Varadi Papp syndrome, an unusual variant of oral–facial–digital syndrome: Report of a rare case

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Abstract

Varadi Papp syndrome or oral–facial–digital syndrome type VI (OFDS VI) is a rare autosomal-recessive disorder distinguished from other OFDSs by metacarpal abnormalities with central polydactyly and by cerebellar abnormalities. Our patient had a broad forehead, arched eyebrows, left-sided squint, hypertelorism, epicanthic folds, fleshy nodular tongue, midline upper lip cleft, high arched palate, both pre-axial and post-axial polydactyly of limbs, hypotonia and cerebellar hypoplasia with molar tooth sign consistent with the diagnosis of Varadi Papp syndrome.

Key Words

Molar tooth sign, oral–facial–digital syndrome, Varadi Papp syndrome

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Introduction

Varadi-Papp syndrome refers to one type of oral–facial–digital (OFD) disorder.[1] The oral–facial–digital syndromes (OFDSs) comprise a group of disorders involving malformations of the mouth, face and digits.[2] Till date, 13 subtypes of the OFDS are recognised, and much overlap exists among OFDS patients. This particular OFD syndrome occurs as part of a group of genetic conditions that result from an abnormality in cerebellar vermis.[2] The disorders that share this cerebellar malformation are known as Joubert syndrome and related disorders (JSRD). [3] These conditions have some characteristics in common, but there is a spectrum of symptoms and abilities in the affected individuals.

Case Report

A 2.5-month-old girl was admitted to our hospital for evaluation of abnormal respiratory pattern (episodic tachypnea and/or apnea) and hypotonia. She was the first child of healthy consanguineous parents. The baby was born at term by vaginal delivery after an uneventful pregnancy and did not cry immediately after birth. On admission to the hospital, the baby was found to have episodes of breathlessness, with a respiratory rate of up to 100 breaths/min, alternating with apnea lasting for 15-20 s with cyanosis. On physical examination, her weight was 2500 g (<3rd percentile), her length was 47 cm (<3rd percentile) and her head circumference was 36.5 cm (3rd percentile). Facial features include broad forehead, arched eyebrows, left-sided squint, epicanthic folds and widely spaced eyes (hypertelorism). Examination of the oral cavity revealed midline upper lip cleft and bilateral fleshy nodules on the under surface of the tongue, bumps of the lower alveolar ridge and high-arched palate [Figure 1]. Skeletal examination revealed post-axial as well as mesaxial (an extra digit between the middle digits) polydactyly of both hands and pre-axial polydactyly of both feet [Figure 2]. Other physical examination, findings were normal. Laboratory investigations including complete blood count (CBC), hepatic enzymes, blood urea nitrogen, creatinine, electrolytes, blood sugar and urine analysis were normal. Echocardiography, abdominal ultrasonography, especially of the kidney, ureter and bladder (KUB) region, and ophthalmological examination were found to be normal, except squint on the left side. X-ray of both hands documented mesaxial polydactyly as evident with Y-shaped metacarpal [Figure 3]. Magnetic resonance imaging showed hypoplasia of the cerebellar hemispheres and vermis and a narrowed isthmus of the mid brain with a characteristic "molar tooth appearance" [Figure 4]. The infant was discharged home and advised to attend the follow-up clinic.

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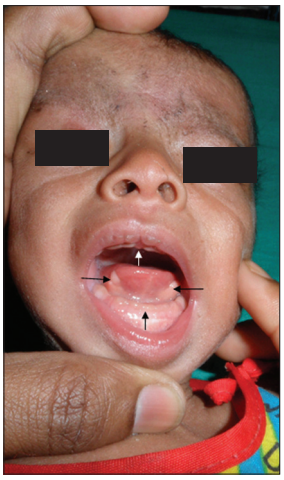

Figure 1: Orofacial features showing broad forehead, arched eyebrows, epicanthic folds, squint (left side), widely spaced eyes (hypertelorism), midline upper lip cleft, bilateral fleshy nodules on the under surface of the tongue, bumps of the lower alveolar ridge and high-arched palate

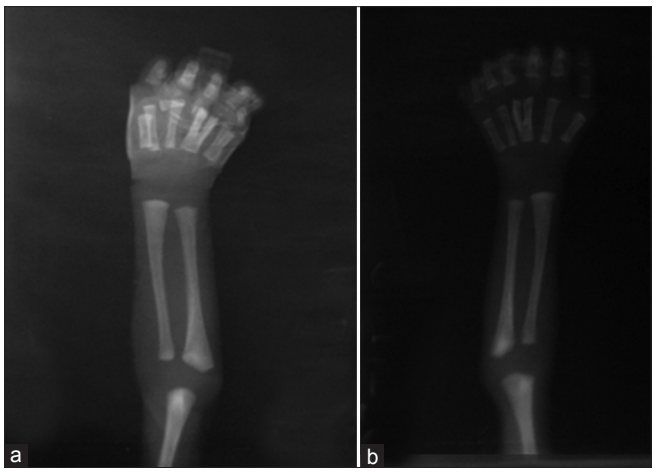

Figure 3: X-ray of both hands showing bifid appearance (Y-shaped) in the 3rd metacarpal on the right hand and the 4th and 5th metacarpals of the left hand with six proximal phalanges seen in both hands

