Crouzonodermoskeletal syndrome

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Crouzon craniostenosis [MIM 123500], is identified on the basis of the additional phenotypical manifestations of acanthosis nigricans, vertebral changes and cementomas of the jaws. Choanal atresia and hydrocephalus are other features. The molecular defect in CDSS is a point mutation in the FGFR3 gene on chromosome 4p, whereas, the mutation in the Crouzon syndrome is in the FGFR2 gene at 10q25.3-26. An affected girl aged 2 years presented at the UWC dental genetics unit with a prior diagnosis of Crouzon syndrome. Choanal atresia had necessitated a permanent tracheostomy, and hydrocephalus was managed by a shunt operation. Clinical examination revealed acanthosis nigricans in the axilliary regions, a diagnosis confirmed by a biopsy of the lesion. Eruption of the primary dentition was delayed with only six out of twenty teeth present. Radiographic examination conducted shortly after birth revealed the presence of several tooth buds in both the maxillae and the mandible. The delayed eruption of the teeth will be of significance in future orthodontic and maxillofacial measures for the improvement of the patient's facial Crouzonodermoskeletal syndrome (CDSS) was separated from the classical appearance. Molecular investigations in the girl and her parents are underway. If the specific mutation in FGFR3 is observed, a positive diagnosis of CDSS will be confirmed and the status of her parents and other family members will be determined. On this basis, appropriate genetic management can be offered to the kindred.
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INTRODUCTION

The Crouzon syndrome (MIM 123500) is a well-known genetic disorder characterised by craniostenosis, maxillary hypoplasia, shallow orbits and ocular proptosis.[1] Dental management in patients with complex craniofacial syndromes of this type is of major importance, since variable oral and dental manifestations may be present.

An uncommon subtype termed the "Crouzonodermoskeletal syndrome" (CDSS) has been delineated on a clinical and a molecular basis. This condition, which is more severe than the conventional Crouzon syndrome is characterised by the presence of acanthosis nigricans, vertebral abnormalities and dental cementomas.[2] Additional manifestations are hydrocephalus, choanal atresia and minor skeletal changes.[3]

We have recently documented a South African child with the CDSS. In this article we briefly review the nosology of the disorder and discuss the general orodental management and genetic implications.

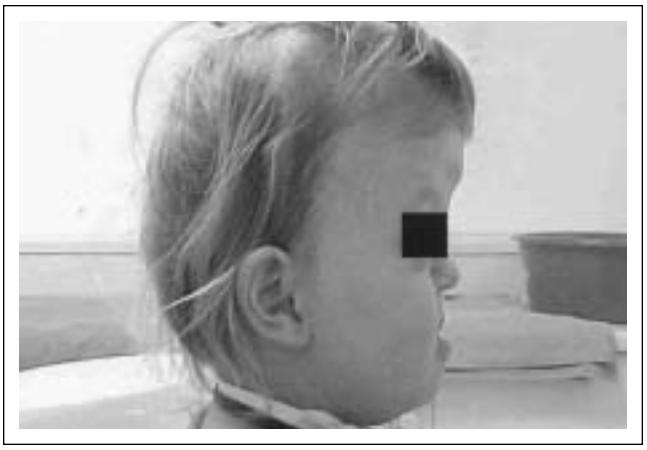

Figure 1. Profile of the face. Frontal bossing is evident.

CASE REPORT

A girl of European stock was born in Cape Town on January 31, 2001. In the third trimester of pregnancy, ultrasonic studies revealed a trilobar configuration of the skull (Kleebattschadel/ Cloverleaf anomaly), which

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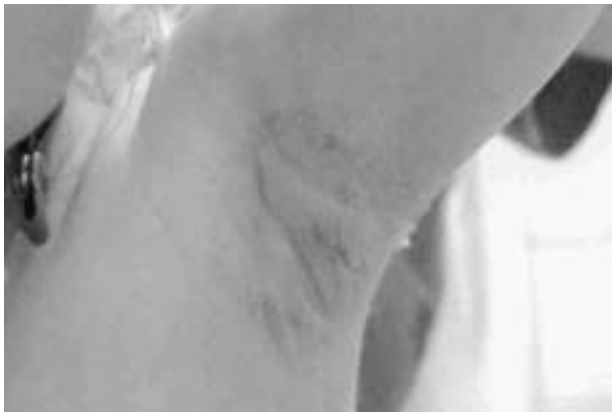

Figure 2. Acanthosis nigricans of the axilla.

