Ophthalmological findings in Joubert syndrome

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Abstract

**Purpose:**
Joubert syndrome (JS) is an autosomal-recessive inherited complex malformation of the midbrain-hindbrain. It has been associated with ocular and oculomotor abnormalities. The aim of our study was to extend the ophthalmic knowledge in JS and to add new findings.

**Methods:**
In a retrospective study, ten consecutive patients, who met the revised diagnostic criteria of JS were included. Mutation analysis was performed in all cases. Each patient underwent a comprehensive neuro-ophthalmologic examination.

**Results:**
Bilateral drusen of the optic disc were found in two patients. Four patients showed bilateral morphological and functional signs of retinal dystrophy (CEP290 mutation in two cases, AHI1 mutation in one case). In nine patients performance during smooth pursuit, saccades and vestibulo-ocular reflex (VOR) cancellation was poor.

**Conclusions:**
To the best of our knowledge, the association of optic disc drusen with JS has not yet been described. In support of previous findings decreased smooth pursuit and VOR cancellation as well as partial to complete oculomotor apraxia seem to be the key oculomotor features of JS. Genotype-phenotype correlations demonstrated the predictive value of CEP290 and AHI1 mutations for retinal involvement.

**Keywords:** Joubert syndrome; Cerebellar vermis hypoplasia; Abnormal eye movements; Retinal dystrophy; Optic disc drusen
Introduction

Joubert syndrome (JS) is a rare autosomal-recessive disorder which is characterized by midbrain-hindbrain malformations mainly in the form of agenesis or dysgenesis of cerebellar vermis.\textsuperscript{1,2} Diagnostic criteria in JS include hypotonia, ataxia, global developmental delay and the neuroradiological finding of “molar tooth sign”.\textsuperscript{3,4} The term “JS related disorders” was introduced referring to a group of pleiotropic conditions presenting the pathognomonic features of JS associated with variable involvement of other organs and systems. Almost all JS related disorder genes, so far identified, encode for proteins expressed in the primary cilium or in the centrosome. This observation has linked these disorders to the field of ciliopathies.\textsuperscript{5}

Ocular and oculomotor involvement is common in JS.\textsuperscript{4,6-10} However, findings differ considerably due to a wide range of phenotypic variability among patients with JS.

Materials and Methods

In a retrospective study, ten consecutive patients, who met the revised diagnostic criteria of JS were included.\textsuperscript{3} Patients’ (3 females) ages ranged from 8 to 29 years (mean: 18.2 years). Each patient underwent a comprehensive neuro-ophthalmologic examination including assessment of ocular alignment and motility.

Results

The clinical data for each patient are summarized in Table 1 and 2.
Ocular findings

Bilateral drusen of the optic disc were found in patients 5 and 6. Drusen were confirmed by B-scan ultrasound and the autofluorescence phenomenon (Fig. 1). In four patients the pigmentation of the peripheral retina was mottled and visual acuity was decreased (patient 3, 4, 5 and 8).

Oculomotor findings

In nine of the patients performance during smooth pursuit, saccades and (vestibulo-ocular reflex) VOR cancellation was poor. The speed in smooth pursuit was uniformly low, catch-up saccades were frequently observed. Abnormal saccades were characterized by increased latency and hypometry if oculomotor apraxia was not complete. In four patients head thrusts, sometimes with a blink, were used to shift gaze. In four patients manifest deviations were found. Three of these patients had an alternating esotropia while one had an alternating exotropia.

Discussion

Surprisingly, we found bilateral optic disc drusen in two patients. The prevalence of optic nerve drusen has been estimated between < 0.4% and 3.7%. Both affected patients had signs of retinal dystrophy. The association between drusen and retinitis pigmentosa is well established and the incidence of the combination has been reported to be between 0% and 10%. The association between JS and optic disc drusen has not been previously reported. However, as optic disc drusen are commonly seen in clinical routine, random coincidence cannot be excluded.
Pigmentary fundus changes, retinal dystrophy and severe visual loss are frequently found in JS.\textsuperscript{6,8-10} Four of our patients had such findings. Genotype-phenotype correlations have emphasized the predictive value of specific mutations for retinal involvement. Retinal involvement is present in about 80\% of patients with $\textit{AHI1}$ (patient 8) and $\textit{CEP290}$ mutations (patients 3 and 4).\textsuperscript{5} Genotype-phenotype correlations may even link JS patients with optic disc drusen to specific genes as MFRP mutations have been identified causing the syndrome of nanophthalmus, retinitis pigmentosa, foveoschisis and optic disc drusen.\textsuperscript{12} Other ocular findings such as cataract (patient 10), optic nerve hypoplasia, chorioretinal coloboma, ptosis and ocular fibrosis are infrequently associated with JS.

Manifest deviations were observed in four out of 10 patients. Ocular misalignment is common in JS.\textsuperscript{7,9,10} Lambert et al. described an alternating hyperdeviation on abduction as a characteristic feature which was seen in two of our patients.\textsuperscript{7} In nine of the patients performance during smooth pursuit, saccades and VOR cancellation was poor. Our findings of ocular motor defects are in agreement with findings of previous studies.\textsuperscript{4,7,9,10} Defects in smooth pursuit and VOR cancellation can be contributed to deformed cerebellar vermis. Saccades and quick phases of nystagmus are generated involving the brainstem. The control of saccades is regulated by cerebral and cerebellar structures including the frontal eye field and the superior colliculus. Accordingly, lesions of cerebellar control centres lead to dysmetric and slow saccades.

