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Joubert syndrome with atrial septal defect and persistent left superior vena cava

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ABSTRACT
Joubert syndrome is a rare disorder characterized by hypotonia, ataxia, episodic hyperpnoea, psychomotor delay, abnormal ocular movements, and molar tooth sign on magnetic resonance imaging (MRI). This syndrome is inherited as an autosomal recessive trait, but the molecular basis and specific chromosomal locus have not yet been identified. MRI features are the most important diagnostic criteria. Molar tooth sign was previously described in Joubert syndrome and was found in 85% of patients with Joubert syndrome. Many authors now claim that this finding can be present in other syndromes, including Dekaban-Arima, Senior-Löken, COACH, and Varadi-Papp. We present a 7-month-old girl with Joubert syndrome in whom MRI showed the typical features of this condition. She also had polydactyly, atrial septal defect, and persistent left superior vena cava.

Key words: • *Joubert syndrome* • *cerebellar hypoplasia* • *magnetic resonance imaging* • *molar tooth sign*

Joubert syndrome was first described by the French neurologist Marie Joubert as an autosomal recessive disorder characterized by ataxia, episodic hyperpnoea, abnormal ocular movements, and psychomotor delay (1–4).

Joubert syndrome is a rare entity. The aim of this report was to show the presence of skeletal and cardiovascular system abnormalities, and to highlight the most important radiological clue, molar tooth sign, resulting from dysplasia of the vermis with brain magnetic resonance imaging (MRI). Molar tooth sign, which was first described in Joubert syndrome, can be present in other syndromes recently referred to as cerebello-oculo-renal syndromes. Important characteristics of these syndromes taken into consideration in the differential diagnosis of Joubert syndrome are also emphasized in this report.

Case report

A 7-month-old female was referred to our pediatric outpatient clinic with cough, hypotonia, and eisodes of hyperpnea and abnormal eye movements. On physical examination, developmental delay, hyperpnea, hypertelorism, a depressed nasal root, a high-set palate, low-set ears, polydactyly, and a prominent forehead were present (Figs. 1–3). Our case was the first child of parents that were not genetically related to each other. Echocardiography revealed a wide atrial septal defect (ASD) with a single apparent atrium. Pulmonary magnetic resonance angiography (MRA) was performed based on the suspicion of pulmonary artery abnormality on echocardiography. Pulmonary arteries were normal on pulmonary MRA. Additionally, a persistent left superior vena cava ending with sinus coronarius was detected (Fig. 4). Cardiomegaly was present and the mediastinum was wide on chest radiography. No pathological signs were detected on radiographs, except for 7 digits on each hand and foot (polydactyly). Abdominal ultrasonography was normal. The cerebellar folia were indistinct and the cortex was abrupted on brain MRI. A bat-wing appearance was present on the 4th ventricle (Fig. 5a). The cerebellar vermis was absent on midline and the superior cerebellar peduncles were elongated and perpendicular. This appearance formed the classic molar tooth sign on axial scans (Figs. 5b, c). The corpus callosum was hypogenetic and the splenium was undeveloped (Figs. 6a, b). Fundoscopic examination was normal and the result of karyotypic analysis was 46 XX.

Discussion

Joubert syndrome is a genetic disorder that primarily affects the balance and coordination center of brain. It is characterized by complete or partial absence of the cerebellar vermis and dysplastic development of the middle brain (1, 2, 5). Maria et al. described other abnormalities in Joubert syn-

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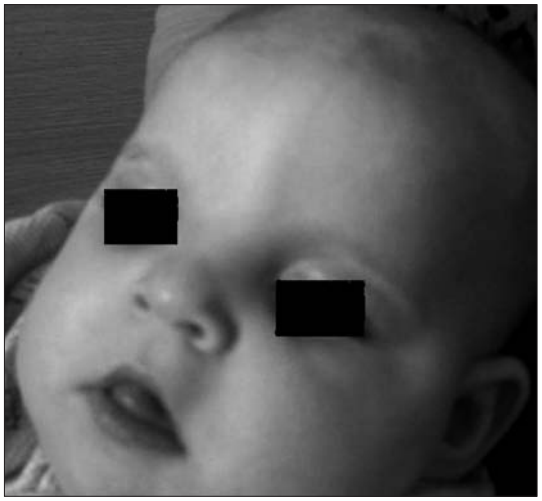

Figure 1. Depressed nasal root, hypertelorism, and frontal bossing.

