Joubert Syndrome: A Rare Cause of Hypotonia and Developmental Delay in Infancy and Childhood

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Pediatricians not uncommonly encounter infants with hypotonia and developmental delay. Among many other causes of hypotonia and developmental delay such as degenerative, metabolic, and infectious diseases, Joubert syndrome is a rare autosomal recessive condition that is associated with hypotonia, developmental delay, abnormal eye movements, breathing problems, and cerebellar dysfunction. Absence of dysmorphic signs and variability of clinical presentations can sometimes delay the diagnosis. We report a patient with developmental delay, hypotonia during infancy, rotatory nystagmus, pigmentary retinal changes, dysarthria, and mental retardation who was diagnosed to have Joubert syndrome at 14 years of age.

Case report

A 14-year-old girl presented with the complaints of abnormal eye movements, failure to gain weight and weakness. Her past history disclosed developmental retardation. Her abilities to sit, walk, and speak had been delayed; she developed these skills at 1, 2 and 4 years of age, respectively. She had been a hypotonic and hypoactive baby, and had had rotatory eye movements since birth. Her birth and family history were unremarkable and she had no respiratory problems. Physical examination revealed a cachectic girl (body weight 40 kg, height 169 cm) with a triangular-shaped open mouth, long arms and legs, pectus excavatus and thoracic kyphosis. She was able to walk independently. She had mild dysmetria and dysarthria, but no ataxia, and was able to maintain balance with eyes closed. Ophthalmological and neuro-ophthalmological examinations revealed rotatory nystagmus, left hyperphoria, and pigmentary retinal changes. Flash visual evoked potentials and electroretinography (ERG) were normal. Pattern ERG and electronystagmography could not be performed due to the lack of the patient's cooperation. Echocardiography was done because of the Marfan-like body habitus of the patient and was normal. Renal ultrasonography was also normal. In a psychiatric interview, the patient's mood was defined as depressed. She scored an IQ of 42 on the Revised Wechsler Intelligence Scale for Children. She was attending to a private school for normal children and was not successful. She was aware of and was anxious about her failure. Magnetic resonance imaging of the brain revealed vermian hypoplasia that was more severe superiorly (Figure 1a). The superior cerebellar peduncles were elongated secondary to vermian hypoplasia (Figure 1b). The patient was diagnosed to have Joubert syndrome. A family interview revealed that the parents had very high expectations and were in denial of the child's disabilities. This created difficulty in counselling them on the disease prognosis and outcome.

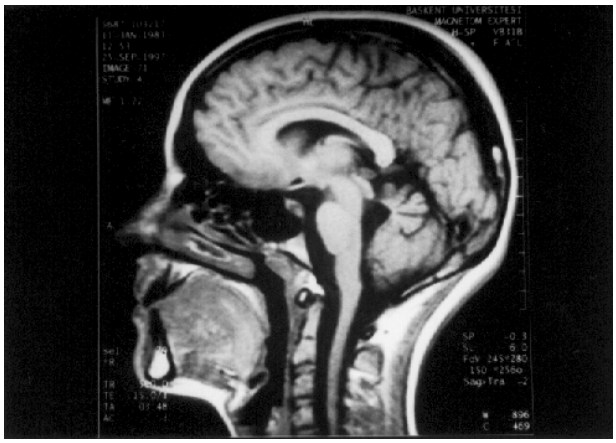

Figure 1a. Sagittal T1 weighted (TR:500 msec, TE: 15 msec) spin echo image of the brain revealed vermian hypoplasia which is more severe superiorly

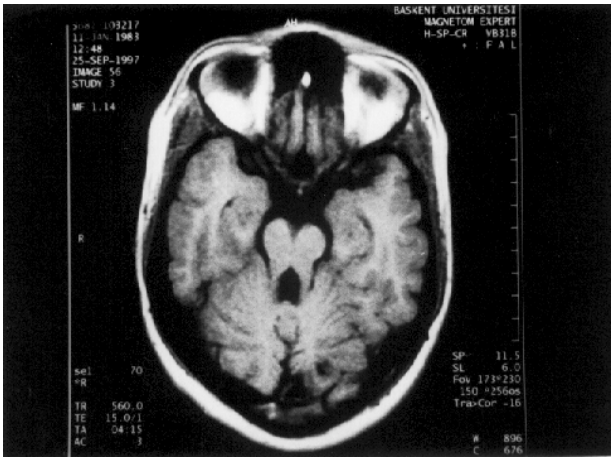

Figure 1b. Transverse T1 weighted (TR: 560 msec, TE: 15 msec) spin echo image of the brain showing elongated superior cerebellar peduncles secondary to vermian atrophy.