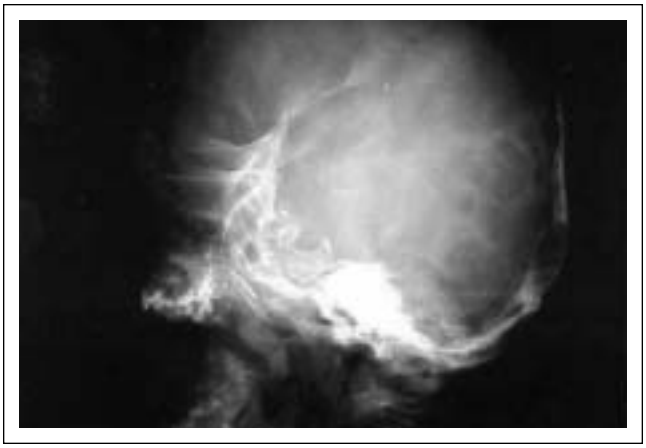

Figure 3. Radiograph of the lateral view of the skull taken at 5 months and 17 days of age. Numerous tooth buds are present in the maxilla and mandible.

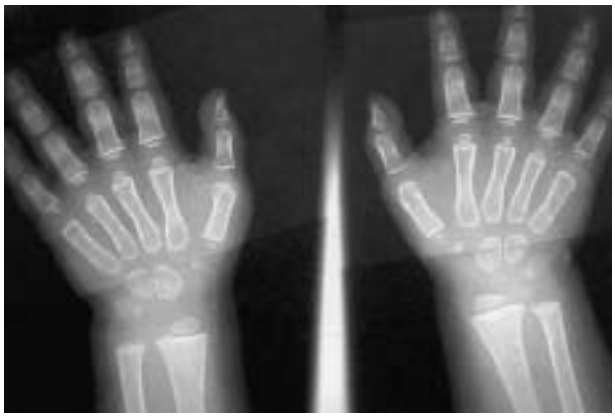

Figure 4. Radiograph of both hands showing short phalanges.

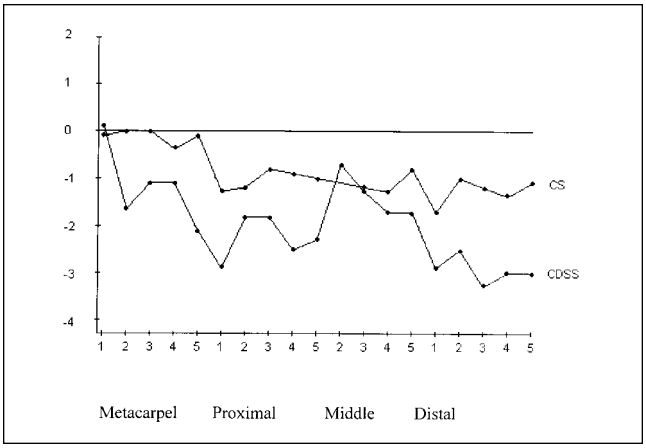

Figure 5. Pattern profile analysis. The metacarpophalangeal pattern profile for the affected girl (lower) compared with the average for 12 persons with the Crouzon syndrome (upper) [adapted from Murdock-Kinch and Ward 1997].

lead to a suspicion of Trisomy 18. Subsequent investigations revealed that the chromosomes were normal. An elective Caesarean section was undertaken at the 38th week of gestation. Birth weight was 3.8kg, length 51cm and head circumference 34cm. In the neonatal period, the craniofacial appearances prompted the diagnosis of the Crouzon syndrome. Choanal atresia was recognised when difficulties with respiration developed, swallowing was impaired and weight gain was compromised; these problems were alleviated by tracheostomy. Craniostenosis was managed by means of excision of cranial sutures. Thereafter, the development of hydrocephalus was confirmed by diagnostic imaging, and a shunt operation was performed.

The patient was assessed in January 2003 at the age of 2 years. She had the characteristic mid-facial hypoplasia and nasal beaking of the Crouzon syndrome (Figure 1). Her tracheostomy was still patent and her mother undertook regular aspiration of secretions. Dark skin pigmentation in the axillae and groin, which was first evident at this time, was suggestive of acanthosis nigricans and this diagnosis was subsequently confirmed histologically (Figure 2).