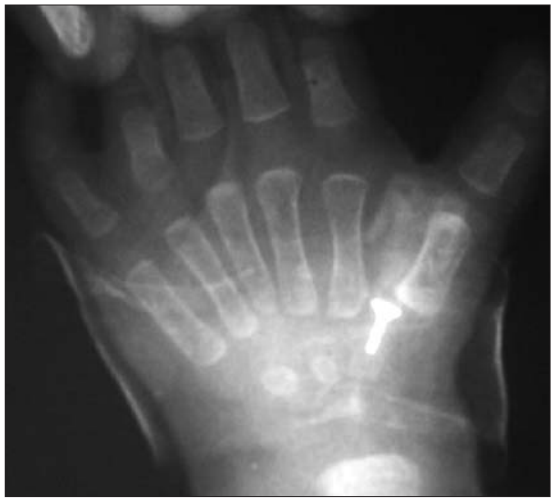

Figure 2. Polydactyl hand.

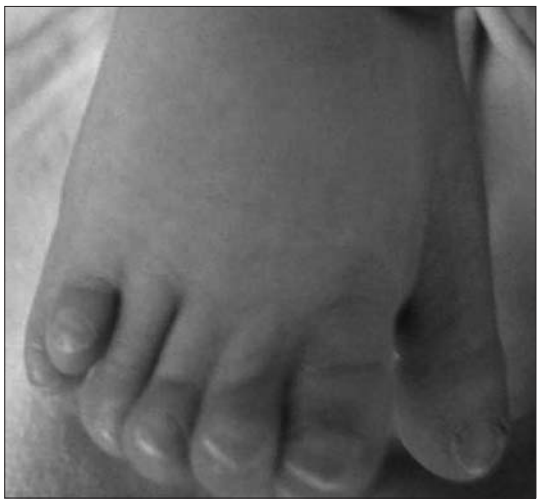

Figure 3. Polydactyl foot.

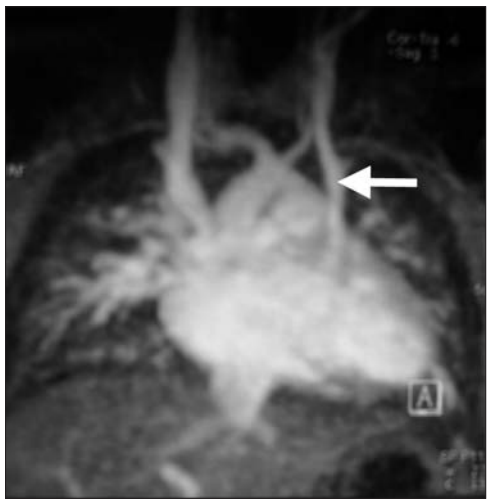

Figure 4. Left persistent superior vena cava *(arrow)* on coronal pulmonary MR angiography image.

drome, such as ocular and oculomotor signs (n = 58, 95%), tongue protrusion (n = 26, 45%), polydactyly (n = 13, 23%), renal abnormalities (n = 9, 16%), megalocephalus (n = 7, 12%), microcephaly (n = 5, 9%), hepatic abnormalities (n = 2, 4%), bradycardia (n = 1, 2%), cardiac murmur (n = 1, 2%), cerebral palsy (n = 1, 2%), hypothalamic abnormalities (n = 1, 2%), and cleft lip (n = 1, 2%) (4).

