Case Report

Joubert Syndrome vs Rhombencephalosynapsis: Differentiation on the Basis of MRI Findings

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Joubert syndrome and rhombencephalosynapsis are both rare congenital hindbrain anomalies. Although they have agenesis or hypogenesis of the cerebellar vermis as a common finding and may have similar clinical findings related to cerebellar dysfunction, the associated posterior fossa and supratentorial anomalies in both entities are quite different.[1,5,8,14]

We present magnetic resonance imaging (MRI) of a 4-year-old male patient with Joubert syndrome and those of a 7-month-old female patient with rhombencephalosynapsis, and discuss both the similarities and differences on the basis of MRI findings.

CASE REPORTS

Case Report 1

A 4-year-old male patient presented with severe mental motor retardation, slurred and disorganized speech, and abnormal eye movements characterized by ocular apraxia in horizontal directions. He also had a medical history of attacks of hyperpnoea during the first few months of life. He began to walk at the age of 2.5 years, and was able to walk with help, associated with a marked unsteadiness and ataxia. The neurological examination of patient revealed markedly disturbed cerebellar functions. He had no family history of neurological disorders or consanguinity.

The patient was referred for a cranial MRI study, which was performed on a 1.5 T MR scanner (1.5 T Philips Gyroscan NT, The Netherlands), with SE T1 (TR = 600 ms, TE = 20 ms, flip angle = 90°), TSE T2 (TR = 4000 ms, TE = 90 ms, flip angle = 90°), and FLAIR (TR = 5000 ms, TE = 100 ms, TI = 1800 ms, flip angle = 90°) sequences on three orthogonal planes. MRI of the patient revealed severe hypoplasia of the cerebellar vermis with total absence of the vermian folia. The brain stem was mildly elongated immediately rostral to the pons, leading to some degree of deepening of anterior interpeduncular fossa, characteristic of mild isthmic dysgenesis (Fig. 1a). Superior cerebellar peduncles were thickened and elongated with an almost perpendicular course to the brain stem (Fig. 1a and b). The combination of thick and elongated superior cerebellar peduncles, deepened posterior interpeduncular fossa, and dysplastic cerebellar vermis created the appearance of molar tooth sign in the axial images at the level of mesencephalon (Fig. 1b). The cerebellar hemispheres apposed each other in the midline secondary to the vermian agenesis, however, they were not continuous with each other, instead there was a vermian cleft separating them, most prominent in the axial images at the mesencephalic level (Fig. 1b–d).

Case Report 2

A 7-month-old female patient presented with delay in developmental milestones, generalized hypotonia with marked unsteadiness, irritability, and visual nystagmus in all directions. She had no family history of neurological disorders, however, the parents were consanguinous.

A cranial MRI study of the patient was performed on a 1.5 T MR scanner (1.5 T Philips Gyroscan NT, The Netherlands), with SE T1 (TR = 600 ms, TE = 20 ms, flip angle = 90°), TSE T2 (TR = 4000 ms, TE = 90 ms, flip angle = 90°), and FLAIR (TR = 5000 ms, TE = 100 ms, TI = 1800 ms, flip angle = 90°) sequences on three orthogonal planes. MRI of the patient showed total absence of the cerebellar vermis, resulting in the fusion of cerebellar hemispheres and dentate nuclei across the midline. The cerebellar folia revealed an almost transverse orientation (Fig. 2a–d). The fourth ventricle was an abnormal heart shape instead of its usual crescent shape (Fig. 2b). The colliculi were also fused (Fig. 2e). MRI findings of the supratentorial compartment were totally normal except an incidental arachnoid cyst within the atrium of right lateral ventricle (Fig. 2d).

DISCUSSION

Joubert et al. [6] reported five children with episodic hyperpnoea, abnormal eye movements, ataxia, and mental retardation in 1969. Joubert syndrome is a relatively rare developmental malformation with autosomal recessive transmission [7]. It is characterized by the aplasia or hypoplasia of cerebellar vermis, but fragmentation and heterotopia of dentate nuclei, inferior olivary nuclei, and basis pontis are associated neuropathological findings. The nuclei and tracts of...
trigeminal nerve, solitary nuclei and tracts, and nuclei gracilis and cuneatus are also hypoplastic or fragmented in Joubert syndrome. The pyramidal decussation is almost totally absent [2,7,12,20].

