Case Report

A case of Robinow-Sorauf syndrome (Craniosynostosis-Bifid Hallux Syndrome): The allelic variant of the Saethre-Chotzen syndrome

Arpita Rai Thakur, Venkatesh G Naikmasur[1]

Department of Oral Medicine and Radiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, [1]SDM College of Dental Sciences and Hospital, Dharwad, Karnataka, India

Abstract

The clinical classification of Robinow-Sorauf syndrome has changed over the last few decades. Robinow-Sorauf syndrome is characterized by facies similar to those of Saethre-Chotzen syndrome with bifid or partially duplicated halluces. The current outlook is that the 'Robinow-Sorauf' families are examples of variable expression of the TWIST mutant phenotype and that the 'Robinow-Sorauf' syndrome lies within the spectrum of the Saethre-Chotzen syndrome. We present a case of 19-year-old female patient exhibiting classical clinical and radiological features of Robinow-Sorauf phenotype of Saethre-Chotzen syndrome. A brief review of previously reported cases and nosology has been presented.

Key words: Robinow-Sorauf syndrome, Saethre-Chotzen syndrome, TWIST mutation

INTRODUCTION

Robinow-Sorauf syndrome belongs to the broad categories of craniosynostosis syndrome.[1] It is characterized by facies similar to those of Saethre-Chotzen syndrome, but differentiated from it by the presence of bifid or partially duplicated halluces.[2] Saethre-Chotzen syndrome is characterized by a broad and variable pattern of malformations. Mutations of TWIST gene, which maps to 7p21.3 and encodes a basic helix-loop-helix motif shared by several DNA-binding transcription factors, have been identified in 46-80% of affected individuals.[3] Recently, mutations of the same gene have been identified in patients with Robinow-Sorauf presentations and it has been argued that Robinow-Sorauf Syndrome should be considered the allelic variant of Saethre-Chotzen syndrome.[2,4] Only a handful of cases with Robinow-Sorauf phenotype have been previously reported. The present case represents the seventh instance of report of this condition which for the first time presented as an isolated occurrence rather that a familial presentation.

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CASE REPORT

A 19-year-old female, reported to the Department of Oral Medicine and Radiology, for complains of pain in mandibular anterior region for duration of 2 days. Patient was one of the two siblings of non consanguineous parents with no family history of orofacial or acral malformations. Detailed history revealed that the antenatal, neonatal and infancy had been uneventful. However, she was diagnosed as having atrial septal defect at the age of 7 years and had undergone surgical management for the same. Patient also reported history of menstrual irregularities (menarche achieved at the age of 16 years). She was moderately built, well nourished and appeared to have normal intelligence. Patient's height was 167 cm, within 75th percentile while weight (42 kgs) and head circumference (20 inches) were both below 3rd percentile. Routine general physical examination revealed broad halluces bilaterally exhibiting valgus deformity and dysmorphic nails [Figure 1a]. In addition, duplication of 5th toe

Address for correspondence:
Dr. Arpita Rai Thakur,
Department of Oral Medicine and Radiology, Faculty of dentistry,
Jamia Millia Islamia, New Delhi - 110 025, India.
E-mail: arpitadoc@gmail.com

of right foot with syndactyly of the supernumerary digit with 5th toe was evident. There was flexion contraction of 4th and 5th toe of left foot and 4th toe of right foot. The upper limbs were essentially normal except for broadened right thumb and nail, and clinodactyly bilaterally [Figure 1b]. No functional deficit in relation to hands or feet was noticed. On extra oral examination, acrocephalic skull, flattened frontal and occipital regions and low hairline was evident. The leptoprosopic flat face with mild maxillary hypoplasia and relative mandibular prognathism was exemplified by a prominent chin [Figure 2]. An increase in gonial angle was evident on profile view. Nose was long, thin, pointed with the nasofrontal angle flattened presenting as wide root of the nose. Thick eyebrows, prominent eyelashes, mild convergent strabismus and marginal hypertelorism were present. Intra-oral examination revealed high arched palate and generalized enamel hypoplasia [Figure 3a]. Patient was currently undergoing orthodontic treatment for correction of crowding within the arches. Also anterior deep bite with 100% overlap of mandibular teeth was evident [Figure 3b]. Patient gave previous history of endodontic treatment and apicoectomy of 31, 41 and at the time of presentation had pain in the same region along with vestibular obliteration and tenderness.

