

Joubert syndrome and related disorders

Zespół Joubert i schorzenia pokrewne

Justyna Paprocka, Ewa Jamroz

Child Neurology Department, Silesian Medical University, Katowice, Poland

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Abstract

The cerebellum plays a role not only in motor control but also in motor learning and cognition. Joubert syndrome is a rare heterogeneous inherited genetic disorder characterized by ataxia, hypotonia, developmental delay, and at least one of the following features: neonatal respiratory disturbances or abnormal eye movement. The estimated frequency of Joubert syndrome in the United States is around 1 : 100 000. The term Joubert syndrome and related disorders (JSRD) has been recently coined to describe all disorders presenting with molar tooth sign on brain neuroimaging. Joubert syndrome is believed to be a representative of a new group of disorders named ciliopathies. The identification of seven causal genes (*NPHP1*, *AHI1*, *CEP290*, *RPGRIP1L*, *TMEM67/MKS3*, *ARL13B*, *CC2D2A*) has led to substantial progress in the understanding of the genetic basis of Joubert syndrome. The authors focus on clinical presentation of JSRD, differential diagnosis and molecular background.

Key words: Joubert syndrome, children, classification, clinical presentation.

Classification of Joubert syndrome and related disorders (JSRD)

Marie Joubert, a French neurologist, was the first to report Joubert syndrome (OMIM 213 300) in five patients who presented breathing disorders and abnormal

Streszczenie

Mózdzek odgrywa istotną rolę w kontroli nie tylko funkcji ruchowych, ale także procesów poznawczych. Zespół Joubert jest rzadkim heterogennym schorzeniem uwarunkowanym genetycznie, charakteryzującym się występowaniem ataksji, hipotonii, opóźnienia rozwoju psychoruchowego, a także jednej z następujących cech: zaburzeń oddychania w okresie noworodkowym lub nieprawidłowych ruchów gałek ocznych. Szacowana częstość występowania zespołu Joubert i zespołów pokrewnych w USA wynosi ok. 1 : 100 000. Zespół Joubert i zespoły pokrewne obejmują schorzenia, w których występuje obraz „zęba trzonowego” w badaniu obrazowym układu nerwowego. Zespół Joubert stanowi przykład nowej grupy chorób nazywanych ciliopatiami. Identyfikacja 7 genów (*NPHP1*, *AHI1*, *CEP290*, *RPGRIP1L*, *TMEM67/MKS3*, *ARL13B*, *CC2D2A*) poczyniła znaczący postęp w zrozumieniu genetycznych podstaw zespołu Joubert. Autorzy prezentują objawy kliniczne zespołu Joubert i schorzeń pokrewnych, diagnostykę różnicową i podłoże genetyczne.

Słowa kluczowe: zespół Joubert, dzieci, klasyfikacja, obraz kliniczny.

eye movements, ataxia, and mental retardation associated with agenesis of the cerebellar vermis [1]. Maria *et al.* proposed the diagnostic criteria for Joubert syndrome: hypotonia, ataxia, developmental delay and ‘molar tooth sign’ [1,2]. The detailed classification of JSRD is presented in Table 1 [3-7].

Correspondence address: Justyna Paprocka, Child Neurology Department, Medical University of Silesia, ul. Medyków 16, 40-752 Katowice, Poland, phone: +48 32 207 16 00, fax: +48 32 207 16 15, e-mail: justyna.paprocka@interia.pl

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Table 1. Classification of Joubert syndrome [3-12]

