JOUBERT SYNDROME: an observation of five cases.

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Learning objectives

The main objective is to perform an update of characteristic findings of Joubert Syndrome in brain MRI.

Background

Joubert syndrome is a rare, autosomal recessive transmitted disease. Twelve genes are known to be involved that encode primary ciliary proteins, which participate in axonal migration and proliferation of the stem and cerebellum.

Clinical symptoms include hypotonia, ataxia, psychomotor retardation, neonatal tachypnea, anomalous eye movements and mental retardation (SJ pure or type 1). However, there is considerable clinical variability, depending on whether or not it is associated with hepatic, renal and/or ocular disorders.

Brain MRI without intravenous contrast is the Gold Standard test for the diagnosis, as it includes two common findings: the molar tooth sign and deformity of the fourth ventricle, due to hypoplasia/agenesis of the cerebellar vermis. This alteration in the development of the superior cerebellar vermis conditions the presence of a thickened and elongated cerebellar peduncle and lack of decussation of the fibers in the white matter of deep interpeduncular fossa at the isthmus and upper decks.

Other associated brain alterations are: hippocampal malformation, dysgenesis of the corpus callosum, hypoplasia of the temporal lobes, cerebellum malformation, ventriculomegaly, and white matter hyperintensity on T2 weighted images reflecting alterations in the development of myelination.

Less frequently, it can also associate: encephalocele, lipoma in the ambient cistern, subcortical periventricular heterotopia, bilateral enlargement of both caudate nuclei or parenchymal cyst.

These abnormalities determine aberrant white matter connections between the cerebellum and cerebral cortex, which is best characterized by tractography and diffusion tensor. In DTI, thickening and alterations in the arrangement of the upper tracts reflect horizontalized cerebellar peduncles. However, this lack of decussation is not a specific finding of SJ.
Prenatal diagnosis of Joubert syndrome can be established by fetal MRI performed after the 17th week of gestation (ideally between weeks 20 and 22).

Depending on the presence or absence of other associated extracerebral alterations there are 6 types known of Joubert syndrome. Type I is a pure Joubert syndrome, characterized by hypotonia, ataxia, and developmental delay, tachypnea in neonatal period, abnormal eye movements and mental retardation, without liver or kidney impairment.

Type II SJ, presents with eye defects, retinal dystrophy and Leber congenital amaurosis, without hepatic or renal impairment. It is associated with the presence of AHI1 gene.

Type III SJ, presents clinically with varying renal impairment, without ocular abnormalities. It is related with NPHP1 and RPGRIP1L genes.

Type IV SJ, presents clinically with nephronopttis and retinal dystrophy, without hepatic disorders and is associated with CEP290 gene.

The SJ type V, presents with clinically variable idiopathic hepatic fibrosis, chorioretinal or optic nerve coloboma and nephronopttis. The gene involved is the TMEM67.

The SJ type VI, is characterized by the presence of forked tongue or hamartomas, multiple oral braces, polydactyly, hypothalamic hamartoma (rare) and congenital absence of pituitary. It is associated to TNEM 67 gene.

The differential diagnosis includes various genetic diseases considered rare because of the scarcity of cases diagnosed, who share a common gene pool with SJ, such as Merckel-Gruber syndrome, Orofaciodigital syndrome, Jeune syndrome, Bardet-Bield, Alström syndrome and nephronophthisis.

**Findings and procedure details**

Retrospective review of 5 cases of Joubert Syndrome diagnosed at our center between 2008 and 2014. Electronic medical records of the five patients were requested, reviewing anthropometric data (age, sex), clinical symptoms and findings on brain MRI images, both in diagnosis and subsequent controls (Fig.1).
The five cases diagnosed with Joubert Syndrome were three boys and two girls, aged 5 to 14 years today, and between 5 months and 7 years at diagnosis. None had relevant family history or consanguineous parents. All five patients were term infants, without neonatal history of interest except one, who had a symptomatic hypoglycemia at birth. All had delayed psychomotor development, aged between 19 and 24 months when they started walking. One of these patients, also had delayed language development.

At diagnosis, all patients presented with ataxia and increased base of support when walking, hypotonia, oculomotor apraxia and mental retardation to varying degrees. In one case, axial hypotonia and action tremor was associated, whereas in another case dislalia and convergent strabismus was associated.

Any additional tests (analytical, eye examination, electroencephalogram, abdominal ultrasound and karyotype) were normal.

