Joubert syndrome with orofaciodigital defects

A report of Joubert syndrome in an infant, with literature review

ABSTRACT

Joubert Syndrome and related disorders (JSRD) are a group of rare autosomal recessive disorders with a hallmark molar tooth sign (MTS) visible on axial magnetic resonance images of the brain. Joubert syndrome with Oro-facial-digital defects (JS-OFD) represents a rare subtype of JSRD. This syndrome is often difficult to diagnose because of its wide range of genotypic-phenotypic variations.

Despite its profound oro-facial manifestations, dental literature describing the syndrome is scarce. This is a case report of an 8-year-old boy who reported to the out-patient department of pediatric dentistry with the chief complaint of abnormal front teeth. The child exhibited facial dysmorphism, strabismus, polydactyly of hands and feet along with oro-dental features of a high arched palate and high lingual frenum attachment. MRI report stated the presence of molar tooth sign.

Key Words: Joubert syndrome and related disorders, Oro-facial-digital syndrome type VI, molar tooth sign

INTRODUCTION

Joubert syndrome (JS) was first described by Marie Joubert in 1968 in four siblings with agenesis of the cerebellar vermis who presented with episodic hyperpnoea, abnormal eye movements, ataxia and intellectual disability [1, 2] . Several years later, it was discovered that JS results from maldevelopment of the midbrain and cerebellar vermis, producing a pathognomonic MTS on

MRI [3] . The common term “ Joubert Syndrome and Related Disorders” (JSRD) was then coined for the group of conditions presenting with the MTS [4] . The incidence of this clinical entity has not been precisely determined, however, it may range between 1/80, 000 and 1/100, 000 live births [2] with only about 200 cases that have been reported worldwide [5] .

CASE REPORT

An 8 year old boy reported to the outpatient Department of Pedodontics and Preventive Dentistry at the Faculty of Dental Sciences, M. S. Ramaiah University of Applied Sciences, Bangalore for the evaluation of abnormal front teeth. History revealed that he was a second child of a second degree consanguineous marriage. Figure I is the pedigree chart depicting the patient’s family history. The mother reported delayed attainment of developmental milestones and the child being a “ slow-learner”.

On intra-oral examination, the child was in the early mixed dentition stage; the teeth present were first permanent molars, permanent mandibular central incisors, erupting maxillary permanent central incisors , primary left central incisor, primary canines of all the quadrants, primary mandibular lateral incisors and first and second primary molars of all the quadrants. The crown of the primary left central incisor (61) was conical in shape and a developing anterior cross-bite was noticed due to palatally erupting 11 and 21. A high-arched palate and high lingual frenum attachment were also seen.

Extra-orally, the patient exhibited facial dysmorphism in form of depressed nasal bridge, broad nasal tip, upper lip notch and his upper lip was short

compared to the broad and thick lower lip. Prominent bilateral epicanthal folds, widely spaced eyes (hypertelorism) and a unilateral squint (strabismus) of the right eye were profound facial characteristics. His cranial morphology and hair were apparently normal.

Bilateral post-axial polydactyly of both the hands and feet were noticed. The remainder of the systemic evaluation was insignificant. However, the patient showed poor muscular control due to delayed gross as well as fine motor development.

On review of the patient’s medical records, it was seen that the possibility of Joubert Syndrome was considered on detection of inferior vermian agenesis and polydactyly on antenatal ultrasonography performed at 28 weeks of intra-uterine life. Eye movements and respiration were reviewed and found to be normal. Foetal MRI was done at another medical center and they considered the possibility of Dandy-Walker anomaly. At 5 months of age, neurologic evaluation was conducted and nystagmus along with very brisk deep tendon reflexes (DTRs 3+ category) was noticed; following which, magnetic resonance imaging (MRI) of the brain was advised. The MRI reports indicated complete agenesis of the cerebellar vermis which resulted in median approach of the two cerebellar hemispheres. Superior cerebellar peduncles appeared thin and distinctly defined across the pontomesencephalic cisterns giving the characteristic “ molar tooth sign”. Also the 4th ventricle was slightly dilated and had assumed a “ bat-wing” appearance. Inspite of the all the MRI findings being suggestive of “ Joubert sydrome”, neither was any definitive diagnosis made nor any neurological follow-up maintained.

With respect to dental treatment rendered, the patient was found to be lacking cooperative ability, but keeping in mind the extreme sensitivity to the respiratory depressant effects of anesthetic agents, sedation and GA was ruled out. Considering this inability, after extraction of his primary central incisor (61), a lower inclined plane appliance was planned to correct the developing cross-bite. Patient did not cooperate for fabrication of a fixed appliance. Upper and lower primary impressions were made, a removable lower inclined plane appliance with Adams clasps on 75 and 85 was fabricated and delivered to the patient. However, the patient showed poor compliance with the appliance and refused to wear it beyond the third day. Following this, we considered the correction of the cross-bite by constructing a bonded resin-composite inclined plane [6, 7] . The labial surface of the mandibular incisors was etched with 37% phosphoric acid (Scotchbond™ Multi-purpose Etchant, 3M, USA) for 15 seconds, rinsed and dried. An adhesive system (Adper™ Single Bond 2, 3M, USA) was applied and cured for 20s using a visible light cure unit (_____). Composite resin (Filtek™ Z350XT, 3M, USA) was formed into an inclined block 45 degree to the longitudinal axis of the teeth. The height was adjusted so as to maintain the only contact between both arches at the level of these incisors. The inclined plane was polished using a polishing disc. The child was motivated to maintain good oral hygiene and the parents were instructed regarding the maintenance of a soft diet. The child was recalled after 1 day and then 1 week to clinically evaluate the treatment progress. At 1 week interval, edge-to-edge bite was achieved while complete correction of the crossbite took place in 2 weeks. Following this, the composite inclined plane was removed using a diamond

point at low speed, the enamel surface was polished and topical fluoride application was done. The child is under regular follow-up at our hospital.