The clinical presentation of Joubert syndrome is usually at a very early age. Clinical findings may include nonspecific features such as hypotonia, ataxia, with mental and motor retardation. Neuro-ophthalmologic examination of the patient reveals the presence of abnormal eye movements, characterized by partial to complete oculomotor apraxia, both in horizontal and vertical directions. Most patients have a medical history of respiratory disturbances, characterizedly episodic attacks of hyperpnoea intermixed with central apnoea especially during the neonatal period [6,7,16].

Fig. 1 – (a) Sagittal SE T1-weighted MRI shows the total absence of verman folia. The superior cerebellar peduncle (black arrow) is clearly observed with an almost perpendicular course to the brain stem. Note that the brain stem is mildly elongated (white arrow) immediately rostral to pons, causing some deepening of anterior interpeduncular fossa. (b) Axial FSE T2-weighted MRI shows the elongated and thickened superior cerebellar peduncles (arrows) with a perpendicular course to the brain stem, and absence of the vermis (molar tooth sign). A midline cleft of the vermis (arrowhead) is obviously seen. (c) Axial FSE T2-weighted MRI reveals agenesis of vermis, the cerebellar hemispheres appose each other in the midline (arrows). (d) Coronal FSE T2-weighted MRI reveals agenesis of vermis, the cerebellar hemispheres appose each other in the midline (arrows). Rostrally a vermian cleft (between arrows) is clearly seen.
Computed tomography (CT), and preferably MRI, studies of patients with both posterior fossa malformations demonstrate the cerebellar malformation and associated intracranial anomalies in detail, some of which were previously detectable only at autopsy.

Neuroimaging findings of Joubert syndrome are quite characteristic. Imaging features are isthmic dysgenesis, which is characterized by elongation and thinning of the pontomesencephalic junction, the so-called isthmus, leading to deepening of the anterior interpeduncular fossa, together with thickening and elongation of the superior cerebellar peduncles. The most consistent radiological change of the syndrome is agenesis or hypogenesis of the vermis with a cleft formation. A portion of the superior vermis may be present in some cases with incomplete fusion of the halves of vermis, creating a sagittal vermian cleft. Sagittal images show a complete or nearly complete lack of the normal vermian folia. Absence of the vermis results in a triangular-shaped mid-fourth ventricle and a bat-wing-shaped fourth ventricle superiorly. Imaging in the axial plane demonstrates the molar tooth sign due to a deep

Fig. 2 – (a) Axial FSE T2-weighted image shows midline fusion (arrows) of the cerebellar hemispheres secondary to the absence of vermis. (b) Axial FSE T2-weighted image demonstrates that fourth ventricle (arrow) has an abnormal heart shape. (c) Axial FSE T2-weighted image reveals continuity of cerebellar folial pattern secondary to the vermian agenesis. The inferior colliculi (C) are also fused. (d) In coronal FLAIR image the cerebellar hemispheres are fused across the midline (white arrows). Note there is an additional arachnoid cyst (black arrow) within the trigone of the right lateral ventricle.
posterior interpeduncular fossa, thick and elongated superior cerebellar peduncles, and hypoplastic or aplastic superior cerebellar vermis. The cerebellar hemispheres appose one another in the midline, but are not fused [1,5,12,14].

Associated supratentorial anomalies are uncommon, however cerebral cortical dysplasia, grey matter heterotopia, occipital meningocephalocele, callosal dysgenesis are rarely detected findings [2,7,12,14,16,17]. Chorioretinal coloboma, retinal dystrophy, facial dysmorphism, sacral dermal sinus, polydactyly, scoliosis, congenital heart defects, congenital hepatic fibrosis, and polycystic kidney disease have been reported as rare extracranial findings in patients with Joubert syndrome [2,3,7,12,16]. The prognosis is generally poor [2,7,12].

Rhombencephalosynapsis was first described by Obersteiner in 1914 from a routine autopsy of a 24-year-old male suicide victim [9]. It is a very rare congenital anomaly of the hindbrain, which is essentially characterized by fusion of the cerebellar hemispheres and dentate nuclei, and absence of the cerebellar vermis [4,8,10]. The total number of reported cases for this rare anomaly in the literature does not exceed 30 [4,8,10,11,13,15,18,19].

Rhombencephalosynapsis has a wide spectrum of presenting features, ranging from early death to variable degrees of cerebellar dysfunction and developmental delay. Clinical presentation of the malformation is usually early, however a few cases have been reported without significant clinical findings at late ages. Clinical findings of rhombencephalosynapsis include generalized hypotonia, nystagmus, ataxia, and mild to severe delays in mental and motor developmental milestones [4,5,8,10,13,15].

