Jalili syndrome presenting with situs inversus totalis and keratoconus: the first case in the Indian subcontinent

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Jalili syndrome (JS) (MIM#217080) is a rare genetic disorder characterized by the comorbid appearance of cone–rod dystrophy (CORD) and amelogenesis imperfecta (AI). JS is an autosomal recessive inherited disorder caused by different mutations, all with a linkage at achromatopsia locus 2 q11 on the metal transporter gene *CNNM4*. The case report presented here describes JS with distinct phenotypic variations such as situs inversus totalis (SIT) along with additional ophthalmic findings such as keratoconus and ectopia lentis. It is the first case of JS reported from the Indian subcontinent, affecting a male patient of Muslim faith from an area having high fluoride levels in the ground water. A positive history of consanguineous marriage among his family members of past generations was also evident. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 120:e210-e218)

Jalili syndrome (JS) was first identified by Jalili and Smith in an Arab family and had been inherited as an autosomal recessive trait.[1] To date, only 71 patients belonging to 17 different families have been reported globally.[2] JS is an inherited condition manifesting as a combination of a dental anomaly (amelogenesis imperfecta) and an ocular disorder (cone-rod dystrophy [CORD]).

Amelogenesis imperfecta (AI) are also an inherited group of diseases, where the common clinical entity is an abnormality of tooth enamel, which may be thin (hypoplastic) or poorly mineralized (hypomineralized), or a combination of the two, affecting primary as well as secondary dentition.[3] CORD is a constellation of retinal disorders characterized by the degeneration of cone photoreceptors and subsequently rod photoreceptors, manifesting as an initial loss of central vision, color vision, and photophobia and may be associated with night blindness and restricted visual fields.[4] Situs inversus (SI), or "situs transversus," is a congenital condition characterized by the presence of the major visceral organs on the contralateral side compared with their normal physiologic positions.[5] SI is an autosomal recessive condition, although it can be X-linked and may be found among identical twins.[6]

Co-occurrence of AI and CORD, being two distinct pathologic entities affecting two different tissues, could be either by chance or may be due to a tight linkage between the individual genes concerned.[2] Michaelides et al.[7] identified a two-generation family from Kosovo, in which the ocular disorder was associated with the hypoplastic or hypomineralized variant of AI. Downey et al.[8] identified the concerned locus on chromosome 2q11, at which AI and CORD co-segregate. Parry et al.[9] coined the term "Jalili syndrome," and ultrastructural analysis of exfoliated teeth showed that enamel was only 50% mineralized in the affected individuals. They also stated that the resulting radiographic appearance of teeth corresponds to the hypomineralized variant of AI. *CNNM4* gene mutations in patients with JS were found simultaneously by Parry et al.[9] and Polok et al.[10]

The present case report illustrates a rare syndrome, Jalili syndrome along with the novel phenotypic findings (situs inversus totalis [SIT], keratoconus, and ectopia lentis). This case report is an endeavor to extend our knowledge about JS.

CASE DESCRIPTION

Methodology

A 35-year-old male patient reported to the Dental Faculty of King George's Medical University (Lucknow, Uttar Pradesh,

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India) with the chief complaint of malformed and discolored teeth since childhood and inability to see clearly in the evening time. During further elaboration of his complaint, the concerned patient revealed that he was able to see more clearly in the daytime and worked as a school teacher in a rural area. Further questioning revealed that the patient's family members had similar ocular and dental features, although to a different degree. The patient as well as his family members did not seek any treatment until now due to the lack of medical and dental facilities in his area. Only when he realized that he had been avoiding hard food substances and suffered from progressive loss of vision, he sought medical consultation in the district hospital and was referred to the Medical University. Based on the patient's complaints, he was sent in for dental, ophthalmologic, and radiologic investigations in order to obtain the correct diagnosis.

Family history

All the affected members in the family including the patient had abnormal and discolored teeth and also suffered from vision loss, sensitivity to bright light, and poor color vision. The history was given solely by the patient and neither was supported by any previous clinical records nor did any family member visit the Medical University for consultation and examination despite repeated attempts to convince the family members.