DISCUSSION

The spectrum of Joubert Syndrome and Related Disorders (JSRD) comprises all disorders presenting the “ molar tooth sign” (MTS) on brain imaging. JSRD include Joubert syndrome [OMIM#213300], along with any related condition(s) presenting with the MTS, like Varadi-Papp syndrome (or Orofaciodigital type VI, [OMIM%277170]), COACH syndrome [OMIM#216360], Dekaban-Arima syndrome [OMIM%243910], Malta syndrome and a few cases with Senior- Loken syndrome [OMIM#266900].

Till date no major gene has been consistently associated with Oro-facio-digital Syndrome type VI (OFD VI) however, mutations in the TMEM216 gene are known to be seen occasionally [] . All JSRD genes isolated so far, encode for proteins of the primary cilium and thus these disorders fall in the “ ciliopathies” group of disorders [9] .

Previously in literature, JS-OFD has also been referred to as Oro-facio-digital Syndrome type VI (OFD VI) or Varadi-Papp Syndrome [10, 11, 12] . However, recently, Brancati *et al.* have discouraged the continued use of such eponyms in favor of a more practical, clinical-genetic classification. They have proposed a classification of JSRDs into six subgroups based on the main organ(s) involvement and the established genotype-phenotype correlates [2] . They classified JSRDs into:

1. Pure JS

2. JS with ocular defect (JS-O)
3. JS with renal defect (JS-R)
4. JS with oculorenal defects (JS-OR)
5. JS with hepatic defect (JS-H)
6. JS with oro-facio-digital defects (JS-OFD)

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A diagnosis of JSRD should be suspected in all infants presenting with hypotonia, abnormal eye movements (in particular oculomotor apraxia, but also nystagmus) and developmental delay. The occurrence of abnormalities in the respiratory pattern, i. e. hyperpneas alternating with periods of apnea, reinforces the clinical suspicion of the disease. In these children, a brain MRI is sufficient to confirm or exclude the diagnosis, based on the detection of the MTS. Once a diagnosis of JSRD has been made, children should enter a diagnostic protocol to assess the possible

multiorgan involvement [2] .

Presence of MTS is considered pathognomic for diagnosis of JS-OFD (or OFD VI). MTS is characterized by presence of a hypoplastic or completely absent cerebellar vermis, which is indicated by the hallmark “ Molar Tooth Sign” found on axial view of brain MRI scan. MTS has not been described in any other type of oro-facial-digital syndrome and its presence allows differentiation of OFD VI from other types [9] . In addition, several other oral, dental and digital malformations are typical of JS-OFD. These have been enlisted in Table I.

Recently, Poretti *et al.* [9] have suggested a diagnostic criterion for OFD VI. The criterion being – MTS and one or more of the following:

1. tongue hamartoma(s) and/or additional frenula and/or upper lip notch;
2. mesoaxial polydactyly of one or more hands or feet;
3. hypothalamic hamartoma.

These criteria allow the diagnosis to be made even in the absence of oral findings and/or polydactyly. The validity of these criteria needs to be reassessed in additional cohorts of patients and after the identification of major genetic determinants of OFD VI. Along with presence of the pathognomic MTS, our patient showed bilateral postaxial polydactyly of hands and feet. Mesoaxial hand polydactyly is extremely rare and specific for OFD VI among the JSRD phenotypes, but not consistent in OFD VI because different forms of polydactyly have been previously reported [13, 14, 15, 16] . Moreover, it is to be noted that the syndrome is known to show a high degree of genotypic-phenotypic variations and it’s often difficult to arrive at a conclusive diagnosis. Thus, it can be said that the reported case probably represents variability within OFD VI.

Compared with other JSRD subgroups, the neurological findings and impairment of motor development and cognitive functions in OFD VI are significantly worse, suggesting a correlation with the more severe neuroimaging findings [9] . Steinlinet al. [17] suggested that outcomes in JS can be divided into three courses: first, children who die young; second, patients who survive but have severe developmental delay with the development quotient (DQ) being less than 30 along with a variety of visual

and motor handicaps; and third, patients whose developmental quotients fall within the mildly delayed range (60-85). A remarkable finding in the case reported was, the level of cognitive development; with intelligence quotient (IQ) being 90 which falls in the “ average” IQ range according to the Stanford-Binet Intelligence Scale: Fifth Edition (SB5) [18] . So far, normal cognitive functions (without formal IQ assessment) have only been reported in one patient, attending a regular school [19] .

Despite the fact that Joubert syndrome is very rare in India, an early diagnosis is necessary for genetic counseling and treatment planning. Treatment is mainly symptomatic and includes possible medico-surgical supportive interventions. Also, the diagnosis is important for future procedures that require anesthesia. Of particular caution is that these patients are sensitive to respiratory depressant effects of anesthetic agents like opiates and nitrous oxide. Hence, anesthesia using inhalational induction, controlled ventilation, avoidance of opioids, and close postoperative monitoring is recommended [20] . The prognosis is almost always poor, leading to early death and those who survive usually require supportive care throughout life. Annual evaluation of the growth status, vision and general wellness is recommended. Periodic neuropsychological follow-up should be maintained.

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