Orthopantomogram confirmed a cystic lesion in mandibular anterior region, increased gonial angles bilaterally and occlusal plane irregularities [Figure 4a]. Further radiographic examination of craniofacial skeleton (P-A skull [Figure 4b] and Lateral skull radiographs [Figure 4c] revealed evidence of coronal sutural synostosis with prominent copper beaten appearance, flattened occiput and frontal bones, shallow orbits, gross prognathism with obtuse mandibular plane angle, maxillary sinus hyperpneumatization and falx calcification. Hand and wrist radiograph showed short and broad distal phalynx of right thumb, however all bones were otherwise normal. Radiograph of feet [Figure 5] revealed duplication of distal phalynx of halluces and valgus deformity at distal interphalyngeal

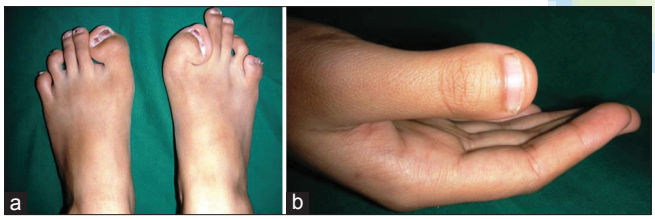

Figure 1: (a) Clinical photograph of feet showing broad halluces bilaterally exhibiting valgus deformity and dysmorphic nails. Duplication of 5th toe of right foot with syndactyly of the supernumerary digit with 5th toe was.There was flexion contraction of 4th and 5th toe of left foot and 4th toe of right foot (b) clinical photograph of hand showing broadened right thumb and nail

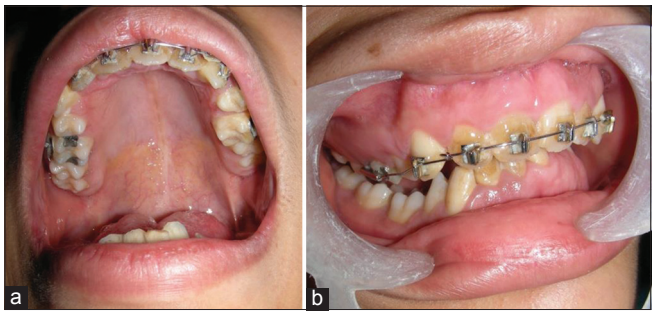

Figure 3: (a) Intraoral photograph showing high arched palate and generalized enamel hypoplasia (b) Intraoral photograph showing anterior deep bite with 100% overlap of mandibular teeth was evident

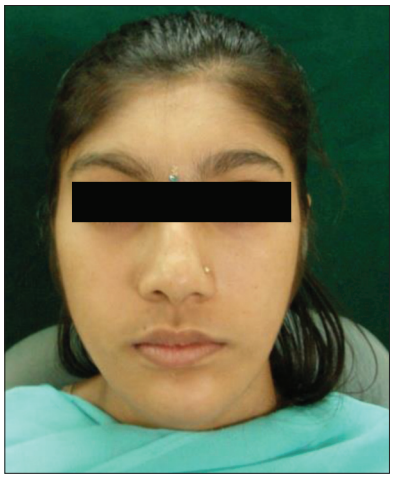

Figure 2: Clinical photograph of face showing leptoprosopic flat face with mild maxillary hypoplasia and relative mandibular prognathism exemplified by a prominent, wide root of the nose, thick eyebrows, prominent eyelashes, mild convergent strabismus and marginal hypertelorism were present