Methods

Dental investigations included orthopantamography and tooth sectioning of extracted teeth to confirm the dental anomaly. Slit lamp biomicroscopy, advanced macular visualization on spectral domain optical coherence tomography (SDOCT), and general ophthalmic examination were done to characterize the positive ocular phenotype and findings. The chest radiograph (posteroanterior view) and ultrasonography of the abdomen were done in order to link the radiological findings with the clinical presentation. The detailed family tree was also charted to confirm the inheritance pattern.

Clinical examinations

Dental phenotype. On intraoral examination, teeth were found to be discolored, grossly malformed, and associated with severe attrition (Figure 1). Teeth #12, #13, #36, and #37 were missing, and tooth #26 had a sole carious lesion. Teeth #16, #17, #46, and #47 and the left upper canine had Grade 3 mobility. Orthopantamography showed absence of enamel in almost all teeth (Figure 2). The surfaces of teeth were rough and exhibited yellowish brown discoloration due to absence of enamel over teeth and dentinal layers showing through. The emergence pattern and teeth eruption timings were within the normal reference range. The patient's teeth were discolored and had an abnormal shape at the time of eruption. Pronounced shift in midline and Class 3 malocclusion with mandibular prognathism was also present. Five teeth were extracted for sound clinical reasons. Macroscopic examination of the extracted teeth showed either no enamel or only vestiges of the enamel in the cervical area. Microscopically, ground sections made with the help of corborundum disk showed

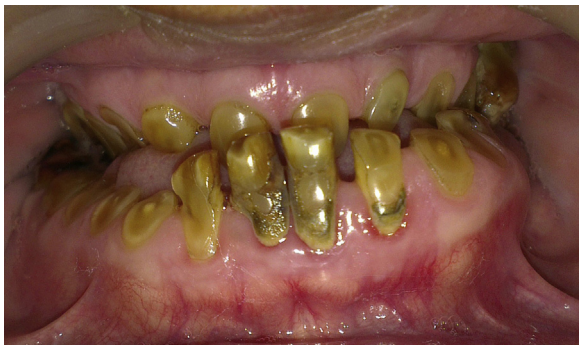

Fig. 1. Intraoral clinical picture revealing severely discolored, attrited, and malformed teeth with heavy staining suggestive of amelogenesis imperfecta.

complete absence of enamel (Figure 3).The features were reported as being compatible with the provisional diagnosis of amelogenesis imperfecta of the hypoplastic or hypomineralized type. The patient had poor oral hygiene status and presence of generalized gingivitis, with severe staining of teeth. The differential diagnosis of enamel and environmental hypoplasia, dentinogenesis imperfecta, dentin dysplasia, and regional odontodysplasia was made. The definitive diagnosis of autosomal recessive inherited amelogenesis imperfecta (AI) of hypoplastic or hypomineralized type was made on the basis of patient's age, history, clinical presentation, radiographic findings, and hereditary nature.

Ocular phenotype. On ophthalmic examination, visual acuity on the first presentation was observed as perception of hand movements in the right eye and finger counting close to 1 m in the left eye. Direct and consensual pupillary reaction was present in both the eyes but was ill-sustained in the left eye. Mild ptosis was present in the left upper lid and was of little clinical significance (Figure 4). Slit lamp biomicroscopy revealed ectopia lentis in the right eye, and in the left eye cornea was clear.

1. Anterior segment examination with slit lamp biomicroscopy showed Vogt's striae secondary to keratoconus in the left eye (Figure 5). The keratometric values K1 and K2 in the right eye were 51.50 D and 32.00 D and in the left eye 43.75 D and 37.27 D, respectively. The ophthalmic findings were suggestive of ectopia lentis in the right eye (Figure 6). However, the clear-cut differentiation with retrolental opacity could not be confirmed due to financial and technical constraints.
2. The posterior segment was examined by using direct and indirect ophthalmoscopy along with slit lamp biomicroscopy. Fundus examination showed generalized depigmentation with retinal pallor and bony spicules scattered throughout the posterior pole, suggesting bilateral CORD. Additionally, there was generalized arterial attenuation with waxy pallor, which was more profound in the temporal half of the optic disk. Focal chorioretinal atrophy was seen inferior to the fovea in the macular region of about 2 disk diameters in size (Figures 7A and 7B). Fundus findings were suggestive of retinitis pigmentosa–type conditions.