Oro-dental features included delayed dental eruption, with only six deciduous teeth being present. These teeth were three mandibular incisors, one maxillary central incisor and two deciduous maxillary molars in 5th and 6th quadrants respectively. A lateral cephalometric radiograph taken shortly after birth indicated the presence of numerous maxillary and mandibular tooth buds (Figure 3). The patient had midface hypoplasia and retrognathism with a pseudoprognathic mandible, which is typical of the Crouzon Syndrome. Her palate is broad and flat, rather than high arched.

Limited radiographic study revealed absence of caudal widening of the interpeduncular distances in the lumbar spine; the sacro-iliac notches were normal. Pattern profile analysis of hand radiographs, using the

method of Poznanski *et al*.[4] revealed shortening of the tubular bones, which was maximal in the distal phalanges (Figures 4 and 5).

The father and mother were healthy young and non-consanguineous. An elder brother was normal. The mother and maternal grandmother had mild proptosis, but were otherwise normal in appearance, intellect and stature.

DISCUSSION

Octave Crouzon (1874-1938) was a French neurologist, who was appointed to the staff of the Salpêtrière hospital, Paris in 1919, where he spent the whole of his career. In 1912 he presented a mother and son with abnormal facies at the Medical Society of Paris and commented upon the hereditary nature of the disorder.[5] Crouzon subsequently documented a family in which 7 persons were affected;[6] more reports followed and Crouzon's name came into use as a designation for the disorder. The accumulation of case reports facilitated the delineation of the phenotype. In this way, the Crouzon syndrome was separated at a clinical level from other disorders of cranio-facial development. Segregation analysis of pedigree data from affected families established the autosomal dominant mode of genetic transmission.

With the advent of molecular technology, the gene for the Crouzon syndrome was localised to the Fibroblast Growth Factor Receptor II gene (FGFR2) at the chromosomal locus 10q 25.3-q26, and more than 30 different mutations within the gene have been documented in separate families. It also turned out that the Apert, Pfeiffer and Jackson-Weiss syndromes resulted from allelic mutations in this gene.

In addition to the major cranio-facial abnormalities in the Crouzon syndrome, and the multiple additional anomalies, which occur in low frequency, a small proportion of affected persons have narrowing of the nasal passages (choanal atresia) and hydrocephalus. In the jaws, dental cementomas are sometimes present.[7] A number of these individuals; mainly females had dark pigmentation of the skin in the axillae, groins and other regions**.** These regions become verrucous and hypertrophic, showing the characteristic histological features of acanthosis nigricans. This condition became known as the "Crouzon syndrome with Acanthosis Nigricans".[8,9]

Meyers *et al.*[10] determined that the molecular defect in this subset of affected persons resided in the FGFR3 gene, on chromosome 4p16.3, rather than the FCFR2 gene on chromosome 10, which characterizes the classical Crouzon syndrome. In a mother and daughter, together with two other unrelated persons with the Crouzon syndrome plus acanthosis nigricans, the specific mutation was found to be alanine 391 to glutamine (GCG to GAG) in the transmembrane domain. Wilkes *et al.*[11] documented similar findings, as did Superti-Furga[3]. Other specific mutations in the FGFR3 gene determine the well-known dwarfing skeletal dysplasia, achondroplasia, and it is not surprising that lack of caudal narrowing of the interpeduncular distances in the lumbar spine is present in both disorders.[3] Other minor radiographic changes were subsequently recognised.[12] These included narrow sacro-iliac notches, short vertebral bodies and broad short metacarpals and phalanges, all of which are reminiscent of achondroplasia. These mild generalized skeletal changes underlie the shortened stature, which is a feature of some patients who have CDSS.

On the basis of the accumulated clinical and genetic evidence, Cohen[2] urged colleagues not to be "prisoners of our own conventional terminology", argued for the separate syndromic identity of this disorder, and proposed the designation "Crouzonodermoskeletal syndrome" (CDSS). He defined this condition as the Crouzonoid phenotype combined with acanthosis nigricans, jaw cementomas and vertebral changes. The CDSS has not yet received a numerical designation, which would indicate an autonomous syndromic identity in the online catalogue of genetic disorders "Mendelian Inheritance in Man (OMIM). It was, however, listed in the 2002 International Nosology and Classification of Constitutional Disorders of Bone.[13]

Several oro-dental manifestations, may require surgical intervention. Management of affected persons, however, may involve neurological, otological, ophthalmologic and other maxillofacial surgical procedures. It is relevant that acanthosis nigricans, as reported in three patients, with a diagnosis of Crouzon Syndrome[11], was not restricted to the axillae and groin areas. The peri-oral areas were affected in two patients and the third patient, presented with acanthosis nigricans at the corners of the mouth. Other affected areas in these patients, who were older than the child reported here, included peri-orbital, neck, antecubital fossae and around the umbilicus. The dark pigmentation was most severe in the oldest of these three patients.[11] The authors are in agreement with the inference made by Wilkes (1996) that the severity of acanthosis nigricans in Crouzonodermoskeletal patients is variable, and that the severity of this feature increases with age.