Based on the presence or absence of retinal dystrophy, 2 types are described. Hypoplasia of the cerebellar vermis with clinical neonatal breathing abnormalities, oculomotor disorders, and hypotonia are present in type I. In addition to these, retinal and renal dysplastic changes are seen in type II, which has a worse prognosis (3, 6).

Hypertelorism, a high-set palate, low-set ears, frontal bossing, polydactyly of hands and feet, ASD, and a persistent left superior vena cava were present in our case, in addition to developmental delay. Cardiovascular system abnormalities may rarely be seen with Joubert syndrome, as described by Maria et al. (4). To the best of our knowledge, there are no Joubert syndrome cases in the literature that had both ASD and a persistent left superior vena cava.

Genetic diagnostic characteristics of Joubert syndrome are still not known. Neuropediatric findings, such as hypotonia, ataxia, and psychomotor developmental delay, are not adequate for diagnosis; therefore, MRI findings are still the best diagnostic criteria (1). MRI characteristics were described by Quisling et al. as elongation and slimming of the isthmic portion of the brain stem at the pontomesencephalic junction, deep interpeduncular fossa, thick and nearly perpendicular cerebellar peduncles, and deformity of the 4th ventricle resulting from complete or partial absence of the vermis (5). Other radiological findings are divergence of the cerebellar hemispheres due to hypoplasia of the vermis and a vermian cleft resulting from peduncular decussation (2). The combination of these findings compose the pathognomonic molar tooth sign on axial MRI scans. This sign was first described for Joubert syndrome and is present in 85% of cases (1, 2, 4, 5, 7). Classical molar tooth sign was present on axial T1- and T2-weighted MRI sequences in our case (Figs. 5b, c).

Molar tooth sign is also seen in Varadi-Papp (oro-facial-digital type IV), COACH, Dekaban-Arima, and Senior-

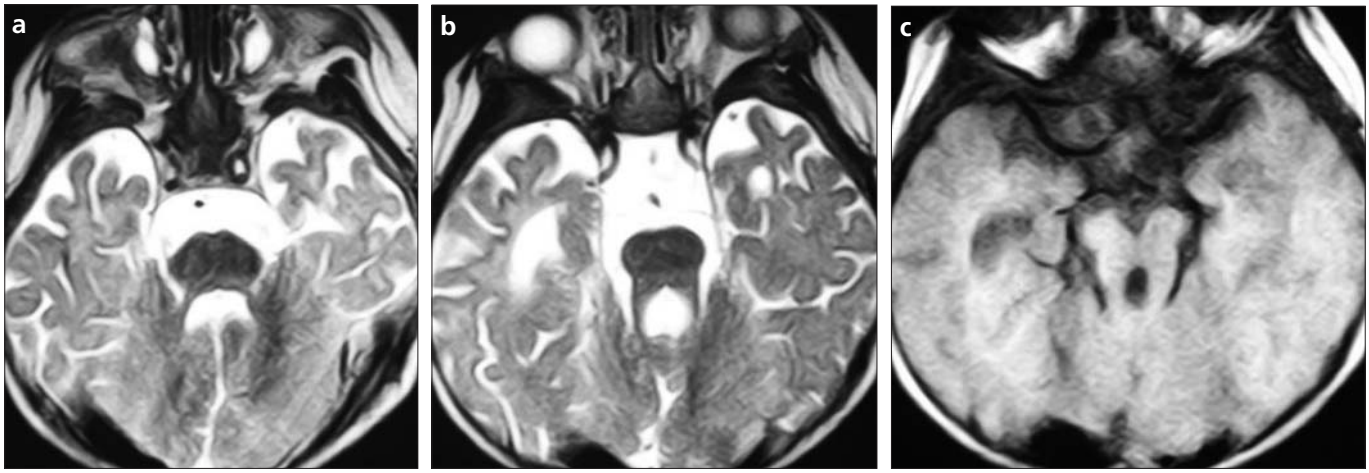

Figure 5. a–c. On axial T2-weighted MR image **(a)**, the cerebellar hemispheres are on midline and contacting directly. The vermis is absent and there is "bat-wing" appearance of the 4th ventricle. On axial T2-weighted MR image **(b)**, elongated and horizontally oriented superior cerebellar peduncles and molar tooth sign are seen. On axial T1-weighted MR image **(c)**, deep interpeduncular distance and molar tooth sign are seen.