Discussion

This characteristic multiple malformation syndrome was first identified in 1978 by Váradi V and Popp Z in a male gypsy child, and published in 1980. Subsequently, the syndrome has been quoted as Váradi–Papp syndrome.[1] The most common features of the affected children with this syndrome consist of orofacial (facial dysmorphism, cleft lip and/or palate abnormality, lingual nodule or tumor of the tongue, buccoalveolar frenula, alveolar and dental abnormalities, strabismus), digital (metacarpal abnormalities with central polydactyly, reduplication of the big toes), cerebral/cerebellar (deformation of the skull, semilobar holoprosencephaly and/or absence or dysgenesis of cerebellar vermis or corpus callosum or hypothalamus or pituitary gland) and genital (cryptorchidism, micropenis) anomalies.[1] These patients are usually growth retarded, and, when survival occurs, psychomotor retardation is present.[4] In addition, the brainstem may be malformed, which may cause an abnormal

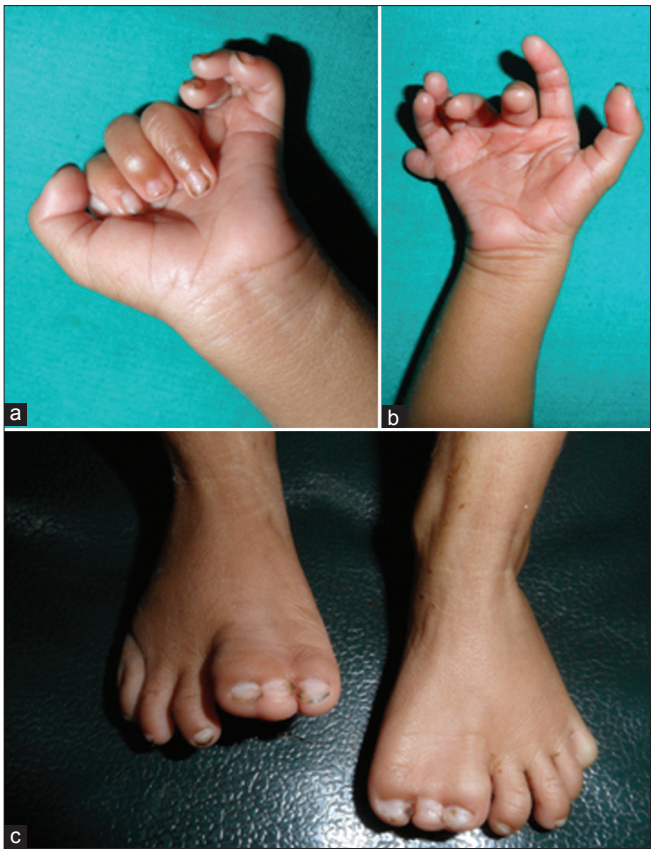

Figure 2: Post-axial polydactyly of both hands and pre-axial polydactyly of both feet

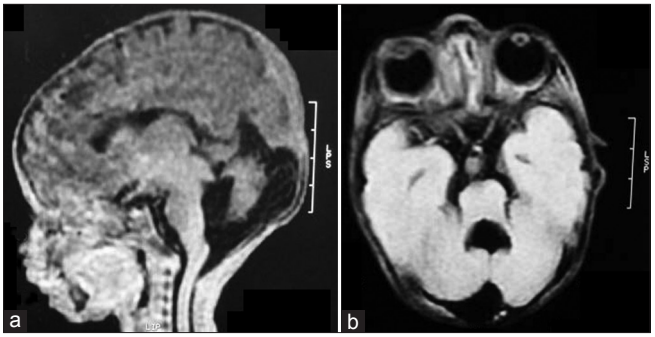

Figure 4: Magnetic resonance imaging of the brain showing elongated 4th ventricle with hypoplastic cerebellar vermis (on T1-W sagital image) leading to apposition of the cerebellar hemisphere and stretched and elongated superior cerebellar peduncle giving the midbrain an appearance of "Mollar Tooth" (on T1-W axial image)

breathing pattern called episodic hyperpnea, which may be followed by apnea.[4] This disorder has an autosomal-recessive inheritance.[2] Recently, it has been identified that mutations in the *TMEM216* gene are responsible for the phenotype of Varadi–Papp syndrome.[5] Our case had the following characteristics: orofacial (broad forehead, arched eyebrows, left-sided squint, epicanthic fold, hypertelorism, midline upper lip cleft and bilateral fleshy nodules on the under surface of the tongue, bumps of the lower alveolar ridge and high-arched palate), digital (post-axial and mesaxial polydactyly of both

hands and pre-axial polydactyly of both feet with Y-shaped metacarpal) and cerebellar (hypoplasia of the cerebellar hemispheres and vermis and a narrowed isthmus of the mid brain with a characteristic "molar tooth appearance") anomalies, consistent with this disorder. The presence of hypotonia along with recurrent apnea and hyperpnea also characterizes Joubert syndrome.[3] Children affected with this disorder may be severely impaired, and, in some cases, may have a shortened life span.[1] Decreased muscle tone is common in children with Varadi–Papp syndrome, as was present in our case. As a result of the poor muscle tone, developmental delay (usually in gross motor, fine motor and speech areas) is common. Many children have also been noted to have abnormal eye and tongue movements.[6] Developmental delays are usually treated through physical therapy, occupational therapy, speech therapy and infant stimulation. Feeding issues that may arise in a case with cleft palates, other oral malformations and low muscle tone can be addressed with the help of specially trained therapists.[6]

Although there is no cure for Varadi–Papp syndrome, it is recommended that individuals diagnosed with Varadi–Papp syndrome regularly see the appropriate specialists necessary to help monitor their various clinical features. Surgical removal of extra fingers and toes may be recommended.[6] Monitoring for some of the complications associated with Varadi–Papp syndrome, such as vision loss or kidney or liver involvement that may become progressive over time, is recommended on an annual basis, although these were not present in our case.

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