Dental malalignment may result from malformation and poor alignment of the jaws. Hence surgical (distraction osteogenesis) and orthodontic measures are important components of management.

The presence of cementomas has been previously reported in some patients with Crouzonodermoskeletal syndrome. This patient has evidence of delayed eruption and hypodontia, but does not have any jaw cementomas at this time. The severity of the hypodontia, the outcomes of the delayed eruption, and the presence or absence of jaw cementomas are more likely to be definitively diagnosed in later life.

The South African girl whom we studied had the characteristic clinical and radiographic features of the CDSS. Her pattern profile analysis was similar in

configuration to that of the conventional Crouzon syndrome,[14,15] but in greater degree. This observation is in keeping with the concept of increased severity of the skeletal changes in CDSS compared with the conventional Crouzon syndrome. Molecular studies are currently underway, in order to provide a basis for genetic management for the family. The fact that the mother of the affected and grandmother have proptosis is relevant in this context.

The delineation of the CDSS as a distinctive entity with a well-defined molecular basis has important implications for prognostication, clinical and genetic management.

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REFERENCES

1. Cohen MM Jr, MacLean RE. Craniosynostosis: Diagnosis, Evaluation and Management. 2nd Ed. New York: Oxford University Press, 1999.
2. Cohen MM Jr. Letter to the Editor. Let's call it "Crouzonodermoskeletal Syndrome" so we won't be prisoners of our own conventional terminology. Am J Med Genet 84: 74, 1999.
3. Superti-Furga A, Locher ML, Steinlin M, Eich G, Huisman T, Steinmann B, Sailer HF, Boltshauser E. Crouzon syndrome with acanthosis nigricans, spinal stenosis and desmo-osteoblastomas: pleiotropic effects of the FGFR-3 ALA-391-GLU mutation. J Craniomaxillofacial Surgery (suppl) 24: 112, 1996.
4. Poznanski AK, Garn SM, Nagy JM, Gall JC. Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. Radiol 104: 1-11, 1972.
5. Crouzon O. Dysostose cranio-faciale héréditaire. Bull Soc Med Hop Paris 33: 545-555, 1912.
6. Crouzon O. Une nouvelle famille atteinte de dysostose cranio-faciale héréditaire. Arch Méd Eng 18: 540, 1915.
7. Reddy BSN, Garg BR, Padiyar NV, Krishnaram AS. An unusual association of acanthosis nigricans and Crouzon disease - a case report. J Dermatol 12: 85-90, 1985.
8. Breitbart AS, Eaton C, McCarthy JG. Crouzon's syndrome associated with acanthosis nigricans: ramifications for the craniofacial surgeon. Ann Plast Surg 22: 310-315, 1989.
9. Orlow SJ. Cutaneous findings in craniofacial malformation syndromes. Arch Dermatol 128(10): 1379-1386, 1992.
10. Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW. Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 11: 462-464, 1995.
11. Wilkes D, Rutland P, Pulleyn LJ, Reardon W, Moss C, Ellis JP, Winter RM, Malcolm S. A recurrent mutation, Ala391Glu, in the transmembrane region of FGFR3 causes Crouzon syndrome and acanthosis nigricans. J Med Genet 33: 744-748, 1996.
12. Schweitzer DN, Graham JM Jr, Lachman RS, Jabs EW, Okajima K, Przylepa KA, Shanske A, Chen K, Neidich JA, Wilcox WR. Subtle radiographic findings of achondroplasia in patients with Crouzon syndrome with acanthosis nigricans due to an Ala391Glu substitution in FGFR3. Am J Med Genet 98: 75-91, 2001.
13. Hall C. Nosology and classification of constitutional disorders of bone. Am J Med Genet 113: 65-77, 2002.
14. Murdoch-Kinch CA, Ward RE. Metacarpophalangeal analysis in Crouzon syndrome: additional evidence for phenotypic convergence with the acrocephalosyndactyly syndromes. Am J Med Genet 73: 61-66, 1997.
15. Anderson PJ, Evans RD. Metacarpophalangeal analysis in Crouzon syndrome. Am J Med Genet 80: 439, 1998.