Brain MRI was performed without intravenous administration of paramagnetic contrast, obtaining T1-weighted sequences in coronal and sagittal planes, axial T2, T2 gradient, and T2 Flair and diffusion.

In two cases, there was an obvious superior cerebellar vermis hypoplasia; and in the other three cases a complete agenesis of it was identified. Associated deformity of the fourth ventricle in an "umbrella or bat wings" form and medialization and elongation of the cerebellar peduncles, determine the characteristic "molar tooth sign". (Fig. 2, 3, 4, 5, 7 and 8). In one case, there was a dysgenesis of the corpus callosum and cerebellum malformation, identified in T1-weighted images in sagittal planes (Fig. 6). No other signs or obvious abnormalities, like heterotopia or abnormalities of cerebral surcation were identified.

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<th>Patient</th>
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<td>26 a</td>
<td>Psychomotor retardation</td>
<td>Convergent squint since 5 years old</td>
<td>Without interest. Brother with psychomotor retardation (patient 2)</td>
<td>Deambulation at 4 year old</td>
<td>Facies, microcephaly Squint Hypereflexia No language Ataxia Tremor trunk</td>
<td>Laboratory test Karyotype Brain MRI EMG: normal Ocular test.</td>
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<td>Cephalic movements deviation</td>
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<td>Normal</td>
<td>Convergent squint No seated stable. Tremor trunk</td>
<td>Laboratory test: normal. EEG: lentificado Brain MRI Ocular test: nistagmus</td>
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<td>Psychomotor retardation Dystonia</td>
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<td>Delayed language acquisition Deambulation at 22 months.</td>
<td>Hypotonia Ataxia Apraxia OM Mild mental retardation Increased basis stall</td>
<td>Laboratory test: N Cerebral US: N Abdominal US: N Karyotype: N Brain MRI</td>
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<td>9 m</td>
<td>16 a</td>
<td>Psychomotor retardation</td>
<td>Wihout interest</td>
<td>Wihout interest</td>
<td>No seating. Crawl at 16 months. Deambulation at 2 years old.</td>
<td>Lingual protrusion Axial hypotonia Hyporeflexia No dump Tremor action</td>
<td>Laboratory test: N Ocular test: N EEG: N Brain MRI. Karyotype: N</td>
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**Fig. 1**
Patient 3

Fig. 2: T2-weighted sequences in axial planes. Complete agenesis of cerebellar vermis. Associated deformity of the fourth ventricle in an "umbrella or bat wings" form and medialization and elongation of the cerebellar peduncles, determine the characteristic "molar tooth sign".
Patient 3

**Fig. 3:** T1-weighted sequences in coronal and sagittal planes. Medialization and elongation of the cerebellar peduncles.
Patient 3

Fig. 4: T1-weighted sequences in coronal planes and T2 gradient in axial plane. No other signs or obvious abnormalities, like heterotopia or abnormalities of cerebral surcation were identified.
**Patient 4**

**Fig. 5:** T1-weighted sequences in axial planes. Complete agenesis of superior cerebellar vermis was identified, with deformity of the fourth ventricle in an "umbrella or bat wings" and the characteristic "molar tooth sign".
Patient 4

**Fig. 6:** T1-weighted sequences in coronal and sagittal planes. Dysgenesis of the corpus callosum and cerebellum malformation. No other signs like heterotopia or abnormalities of cerebral surcation were identified.
**Patient 5**

![MRI images](image)

**Fig. 7:** T2-weighted sequences in axial planes. Hypoplasia of superior cerebellar vermis was identified, with deformity of the fourth ventricle in an "umbrella or bat wings" and the characteristic "molar tooth sign".
Patient 5

Fig. 8: T1-weighted sequences in coronal and sagittal planes. No other signs or obvious abnormalities were identified.
Conclusion

Joubert Syndrome should be suspected in any child with clinically hypotonia, abnormal eye movements and impaired breathing pattern. Early diagnosis of these patients is important because follow-up is necessary to detect and establish early multiorgan treatment of associated disorders and, secondly, to perform genetic counseling.

Brain MRI is the gold standard to confirm the diagnosis. The DTI may be useful in defining the aberrant white matter connections associated to the disease.

Personal information

References

1. "Joubert Syndrome and "molar sign" in the renal-ocular-cerebelar complex in two patients". Hilda Bibas B.¹, Ana M. Coronel M.², Ricardo Fauze B.¹, Marcela Sialle G