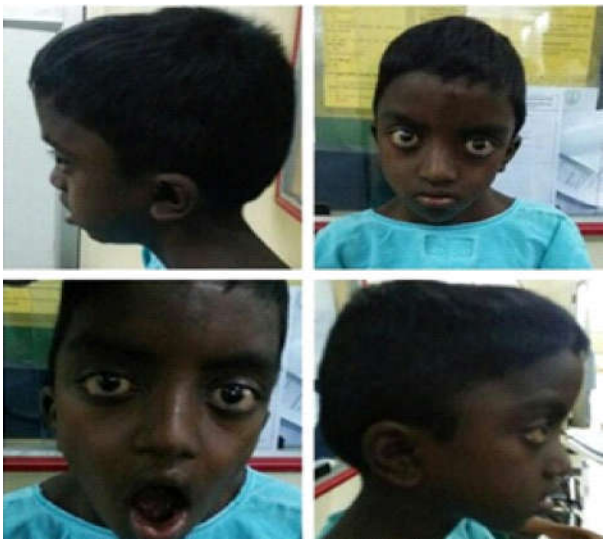

Fig. 1 & 2: Frontal and lateral view face showing the frontal bossing, midface hypoplasia and a relatively large mandible, shallow orbits, hypertelorism, exophthalmos, short and incompetent upper lip, depressed nasal bridge, (Fig 2) lateral view of the face.

On intraoral examination, V-shaped maxillary arch with high-arched palate and bilateral palatal swellings which was mimicking a pseudocleft, retruded maxilla with a relatively large mandible were found. His oral hygiene was poor with crowding of upper and lower teeth, reverse over-jet with posterior cross-bite and anterior open bite, tongue tie and decayed teeth were present.

The skull radiographs revealed the 'scaphocephalic' skull shape, hypoplastic maxilla and zygoma with shallow orbits (Figure 3 & 4) Prominent cranial markings of the inner surface of the cranial vault seen as multiple radiolucencies appearing as depressions resulting in the 'hammered silver' (beaten metal/copper beaten) appearance indicating internal remodeling of the calvaria due to an increase in intracranial pressure as a result of premature cranial suture fusion.

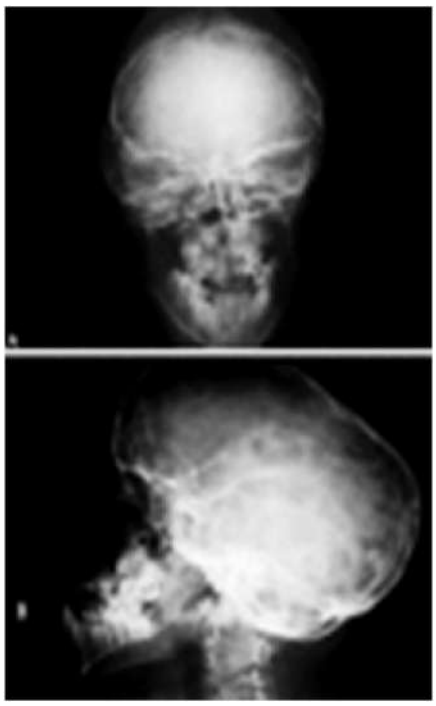

Fig. 3 & 4: AP and lateral view of the skull

AP and lateral view of the skull–demonstrating maxillary retrusion, relative mandibular prognathism and 'hammered silver' (beaten metal/copper beaten) appearance

Three-dimensional computed tomographic (CT)

scans of the skull showed fused sagittal and lambdoid sutures and surgically opened coronal suture, moderate degree of hydrocephalus with diffuse indentation of inner table of skull Other systemic examination was found to be normal. Routine hematological and biochemical tests were within normal limits.

Discussion

CS is inherited as an autosomal dominant fashion but there is an equal incidence of sporadic cases which probably represent new 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. However, the fact that the same mutation can produce a wide range of phenotypic expression makes the mechanism of anomalous development more complex [9]. Penetrance is high although severity is variable. Within the family, members tend to have similar facial deformities but variable calvarial deformities and this phenotypic heterogeneity makes genetic counseling difficult. The phenotypic features of CS may be absent at birth and evolve gradually during the first few years of life [10]. The variability in both cranial and facial malformations depends on the order and rate of progression of sutural synostosis. Premature synostosis commonly involves the sagittal and coronal suture. Lambdoidal sutures are occasionally involved. The craniosynostosis of the sagittal is predominant in boys, while the coronal is more common in girls. The type of obliterated sutures determines the shape of the cranial vault. The skull shape can vary from brachycephaly (most commonly observed) to scaphocephaly (boat-shaped head), oxycephaly, plagiocephaly, trigonocephaly (triangle-shaped head) or in severe disease cloverleaf skull (kleeblattschädel) like deformity-In the present case premature closure of the sutures had caused restricted skull growth and lack of space for the growing brain resulted in 'compensatory' change in the growth of skull and brain toward frontal region, where the coronal sutures were opened surgically causing frontal bossing creating an elongated narrow scaphocephalic skull [11].

The facial and oral malformations consist of hypoplastic maxilla and zygoma, pointed nose (psittichorhina/parrot beak-like nose) due to the short and narrow maxilla, narrow high-arched palate, bilateral palatal swellings (pseudocleft) or cleft palate in some patients and crowding of teeth as well as posterior crossbite and reverse overjet with anterior open bite and relative mandibular prognathism [12].

