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, 10 consecutive patients, who met the revised diagnostic criteria of JS were included. Mutation analysis was carried out in all the cases. Each patient underwent a comprehensive neuro-ophthalmological 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 and *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 the earlier 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 showed the predictive value of *CEP290* and *AHI1* mutations for retinal involvement.

Eye (2010) 24, 222–225; doi:10.1038/eye.2009.116; published online 22 May 2009

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.^{1,2} Diagnostic criteria in JS include hypotonia, ataxia, global developmental delay, and the neuroradiological finding of ‘molar tooth sign’.^{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.⁵

Ocular and oculomotor involvement is common in JS.^{4,6–10} However, findings differ considerably because of a wide range of phenotypic variability among patients with JS.

Materials and methods

In a retrospective study, 10 consecutive patients, who met the revised diagnostic criteria of JS were included.³ Patients’ (three females) ages ranged from 8 to 29 years (mean: 18.2 years). Each patient underwent a comprehensive neuro-ophthalmological examination including assessment of ocular alignment and motility.

Results

The clinical data for each patient are summarized in Tables 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 (Figure 1). In four patients the pigmentation of the peripheral retina was mottled and visual acuity was decreased (Patient 3, 4, 5 and 8).

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Received: 2 December 2008

Accepted in revised form: 17 April 2009

Published online: 22 May 2009

Proprietary interest: None

Table 1 Ocular findings in patients with Joubert syndrome

Patient/sex/ age (years)	Genetic mutation	BCVA (Snellen charts)	Cycloplegic refraction	Anterior segment	Fundus	Pupillomotor testing	Full-field ERG	OCT
1/M/8	None found	Bil: 1.0	R: +2.0/-0.75 × 180 L: +2.0/-0.75 × 180	Bil: normal	Bil: normal	Bil: normal	—	—
2/M/16	None found	R: 0.8 L: 1.0	R: +2.25/-0.5 × 170 L: +2.5/-0.25 × 180	Bil: normal	Bil: normal	Bil: normal	Normal	Bil: normal retinal thickness
3/M/20 ^a	CEP290	Bil: 0.1	R: +7.5/-1.25 × 5 L: +7.5/-2.0 × 5	Bil: normal	Bil: cellophane maculopathy, peripheral retina with mottled pigmentation, attenuated retinal arterioles	Bil: very sluggish pupillary response, sometimes even paradox light reaction	Bil: absent	Bil: reduced retinal thickness
4/M/18 ^a	CEP290	R: 0.63 L: 0.8	R: +2.0/-2.0 × 10 L: +2.0/-2.0 × 180	Bil: normal	Bil: optic nerve drusen, peripheral retina with slightly mottled pigmentation	Bil: normal	Bil: highly reduced photopic and scotopic ERG	Bil: normal retinal thickness
5/F/16	None found	Bil: 0.5	R: -4.0/-3.5 × 175 L: -3.5/-3.5 × 180	Bil: normal	Bil: optic nerve drusen, cellophane maculopathy, peripheral retina with slightly mottled pigmentation	Bil: slow pupillary response	Bil: highly reduced photopic and scotopic ERG	Bil: normal retinal thickness
6/M/28	None found	Bil: central, steady, maintained	R: +1.0/-3.75 × 125 L: -0.5/-2.5 × 20	Bil: normal	Bil: normal	Bil: normal	—	—
7/F/15	None found	Bil: 1.0	R: -0.5 × 180 L: +0.5/-1.0 × 180	Bil: normal	Bil: normal	Bil: normal	—	Bil: normal retinal thickness
8/F/29 ^b	AHI1	R: 0.2 L: 0.16	R: -4.75/-3.5 × 165 L: -2.25/-2.25 × 180	Bil: normal	Bil: retina with mottled pigmentation, attenuated retinal arterioles	Bil: sluggish pupillary response	Bil: absent	Bil: reduced retinal thickness
9/M/23	RPGRIPI1L	Bil: central, steady, maintained	R: -4.0/-1.0 × 10 L: -3.0/-1.5 × 180	Bil: normal	Bil: normal	Bil: normal	—	—
10/M/9 ^c	None found	Bil: central, steady, maintained	R: +5.5/-1.75 × 125 L: +8.0/-1.25 × 130	R: quiet pseudophakia L: normal	Bil: normal	Bil: sluggish pupillary response	—	—

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

^aSiblings.^bParenteral consanguinity.^cCongenital cataract.

Table 2 Oculomotor findings in patients with Joubert syndrome

Patient	Eye movement findings				Motility		Strabismus		
	Nystagmus	Smooth pursuit	Saccades		Head thrusts ^a	VOR cancellation			
			Quick phases ^b	Reflexive ^c		VOR		VOR	
1	Absent	Decreased	Decreased	Decreased	Absent	Normal	Decreased	Bil: overaction of the inferior oblique muscle	Orthophoria
2	Absent	Decreased	Decreased	Decreased	Present	Normal	Decreased	Bil: overaction of the inferior oblique muscle	Alternating esotropia
3	Pendular rotatory	Decreased	Decreased	Decreased	Absent	Normal	Absent	Bil: limitation of elevation, convergence insufficiency	Alternating esotropia
4	Absent	Decreased	Decreased	Decreased	Absent	Normal	Absent	Bil: convergence insufficiency	Orthophoria
5	Pendular rotatory	Normal	Normal	Normal	Absent	Normal	Normal	No limitation	Compensated esophoria
6	Absent	Decreased	Decreased	Decreased	Present	Normal	Decreased	Bil: alternating hyperdeviation on abduction	Compensated esophoria
7	Absent	Decreased	Decreased	Decreased	Absent	—	—	No limitation	Orthophoria
8	Pendular rotatory	Decreased	Decreased	Decreased	Present	Normal	Absent	Bil: limitation of abduction and elevation	Alternating esotropia
9	Absent	Decreased	Decreased	Decreased	Present	Normal	Decreased	Bil: limitation of abduction	Orthophoria
10	Absent	Absent	Decreased	Decreased	Absent	Normal	Decreased	Bil: alternating hyperdeviation on abduction	Alternating exotropia

Bil, bilateral; VOR, vestibulo-ocular reflex.

^aHead thrusts noted during saccades tasks.

^bQuick phases of VOR or OKN.

^cSaccades generated in response to a novel stimulus (aurally and visually guided saccades).

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, whereas one had an alternating exotropia.

Discussion

It is surprising that we found bilateral optic disc drusen in two patients. The prevalence of optic nerve drusen has been estimated between <0.4% and 3.7%.¹¹ 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%.¹¹ The association between JS and optic disc drusen has not been earlier 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.^{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 the patients with *AHI1* (patient 8) and *CEP290* mutations (patients 3 and 4).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.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.^{7,9,10} Lambert *et al.*⁷ described an alternating hyperdeviation on abduction as a characteristic feature, which was seen in two of our patients. 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 the findings of earlier studies.^{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

Figure 1 (a) Colour fundus photograph of the right eye showing optic disc drusen (patient 5). (b) Autofluorescence of the right eye showing optic disc drusen (patient 5).

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.

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