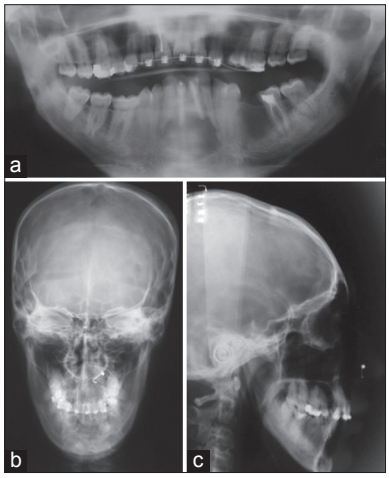

Figure 4: (a) Orthopantomogram showing cystic lesion in mandibular anterior region, increased gonial angles bilaterally and occlusal plane irregularities (b) A skull radiograph showing prominent copper beaten appearance, shallow orbits, maxillary sinus hyperpneumatization and falx calcification (c) Lateral cephalogram of the patient showing gross prognathism with obtuse mandibular plane angle

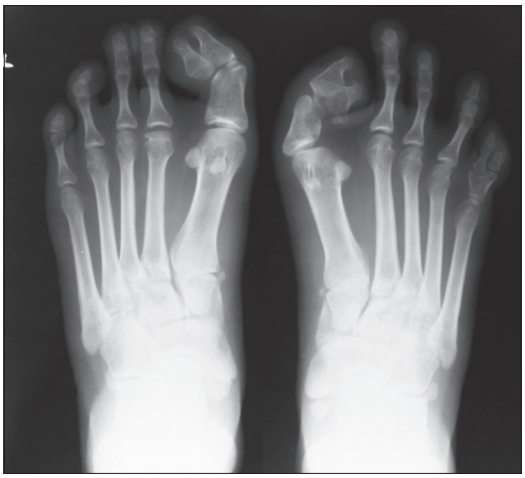

Figure 5: Radiograph of feet showing duplication of distal phalanx of halluces and valgus deformity at distal interphalangeal joint bilaterally. Partial duplication of 5th toe; Y-shaped proximal phalanx with one supernumerary phalanx in postaxial position exhibiting soft tissue syndactyly with 5th toe. Fourth and fifth digits of left foot were bent in clinically fixed flexion

joint bilaterally. There was also evidence of partial duplication of 5th toe; Y-shaped proximal phalynx with one supernumerary phalynx in postaxial position exhibiting soft tissue syndactyly with 5th toe. Fourth and fifth digits of left foot were bent in clinically fixed flexion.

The diagnosis of Robinow-Sorauf syndrome was made based on clinical and imaging features. Surgical enucleation of radicular cyst and apicoectomy of mandibular anteriors was done following intentional root canal treatment of 32 and 42. Opinion regarding surgical correction of limb anomalies was sought. Patient is currently undergoing treatment for functional and esthetic corrections.

DISCUSSION

Robinow-Sorauf syndrome has a very interesting history. Carter *et al.*,[5] in 1982 described a distinct acrocephalosyndactyly syndrome having autosomal dominant inheritance, Saethre-Chotzen facies and split terminal phalynx to the hallux. The authors suggested that this association of craniosynostosis and broad big toes should be differentiated from both Saethre-Chotzen and Pfeiffer syndrome. They recommended that this condition which was almost certainly genetically distinct from Saethre-Chotzen syndrome should be called the Robinow-Sorauf syndrome in recognition of the prior description of similar cases by those authors. It was pointed out in their paper by Carter *et al*. that three previous reports of Similar patients, all with apparent dominant inheritance, had been previously reported by Robinow and Sorauf[6] from North America, under the title of Noack syndrome, by Naveh and Friedman[7] from Israel, under the title of Pfeiffer syndrome, and by Kopysc[8] *et al*. from Poland, under the title of Saethre-Chotzen syndrome.

The original report by Robinow and Sorauf[6] described a large family with autosomal dominant craniosynostosis and hallucal duplication. The clinical features include craniosynostosis, plagiocephaly, flat face, hypertelorism, thin, long, and pointed nose, shallow orbits, strabismus, and broad great toes with a duplication of the distal phalynx. The craniofacial features and phalangeal syndactyly were consistent with those described by Saethre and Chotzen in the 1930s however polydactyly as well as prominent hallux valgus with broad duplicated big toes led to the differential diagnosis.