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Discussion

Joubert syndrome is a rare autosomal recessive disorder characterized by almost total aplasia of the cerebellar vermis. Although the syndrome was first reported in 1969 by Joubert et al. (1), the prognosis and long-term outcome remains unclear. Patients present with abnormal eye movements such as nystagmus, abnormal breathing patterns, truncal ataxia, developmental delay, hypotonia, and mental retardation. They may have associated anomalies, such as occipital encephaloceles (2), retinal dysplasia, syndactyly, polydactyly, renal cystic disease (3,4), and hepatic fibrosis (5).

Joubert syndrome includes a large spectrum of clinical presentations. The characteristic finding of episodic hyperpnea and apnea was reported in eight of 15 patients in one series. All the patients had developmental delay, hypotonia, and ataxia, except one who was not ataxic (6). Episodic hyperpnea has long been considered the sole "clinical hallmark" of the syndrome but several reports describe this finding only in some patients (3). Saraiva et al. (3) attempted to define the diagnostic criteria for Joubert syndrome: vermis hypoplasia, hypotonia, developmental delay, and at least one additional manifestation such as abnormal breathing or abnormal eye movements, should be present. In their review of 101 cases reported in the literature, they found that 94 of the 101 cases fulfilled these criteria. Our patient had signs of cerebellar dysfunction including dysmetria and rotatory nystagmus, but she was not ataxic. She also had pigmentary retinal changes and a triangular-shaped open mouth, a feature which has been reported as part of the typical facial expression of these patients (7). Moreover, the patient had pectus excavatum and mild thoracic kyphosis.

In addition to abnormalities of eye movement, retinal changes are also reported in Joubert syndrome (3,6,7). Some of the patients with retinal dystrophy had renal cysts, but these cysts were not found in patients without retinal dystrophy. The retinal changes observed in Joubert Syndrome are accompanied by a nonrecordable or significantly attenuated ERG (3). Our patient had pigmentary retinal changes but a normal ERG. Her kidneys were normal on ultrasonography.

Joubert syndrome is characterized radiologically by vermian agenesis or hypoplasia. The imaging studies of these patients are quite characteristic. Absence of the vermis results in a triangular-shaped mid-fourth ventricle and a bat wing-shaped fourth ventricle superiorly. The superior cerebellar peduncles are clearly seen extending superiorly, toward the midbrain (8). Congenital ocular motor apraxia should be considered in the differential diagnosis of Joubert syndrome since similar imaging findings may be seen in this condition (9) . Children with Joubert syndrome are known to have more severe involvement of the superior portion of the superior vermis, as evidenced by our case. Involvement of the inferior portion of the vermis is more common in congenital ocular motor apraxia which may sometimes create difficulty in differential diagnosis due to similar ophtalmologic findings. Joubert syndrome is both a clinical and radiological diagnosis. Although the neuroimaging is typical, the diagnosis should be supported by clinical evidence.

Since dysmorphic signs are not prominent or specific, the diagnosis is sometimes delayed, as was the case with our patient. Most individuals are diagnosed before the age of one year, however the latest diagnosis in one series was made at 33 years (6). This patient had no history of hyperpnea/apnea episodes, and had mild hypotonia, and impaired cerebellar activity.

The genetic basis of Joubert syndrome is not known. Mutations in genes that regulate early differentiation and development of cerebellum, particularly mutations in homeotic genes that establish the isthmic region, may produce the specific alterations of Joubert syndrome (6).

As a result of the variable clinical presentation of the disease, the long-term outcome was not clearly documented until a report by Steinlin et al. in 1997 (7). As was noted in this study, some patients die in early childhood due to breathing problems. Some show variable motor development, with a delay in walking ability between 2 and 10 years of age. Cognitive development is also variable. Rarely patients are almost fully independent, have good social interaction and limited success in school. Our patient is a 14-year-old girl with an IQ score of 42. She is attending to a school for normal children and has the anxiety of being unsuccessful. She is preoccupied with her disabilities and is sometimes aggressive. She has a depressive mood but no autistic features. Her history shows a gradual improvement in her motor and cognitive functions. One of the problems with her condition is the denial of her parents. An earlier diagnosis would have made it easier to cope with the problem.

Increased awareness of the possibility of this syndrome occurring in patients who exhibit developmental delay, nystagmus, and hypotonia in early childhood will lead to earlier diagnosis, appropriate counselling, and proper rehabilitation.

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