Joubert syndrome
Large clinical variability and a unique neuroimaging aspect

Emília Katiane Embiruçu Leão¹, Marcília Martyn Lima¹, Otacílio de Oliveira Maia Júnior², Juliana Parizotto³, Fernando Kok¹

ABSTRACT
Joubert syndrome (JS) is an autosomal recessive inherited disorder characterized by hypotonia, cerebellar vermis hypoplasia, ocular abnormalities (e.g., pigmentary retinopathy, oculomotor apraxia and nystagmus), renal cysts and hepatic fibrosis. Respiratory abnormalities, as apnea and hyperpnea, may be present, as well as mental retardation. At least seven JS loci have been determined and five genes identified. Herein, we report five children, belonging to independent families, with JS: they shared the same typical MRI abnormality, known as molar tooth sign, but had an otherwise quite variable phenotype, regarding mostly their cognitive performance, visual abilities and extra-neurological compromise.

Key words: Joubert syndrome, molar tooth sign, cerebellar malformation.

Joubert syndrome (JS) is a rare genetically heterogeneous inherited disorder with an estimated prevalence in the United States of 1 in 100,000. JS is characterized by congenital ataxia, hypotonia, developmental delay, and at least one of the following features: neonatal respiratory disturbances and abnormal eye movements, including nystagmus and oculomotor apraxia. In some cases, Leber congenital amaurosis, pigmentary retinopathy, renal and hepatic abnormalities can also be found. The presence of a characteristic neuroimaging finding, known as molar tooth sign, is highly suggestive of JS diagnosis. A combination of midline cerebellar vermis hypoplasia, deepened interpeduncular fossa, and thick, elongated superior cerebellar peduncles gives to the axial view of the midbrain an appearance of a molar tooth. Recently, Valente, Brancati and Dallapiccola proposed a clinical classification of JS in which molar tooth sign was considered an obligatory criterion, and hypotonia, developmental delay, ataxia, and abnormal eye movements were pointed as primary criteria. They were able to recognize six subgroups of JS:
1. Pure JS: only primary criteria;
2. JS plus retinopathy: primary crite-

Correspondence
Emília Katiane Embiruçu Leão
Serviço de Neurologia Infantil
de Hospital das Clínicas
Faculdade de Medicina da USP
Av. Dr. Enéas de C. Aguiar 255 / S 5011
05403-000 São Paulo SP - Brasil
E-mail: ekeleao@yahoo.com.br

Received 29 April 2009
Received in final form 27 November 2009
Accepted 10 December 2009
Joubert syndrome
Leão et al.
Arq Neuropsiquiatr 2010;68(2)

Joubert syndrome (JS) is characterized by the triad of hypotonia, ataxia and retinal abnormality (congenital Leber amaurosis, pigmentary retinopathy or unspecific retinitis);

3) JS plus renal disease: primary criteria and kidney involvement (nephronophthisis, abnormal kidney ultrasound and/or urinary concentration defect);

4) CORS (cerebello-oculo-renal syndrome) or Senior-Loken syndrome: primary criteria, retinal abnormality and kidney involvement;

5) COACH (cerebellar vermis hypoplasia/aplasia, oligophrenia, ataxia, ocular coloboma, and hepatic fibrosis): primary criteria, mental retardation, liver disorder (fibrosis or histological abnormalities), optic nerve or chorioretinal coloboma. Nephronophthisis might be present;

6) Oro-facio-digital syndrome VI: primary criteria plus orofacial abnormality (cleft lip/palate, notched upper lip, tongue tumors, multiple frenula, etc.) plus mesial or pre-axial polydactyly.

JS is genetically heterogeneous, and seven loci have been so far assigned, with five of their associated genes identified (Table 1). It is believed that other loci and genes will be recognized in the future. There is no clear correlation between genetic and clinical classification in JS. Nevertheless, AHI1 mutations are usually associated with pure JS (subgroup 1) and approximately half of individuals with cerebello-oculo-renal syndrome (subgroup 4) have CEP290 mutations. In large series of patients