Naveh and Friedman[7] described a 5-year-old boy and his father presenting with acrocephaly, hypertelorism, antimongoloid slant of the palpebral fissures, protrusion of the eyes, large and broad nose, small mandible, irregularly placed teeth, additional upper canine, high-arched palate, partial syndactyly of fingers and toes, brachydactyly of toes, valgus deformity of hypertrophied triangular great toes, broad phalanges of the great toes and broad first metatarsals, accessory epiphyses lateral to the interphalangeal joint of the great toes, and normal intelligence. The authors pointed out the differences between their cases and previously described cases of Pfeiffer syndrome mainly highlighting that the syndrome was confined mainly to the head and feet (upper limbs were spared except for partial skin syndactyly between the finger) and the patients demonstrated triangular hypertrophied great toes with valgus deformity (contrary to Pfeiffer syndrome).

Kopysc *et al.*,[8] diagnosed six members of one family as having of the Saethre-Chotzen syndrome based on the finding of a typical skull deformation (oxybrachycephalia), low hairline, flattened nasofrontal angle, lateral deviation of the nasal septum, facial dysmorphy, prolapse of upper eyelids, antimongoloid placement of palpebral fissures, protruding eyes, hypertelorism, dysmorphy of auricles, imperfect hearing, highly arched palate, improper dentition, and characteristic skin syndactyly of hands and feet. In addition partial bifid distal phalanges of the great toes were noted which had not been described previously in the Saethre-Chotzen syndrome.

Following defining of Robinow-Sorauf syndrome by Carter *et al.*,[5] in 1982, Young and Harper[9] (1982) offered to name the unusual form of acrocephalosyndactyly

in at least six members of a family as Robinow-Sorauf syndrome. The most characteristic feature in the more severely affected individuals in their series was duplication of the distal phalynx of the hallux.

Reardon and Winter[10] reviewed observations in 1994 and suggested that there was not enough continued justification for affording the Robinow-Sorauf syndrome an entry separate from that for Saethre-Chotzen syndrome.

Kunz *et al.*,[4] in 1999 reported the identification of a frameshift mutation in TWIST in a family with clinical features of Robinow-Sorauf syndrome. Mutations in this gene had already been identified in patients with Saethre-Chotzen syndrome by El Ghouzzi *et al.*,[3] and Howard *et al.*,[11] (1997). This finding supported the assumption that Robinow-Sorauf syndrome was an allelic variant of the Saethre-Chotzen syndrome, rather than a separate entity. Since nonsense, missense, duplication, deletion as well as frameshift mutations have been identified in the coding region of TWIST gene in different phenotypic presentations, these authors concluded that the mutational spectrum in Saethre- Chotzen/Robinow-Sorauf syndrome does not allow phenotype-genotype correlation.

Recently, Cai *et al.*,[2] revisit the original Robinow-Sorauf family and found that 11 of 26 members of the family were affected. They also recognized novel nonsense mutation 5` of the DNA-binding region of TWIST gene where other nonsense mutations had been found in families with Saethre-Chotzen syndrome. This paper provided further evidence that the condition originally described by Robinow and Sorauf was, in fact, an allelic variant of Saethre-Chotzen syndrome.

The present case, undoubtedly, represents the Robinow-Sorauf phenotype. Clinical and radiological findings confirm the diagnosis. The interesting point in this case is its isolated occurrence in the family, unlike previously reported cases in which several members of a family have been affected and an autosomal dominant inheritance with high degree of penetrance and variable expressivity has been suggested. Also, in light of current evidence based on molecular analysis suggesting mutations of TWIST gene in both Robinow-Sorauf and Saethre-Chotzen syndrome, it would be prudent to consider the present case as an allelic variant of Saethre-Chotzen syndrome.

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