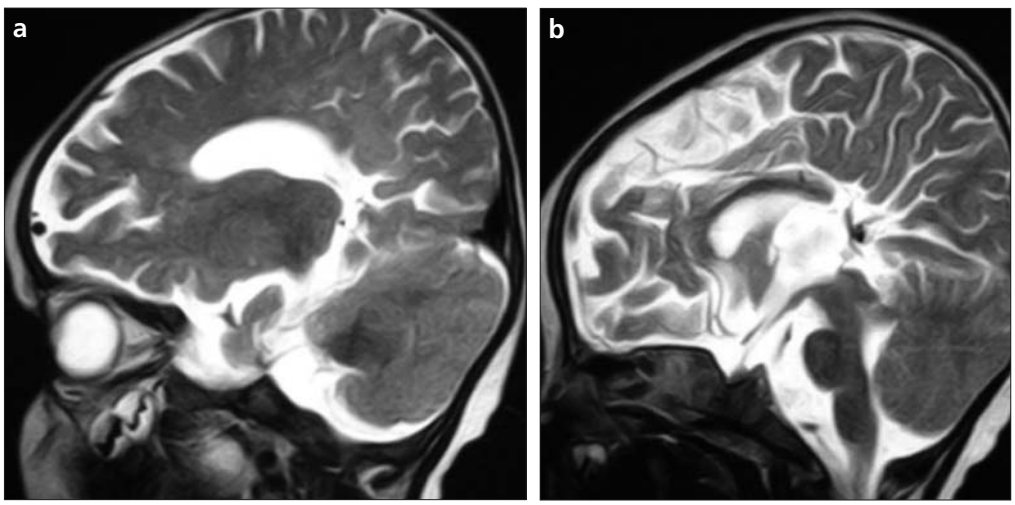

Figure 6. a, b. Sagittal T2-weighted MR image **(a)** shows indistinct cerebellar folia and abrupted dysplastic hemispheres. On sagittal midline T2-weighted MR image **(b)**, hypoplasia of the corpus callosum (splenium part) and absence of the cerebellar vermis are seen.

Löken syndromes. A Y-shaped metacarpus, cleft lip, cleft palate, and lingual nodule are also seen in Varadi-Papp syndrome. A Y-shaped metacarpus is characteristic of this syndrome. Oligophrenia, ataxia, coloboma, and hepatic fibrosis are seen in addition to cerebellar vermian hypoplasia in COACH syndrome. Renal and retinal pathologies are also seen in Dekaban-Arima and Senior-Löken syndromes, in addition to molar tooth sign, and distinguish them from type II Joubert syndrome, which has a poor prognosis (6).

The corpus callosum can be dysgenetic in Joubert syndrome. Complete absence of the corpus callosum is rare (1, 5). The cerebellar hemispheres are generally normal and, rarely, hypoplastic hemispheres can be seen. Partial absence of the corpus callosum splenium was evident in our case. Indistinct cerebellar folia and abrupted dysplastic cortex were also seen. The cerebellar hemispheres are normal in two thirds of patients. Mild enlargement of the subarachnoid space, cortical atrophy, mild ventriculomegaly, dysgenesis of white matter, and a delayed myelination pattern can be seen in one third of patients (5).

Our presented case did not have a Y-shaped metacarpus or retinal and renal pathology. Therefore, the clinical and radiological findings were consistent with type I Joubert syndrome.

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