Table 1. Joubert syndrome identified loci, genes and their products.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Location</th>
<th>Gene</th>
<th>Protein</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>JBTS1</td>
<td>9q34.3</td>
<td>Not known</td>
<td>Not known</td>
<td>Saar et al., 1999²</td>
</tr>
<tr>
<td>JBTS2</td>
<td>11p12-q13.3</td>
<td>Not known</td>
<td>Not known</td>
<td>Keeler et al., 2003³</td>
</tr>
<tr>
<td>JBTS3</td>
<td>6q23.3</td>
<td>AHI1</td>
<td>Jouberin</td>
<td>Ferland et al., 2004⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dixon-Salazar et al., 2004⁴</td>
</tr>
<tr>
<td>JBTS4</td>
<td>2q13</td>
<td>NPHP1</td>
<td>Nephrocystin-1</td>
<td>Parisi et al., 2004⁴</td>
</tr>
<tr>
<td>JBTS5</td>
<td>12q21.34</td>
<td>CEP290 (NPHP6)</td>
<td>Nephrocystin-6</td>
<td>Sayer et al., 2006¹⁰</td>
</tr>
<tr>
<td>JBTS6</td>
<td>8q21.1-q22.1</td>
<td>TMEM67</td>
<td>Meckelin</td>
<td>Baala et al., 2007¹¹</td>
</tr>
<tr>
<td>JBTS7</td>
<td>16q12.2</td>
<td>RAPGRIPL1</td>
<td>Protein phantom</td>
<td>Delous et al., 2007¹, Arts et al., 2007</td>
</tr>
</tbody>
</table>

JS, mutations in AHI1 are found in 10 to 15% of cases and of CEP290 in 10%.

Herein, we present a series of five patients affected by JS, which are representative of the remarkable clinical variability observed in this condition.

**METHOD**

Patients fulfilling criteria for JS performed a complete clinical, neurological and ophthalmological evaluation, brain MRI, total abdominal ultrasound and biochemical analysis to evaluate kidney and liver function.

The Institutional Review Board approved this study and children's legal guardians gave their informed consent to participate.

**RESULTS**

Table 2 presents a summary of the clinical findings. Parents of case 1 were first cousin; consanguinity was denied in the remaining families. In all patients, it was present hypotonia, ataxia and developmental delay of variable intensity. Mental retardation varied from profound to mild, and no respiratory abnormality was reported. Abnormal eye movements reported at early age in cases 1, 2, and 5, improved with time. Severe behavior disturbance, with autistic features, was seen in a two individuals (cases 4 and 5). Facial distinctive features as broad

Figure. Brain axial MRI of patients 1 [A], 2 [B], 3 [C], 4 [D] and 5 [E], showing molar tooth sign (arrows).
nasal base and thick eyebrow were seen in three patients. Tent-shaped upper lip was observed in the younger patients (cases 3 and 4).

MRI disclosed the typical molar tooth sign in all patients (Figure). Electroretinogram was performed in three patients and its response was extinct. In patients 4 and 5, abdominal ultrasound disclosed increased renal echogenicity, suggestive of parenchymatous nephropathy. In patient 4, kidney cysts were also detected. At 11 years of age, patient 5 had a moderate elevation of ALT [221U/L; reference value (RV)<31 U/L], AST (145 U/L; RV<31 U/L). These results were normal at age of 3 years.

**DISCUSSION**

Of the five studied cases in this series, two (patients 1 and 2) might be assigned, according to Valente et al.³, as pure JS (subgroup 1): their clinical phenotype are milder and no extra-neurological abnormalities were detected. Neurological compromise was more severe in the three remaining cases: presence of associated retinopathy in patient 3 is characteristic of subgroup 2; in patient 4, the more severely affected, association with Leber congenital amaurosis and kidney cysts are diagnostic of CORS (subgroup 4); and presence of optic coloboma and hepatic abnormalities in patient 5 allow us to make the diagnosis of COACH (subgroup 5).

Abnormal visual function, caused by optic coloboma or retinitis, was present in three of the five studied patients. In all them, vision was severely affected. Interestingly, in two of these patients abnormal behavior with autistic features were also present. Abnormal eye movements, without visual impairment, were seen in a single patient.

Respiratory abnormalities, as hyperpnea and apnea, one of primary diagnostic criteria¹², were not seen in our series. Periodic clinical reevaluation is highly recommended; for instance, liver abnormal laboratorial tests in patient 5 were detected only after the first decade of life. JS prognosis at an early age is difficult to be determined.

Recognition of molar tooth sign at brain MRI is an essential cue for the diagnosis of JS. Early signs, as abnormal eye movements and respiratory abnormalities might suggest this possibility, but in most of cases, clinical features are non-specific. Once diagnosis of JS is made, it is recommended to perform a comprehensive functional and morphological evaluation of liver, kidney and visual function. Clinical variability in JS is explained not only by its genetic heterogeneity but also by the remarkable phenotype diversity seen with different mutations in the same gene. Clinical features may vary in each family and even between affected siblings.

**REFERENCES**