In conclusion, patients were affected by complex but variable ocular and oculomotor deficits. This phenotypic variability might be supported by multiplex neuropathological findings of the cerebellar vermis and of several pontine and medullary structures. Furthermore it may arise from the wide genetic heterogeneity of
JS and related disorders, as only about 25% of causative genes and loci have been detected today.

References


8 Steinlin M, Schmid M, Landau K, Boltshauser E. Follow-up in children with Joubert syndrome. *Neuropediatrics* 1997; **28**: 204-211.


Titles and legends to figures

Figure 1.
(a) Colour fundus photograph of the right eye showing optic disc drusen (patient 5).
(b) Autofluorescence of the right eye demonstrating optic disc drusen (patient 5).
**Table 1. Ocular findings in patients with Joubert syndrome**

<table>
<thead>
<tr>
<th>Patient / Sex / Age (years)</th>
<th>Genetic mutation</th>
<th>BCVA (Snellen charts)</th>
<th>Cycloplegic refraction</th>
<th>Anterior segment</th>
<th>Fundus</th>
<th>Pupillomotor testing</th>
<th>Full-field ERG</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / M / 8</td>
<td>None found</td>
<td>Bil: 1.0</td>
<td>R: +2.0/-0.75 x 180</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 / M / 16</td>
<td>None found</td>
<td>R: 0.8</td>
<td>R: +2.25/-0.5 x 170</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>Normal</td>
<td>Bil: normal retinal thickness</td>
</tr>
<tr>
<td>3 / M / 20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CEP290</td>
<td>Bil: 0.1</td>
<td>R: +7.5/-1.25 x 5</td>
<td>Bil: normal</td>
<td>Bil: cellophane maculopathy, peripheral retina with mottled pigmentation, attenuated retinal arterioles</td>
<td>Bil: very sluggish pupillary response, sometimes even paradox light reaction</td>
<td>Bil: absent</td>
<td>Bil: reduced retinal thickness</td>
</tr>
<tr>
<td>4 / M / 18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CEP290</td>
<td>R: 0.63</td>
<td>R: +2.0/-2.0 x 10</td>
<td>Bil: normal</td>
<td>Bil: optic nerve drusen, peripheral retina with slightly mottled pigmentation</td>
<td>Bil: normal</td>
<td>Bil: highly reduced photopic and scotopic ERG</td>
<td>Bil: normal retinal thickness</td>
</tr>
<tr>
<td>5 / F / 16</td>
<td>None found</td>
<td>Bil: 0.5</td>
<td>R: -4.0/-3.5 x 175</td>
<td>Bil: normal</td>
<td>Bil: optic nerve drusen, cellophane maculopathy, peripheral retina with slightly mottled pigmentation</td>
<td>Bil: slow pupillary response</td>
<td>Bil: highly reduced photopic and scotopic ERG</td>
<td>Bil: normal retinal thickness</td>
</tr>
<tr>
<td>6 / M / 28</td>
<td>None found</td>
<td>Bil: central, steady, maintained</td>
<td>R: +1.0/-3.75 x 125</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7 / F / 15</td>
<td>None found</td>
<td>Bil: 1.0</td>
<td>R: -0.5 x 180</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>Bil: normal</td>
<td>-</td>
<td>Bil: normal</td>
</tr>
</tbody>
</table>

<sup>a</sup> indicates a genetic mutation that has been identified in Joubert syndrome patients.
<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Eye Details</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 / F / 29&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AHI1</td>
<td>R: 0.2 L: 0.16</td>
<td>L: +0.5/-1.0 x 180</td>
<td>Bil: normal</td>
<td>Bil: retinal thickness</td>
</tr>
<tr>
<td>9 / M / 23</td>
<td>RPGRIP1L</td>
<td>Bil: central, steady, maintained</td>
<td>R: -4.75/-3.5 x 165 L: -2.25/-2.25 x 180</td>
<td>Bil: normal</td>
<td>Bil: sluggish pupillary response</td>
</tr>
<tr>
<td>10 / M / 9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>None found</td>
<td>Bil: central, steady, maintained</td>
<td>R: +5.5/-1.75 x 125 L: +8.0/-1.25 x 130</td>
<td>Bil: normal</td>
<td>Bil: sluggish pupillary response</td>
</tr>
</tbody>
</table>

**BCVA:** best corrected visual acuity; **ERG:** electroretinogram; **OCT:** optical coherence tomography; **M:** male; **Bil:** bilateral; **R:** right; **L:** left; **F:** female

<sup>a</sup>siblings
<sup>b</sup>parenteral consanguinity
<sup>c</sup>congenital cataract
### Table 2. Oculomotor findings in patients with Joubert syndrome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Eye Movement Findings</th>
<th>Motility</th>
<th>Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nystagmus</td>
<td>Smooth pursuit</td>
<td>Head thrusts</td>
</tr>
<tr>
<td></td>
<td>Saccades</td>
<td>Quick phases</td>
<td>Reflexive</td>
</tr>
<tr>
<td>1</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>2</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>3</td>
<td>Pendular rotatory</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>4</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>5</td>
<td>Pendular rotatory</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>7</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>8</td>
<td>Pendular rotatory</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>9</td>
<td>Absent</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>10</td>
<td>Absent</td>
<td>Absent</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

VOR: vestibulo-ocular reflex; Bil: bilateral
quick phases of VOR or OKN
saccades generated in response to a novel stimulus (aurally and visually guided saccades)
head thrusts noted during saccades tasks