Neuroimaging studies of the patients reveal total absence or severe hypogenesis of the vermis so that both cerebellar hemispheres fuse across the midline, but without the cleft seen in Joubert syndrome. The cerebellum may also be hypoplastic, leading to the appearance of pear-shaped cerebellum. The cerebellar folia usually show abnormal transverse orientation, especially in the inferior cerebellum. Rhombencephalosynapsis is characterized by the fusion of dentate nuclei of the cerebellum, cerebellar peduncles, and the inferior colliculi as well. Fusion of the dentate nuclei across the midline may cause formation of a horseshoe shaped arc posterior to the fourth ventricle. The fourth ventricle also loses its normal crescent shape, and it gains a heart or teardrop shape. Aqueductal stenosis, which may cause congenital hydrocephalus, is commonly associated with this anomaly [1,4,5,8,10,13,15,18,19].

Rhombencephalosynapsis appears to represent a unique malformation of the posterior fossa, however variable supratentorial anomalies have occasionally been reported such as hydrocephalus, agenesis of the septum pellucidum, hypoplasia or aplasia of anterior commissure, agenesis of olfactory tracts, dysgenetic corpus callosum, pachygyria, meningoencephalocele, schizencephaly, anomalies related to hypothalamic–hypophyseal axis, and thalamic fusion [4,8,10,15]. Musculoskeletal, cardiovascular, respiratory, and urinary system anomalies are very rarely associated extracranial findings [4,8,10,15]. The severity of clinical manifestations and the prognosis of rhombencephalosynapsis generally depend on the associated supratentorial anomalies [8–10,19].

Although cerebellar development is not well understood, there is a general agreement in the literature that insults leading

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to the development of these two posterior fossa anomalies occur between 4–8 weeks of gestation. A derangement in the formation of pontomesencephalic junction, so called rhombomere, and disorganization of the formation, migration, and organization of nuclei and tracts of the brain stem and cerebellum, which develop from embryonic rhombic lips, are thought to be responsible for Joubert syndrome [16,20]. During the intense neuroblastic activity leading to the formation of embryonic rhombic lips, an insult is postulated to occur prior to the development of cerebellar vermis, that may also prevent or impair the histogenesis of dentate nuclei and cerebellar peduncles, in addition to the vermis in the case of rhombencephalosynapsis. The time frame for rhombencephalosynapsis matches some supratentorial midline anomalies, which may explain their association with this posterior fossa anomaly [8,13,19].

Table 1 summarizes both the similarities and differences between Joubert syndrome and rhombencephalosynapsis in terms of their clinical and radiological aspects. In short, the main common feature of these two anomalies is aplasia or hypoplasia of the cerebellar vermis associated with a malformed cerebellum and fourth ventricle. Distinguishing features include: (a) apposition of cerebellar hemisphere that may be associated with a vermian cleft in Joubert syndrome vs. the fusion of cerebellar hemispheres across the midline in rhombencephalosynapsis; (b) the thickened and elongated superior cerebellar peduncles causing molar tooth sign in Joubert syndrome vs. the fusion of peduncles in rhombencephalosynapsis; (c) the absence of vermian folial pattern in Joubert syndrome vs. abnormal orientation of folia in rhombencephalosynapsis; (d) the dysplasia and heterotopia of dentate nuclei in Joubert syndrome vs. fusion of nuclei across the midline; (e) the presence of isthmic dysgenesis and brain stem tract and nucleus anomalies in Joubert syndrome; (f) the fusion of inferior colliculi in rhombencephalosynapsis; (g) the more common association of supratentorial anomalies and hydrocephalus in rhombencephalosynapsis; and (h) the more common association of extracranial anomalies in Joubert syndrome make the differentiation of these two developmental anomalies easy with neuroimaging studies, especially MRI.

The clinical findings of our patients were highly suggestive of these posterior fossa malformations, although they were not specific. Neither of the patients revealed a serious extracranial anomaly. Other than an incidentally detected arachnoid cyst within the trigone of right lateral ventricle in the patient with rhombencephalosynapsis, we could not detect any supratentorial anomaly in our patients. Agenesia of the cerebellar vermis was a common finding in both of the cases, and the distinguishing characteristic posterior fossa anomalies, were most easily detected on MRI studies, allowing differentiation between them.

In conclusion, although the vermian agenesis or dysgenesis is a common MRI finding in both Joubert syndrome and rhombencephalosynapsis, the presence of associated posterior fossa findings and of rarely supratentorial anomalies on MRI helps to differentiate between these two disorders.

REFERENCES