Approximately one-third of patients with CS suffer from hearing loss due to middle ear deformities and upper airway obstruction occurs due to midfacial hypoplasia and narrow epipharynx. Optic atrophy is frequently seen and has been reported in 30 to 80% of patients [12]. Affected individuals exhibit ocular malformations including hypertelorism, proptosis due to the shallow orbits. Mental ability and psychomotor development is generally within normal limits. However, when the premature closure of the cranial suture lines impairs brain development due to increased intracranial pressure it can lead to mental retardation [13]. The gene for CS could be localized to the FGFR2 at the chromosomal locus 10q 25.3-q26 in more than 50% of cases [14]. Mutation of the FGFR gene is also responsible for other craniosynostosis, such as Apert's, Pfeiffer's, Jackson-Weiss' and Saethe-Chotzen's syndromes [15]. Rarely, acanthosis nigricans may coexist with CS in childhood and is caused by mutation in the FGFR3 gene (locus 4p16.3).

Thorough clinical, radiological and genetic analysis is required for early diagnosis of CS. Prenatal diagnostic testing for FGFR gene mutation is an option for couples at risk for having a child with CS. Ultrasonic prenatal diagnosis of exophthalmos might give a clue regarding the developing problems.

The management requires a multidisciplinary approach and the surgical treatment usually begins in the child's first year with cranial decompression. In the presented case early craniectomy of coronal sutures was done at the age of 9 months to relieve increased intracranial pressure caused by premature multiple suture synostosis [6]. An increased intracranial pressure impairs brain development and can lead to mental retardation. Because of the early diagnosis and intervention in this case, no complications were found in our case except for dysmorphic features and the patient presented with normal intelligence. Skull reshaping may need to be repeated when the child grows and subsequent development of midfacial hypoplasia also needs correction. Procedures for this purpose will include Le Fort III osteotomy or its segmental variants, monobloc frontofacial advancement, or bipartition osteotomy which helps in the cosmetic reconstruction of facial dysmorphisms. The goal is to stage reconstruction to coincide with facial growth patterns and psychosocial development. The prognosis in the case of CS depends on severity of malformation and the patients usually have a normal lifes pan [16].

In our case, complex treatment plan involving prophylactic and therapeutic approach was

formulated for the patient which includes regular mechanical and chemical professional plaque control, with fluoride and chlorhexidine applications to control the intense carioactivity and gingival inflammation.

Conclusion

Clinical diagnosis of Crouzon syndrome is based on clinical findings, molecular genetic testing of FGFR2 gene mutation. Being an autosomal dominant disorder, there is a 50% chance of passing the disease to each child. Prenatal testing of pregnancies with high risk is necessary. Treatment is palliative and surgical management is tailored to individual needs. Prevention of secondary complications such as hydrocephalus, cognitive impairment depends on early treatment of craniofacial anomalies. Exposure keratitis in these children can be prevented by adequate ophthalmologic lubrication in those with severe proptosis.

References

1. Crouzon O. Dysostose cranio-faciale hereditaire. Bull Mem Soc Med Hop Paris. 1921; 33:545–555.
2. Reardon W, Winter RM, Rutland P, Pulleyn LJ, Jones BM, Malcolm S. Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. Nat Genet. 1994; 8(1):98–103.
3. Al-Qattan MM, Phillips JH. Clinical features of Crouzon's syndrome patients with and without a positive family history of Crouzon's syndrome. J Craniofac Surg. 1997; 8(1):11–13
4. Bowling EL, Burstein FD. Crouzon syndrome. Optometry. 2006; 77(5):217–222.
5. Kaur H, Waraich HS, Sharma CM. Crouzon syndrome: A case report and review of literature. Indian J Otolaryngology Head Neck Surg. 2006; 58(4):381–382.
6. Regezi JA, Sciubba JJ, Jordan RCK. Oral pathology: Clinical pathologic correlations. London: WB Saunders Company; 1999.p.436–437.
7. Da Silva DL, Palheta NFX, Carneiro SG, Palheta ACP, Monteiro M, Cunha SC, Nunes CTA. Crouzon's syndrome: Literature review. Intl Arch Otorhinolaryngol. 2008; 12(3):436–441.
8. Glaser RL, Jiang W, Boyadjiev SA, Tran AK, Zachary AA, Van Maldergem L, Johnson D, Oldridge M, Wall SA. et al. Paternal origin of FGFR2 mutations in sporadic cases of Crouzon syndrome and Pfeiffer syndrome. Am J Hum Genet. 2000; 66(3):768–777.
9. Cohen MM Jr., editor. Craniosynostosis: Diagnosis, evaluation, and management Crouzon syndrome. In: Cohen MM Jr (Ed). Craniosynostosis: Diagnosis, evaluation, and management. (2nd ed) New York: Oxford University Press; 2000.p.361.
10. Golabi M. Radiographic abnormalities of Crouzon Syndrome. A survey of 23 cases. Proc Greenwood Genet Ctr. 1984; 3:102.
11. Neville BW, Damm DD, Allen CM, Bouquet JE. Oral and maxillofacial pathology . Developmental defects of the oral and maxillofacial region. Elsevier Publishers; 2004.p.40.
12. Abdallah AM. A severe form of Crouzon's syndrome: Clinical and radiological correlation. Saudi J Ophthalmol. 2003; 17:183–185.
13. Jeftha A, Stephen L, Morkel JA, Beighton P. Crouzonodermo- skeletal syndrome. J. Clin. Pediatr Dent. 2004; 28(2):173–176.
14. Preising MN, Schindler S, Friedrich M, Wagener H, Golan I, Lorenz B. On the effect of mutations of the fibroblast growth factor receptors as exemplified by three cases of craniosynos- toses. Klin Monbl Augenheilkd. 2003; 220(10):669–681.
15. Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW. Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosisnigricans. Nat Genet. 1995; 11(4): 462–464.
16. Atkinson FR. Hereditary Craniofacial dysostosis or Crouzon's disease. Med Press Circular.1937; 195: 118–124.