Article

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Joubert syndrome

Large clinical variability and a unique neuroimaging aspect

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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.

Síndrome de Joubert: grande variabilidade clínica e uma neuroimagem característica

RESUMO

A síndrome de Joubert (SJ) é uma doença hereditária, autossômica recessiva, caracterizada por hipotonia, hipoplasia do *vermis* cerebelar, anormalidades oculares (p.ex., retinite pigmentar, apraxia oculomotora e nistagmo), cistos renais e fibrose hepática. Anormalidades respiratórias tais como apnéia e hiperpnéia podem estar presentes, assim como deficiência mental. Pelo menos sete *loci* e cinco genes diferentes associados à SJ já foram identificados. Este artigo relata cinco crianças com SJ, pertencentes a diferentes famílias. Todos os pacientes compartilham a mesma anormalidade típica da RM, conhecida como *sinal do dente molar*, e apresentam ampla variabilidade clínica em relação ao desempenho cognitivo, comprometimento visual e alterações extra-neurológicas.

Palavras-chave: síndrome de Joubert, sinal do dente molar, malformação de cerebelo.

Joubert syndrome (JS) is a rare genetically heterogeneous inherited disorder with an estimated prevalence in the United States of 1 in 100,000[1]. 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[2]. In some cases, Leber congenital amaurosis, pigmentary retinopathy, renal and hepatic abnormalities can also be found[1,3,4]. The presence of a characteristic neuroimaging finding, known as *molar tooth sign*, is highly suggestive of JS diagnosis[2]. 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 (Figure)[1,2]. Recently, Valente, Brancati and Dallapiccola[3] 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-

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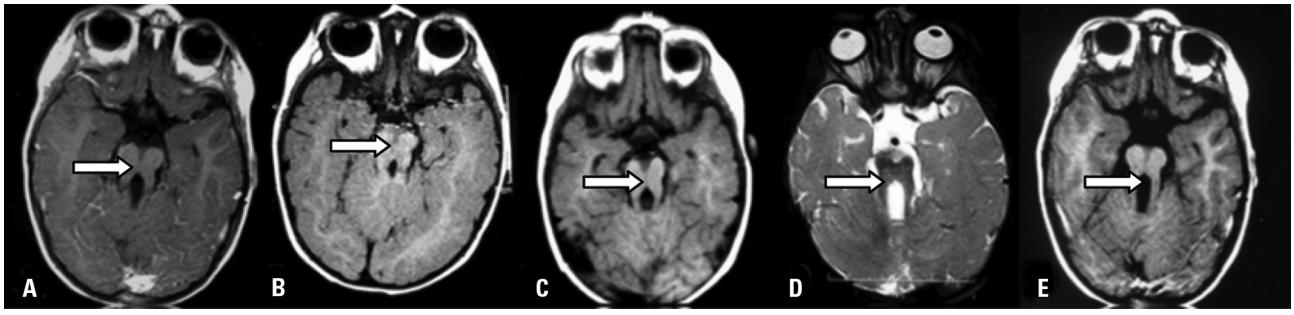

Figure. Brain axial MRI of patients 1 [A], 2 [B], 3 [C], 4 [D] and 5 [E], showing molar tooth sign (arrows).

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

Locus	Location	Gene	Protein	Reference
JBTS1	9q34.3	Not known	Not known	Saar et al., 1999[5]
JBTS2	11p12-q13.3	Not known	Not known	Keeler et al., 2003[6]
JBTS3	6q23.3	*AHI1*	Jouberin	Ferland et al., 2004[7] Dixon-Salazar et al., 2004[8]
JBTS4	2q13	*NPHP1*	Nephrocystin-1	Parisi et al., 2004[9]
JBTS5	12q21.34	*CEP290 (NPHP6)*	Nephrocystin-6	Sayer et al., 2006[10]
JBTS6	8q21.1-q22.1	*TMEM67*	Meckelin	Baala et al., 2007[11]
JBTS7	16q12.2	*RPGRIP1L*	Protein phantom	Delous et al.[12], Arts et al.[13], 2007

ria 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 mesaxial or pre-axial polydactylia.

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[3]. In large series of patients with JS, mutations in *AHI1* are found in 10 to 15% of cases and of *CEP290* in 10%[1].

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

Table 2. Diagnostic features of Joubert syndrome.

Patient	Gender	Age at diagnosis (yr)	Age at ascertainment (yr)	Parental consanguinity	Face	Speech	Independent walk	Ophthalmological evaluation			Mental retardation	Laboratory & Ultrasound
								Ocular abnormalities	Fundoscopy	ERG		
1	F	4	6	Y, first cousin	Hypertelorism, arched eyebrow, large nasal base	Dyslalic	Y	Oculomotor apraxia, strabismus	Normal	Not done	Y, mild	Normal
2	M	2	7	N	Large forehead	Dysarthric	Y	Disconjugate eye movements	Normal	Not done	Y, mild	Normal
3	F	2	4	N	Tent shaped upper lip	Isolated words	Y, ataxic	Erractic eye movements	Retinal dystrophy	Extinct	Y	Elevated liver enzimes
4	M	4	4	N	Narrow forehead	Absent	N	Erractic eye movements	Leber congenital amaurosis	Extint	Y, with autistic features	Renal cysts Parenquimatous nephropathy
5	F	3	13	N	Large forehead, deep set eyes	Absent	Y, ataxic	Erractic eye movements	Retinal dystrophy, coloboma	Extint	Y, with autistic features	Elevated liver enzimes Parenquimatous nephropathy

ERG: electroretinogram; N: no; Y: yes; yr: year.

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 parenquimatous 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 criteria[1,2], 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.

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