Clinical subtypes	Main features	Associated features	Molecular background
Pure Joubert syndrome (JS)	molar tooth sign		mutation in many genes: <i>JBTS1/INPP5E</i> (9q34.3), <i>JBTS2/TMEM216</i> (11q13), <i>JBTS3/AHI1</i> (6q23), <i>JBTS4/NPHP1</i> (2q13), <i>JBTS5/CEP290</i> (12q21,32), <i>JBTS6/TMEM67</i> (8q21), <i>JBTS7/RPGRIP1L</i> (16q12.2), <i>JBTS8/ARL13B</i> (3q11.2), <i>JBTS9/CC2D2A</i> (4p15.3), <i>JBTS10/OFD1</i> (Xp22.3)
Joubert syndrome with ocular defect (JS-O)	molar tooth sign, retinal dystrophy, including Leber congenital amaurosis		<i>AHI1</i>
Joubert syndrome with renal defect (JS-R)	molar tooth sign, nephronophthisis (renal fibrocystic disease)		<i>NPHP1</i> <i>RPGRIP1L</i>
Joubert syndrome with oculorenal defects (JS-OR)	molar tooth sign retinal dystrophy (often with Leber congenital amaurosis), nephronophthisis	in some patients – congenital hepatic fibrosis	<i>CEP290</i>
Joubert syndrome with hepatic defect (JS-H)	molar tooth sign, congenital hepatic fibrosis	colobomas, nephronophthisis	<i>TMEM67</i>
Joubert syndrome with oro-facio-digital defects (JS-OFD)	molar tooth sign, lobulated/bifid tongue (including hamartomas), polydactyly	cleft lip/palate	<i>TMEM216</i>

Clinical presentation

The typical dysmorphic features in Joubert syndrome include prominent forehead, upturned nose, and open mouth. The main neurological symptoms in JSRD are hypotonia, ataxia, developmental delay, intellectual disability, and abnormal ocular movements [5-8]. Epileptic seizures in association with Joubert syndrome are very rare (3%) [3-6]. In the neonatal period there is an altered respiratory pattern with episodes of apnea and hyperpnea or episodes of hyperpnea alone. These symptoms can range from short intervals to prolonged attacks requiring assisted ventilation. They usually improve with age and disappear around the sixth month of life. Abnormal eye movements comprise oculomotor apraxia, primary position nystagmus, and occasionally strabismus or ptosis [7,8,13].

All patients diagnosed with JSRD have developmental/intellectual disability. Reported developmental and intelligence quotients are usually between 30 and 80 [4,7]. The major abnormality in JSRD is in the cerebellum.

However, accompanying abnormalities of the brainstem (as known in Joubert syndrome) and/or cerebrum might also have an influence on cognitive functions. Thus, the cerebellar role for the cognitive problems in these children seems to be important, but additional cerebral dysfunction cannot be ruled out. Although cerebellar contribution to cognitive problems is strongly suggested by volumetric and structural abnormalities, a secondary transsynaptic effect on the cerebellum by abnormalities/dysfunction of other cerebral regions has to be considered [14,15]. A transsynaptic effect, however, cannot explain all findings; a model with a disturbed interplay between cerebellum and cerebrum might explain the cognitive dysfunction observed in these children [14].

Another organ frequently involved in JSRD is the retina. In Leber congenital amaurosis, the clinical presentation may range from cortical blindness to retinal dystrophy with different course and different degree of preserved vision [5-7]. A rare cause of visual disturbances described in JSRD is coloboma; its frequency rises to 30% in Joubert syndrome with hepatic defect [13,15].

Renal disorders affect almost 25% of patients with JSRD [13]. Saraiva *et al.* reported renal abnormalities in 30% of cases and Doherty found them in about 23% of patients [5,6,16]. In most cases, they present as a structural tubule-intestinal disease with irregular, thickened basal membrane or a tubular epithelium, progressive interstitial fibrosis and small cysts at the corticomedullary junction. The first symptoms of isolated nephronophthisis (NPH) may remain unrecognized and manifest as polyuria and polydipsia. In the late first decade of life, acute or chronic renal insufficiency occurs. In some patients renal disease may manifest as cystic dysplastic kidney. Such abnormality may also be observed in Dekaban-Arima syndrome and in Meckel syndrome [3-5].

Congenital hepatic fibrosis present in a minority of patients with JSRD results from malformation of the ductal plate with cystic dilatation of biliary structures and fibrous enlargement of the portal tracts. The disease may manifest with elevated liver enzymes, hepatosplenomegaly or even portal hypertension, esophageal varices and end-stage liver cirrhosis [3,5,7-9].

The most often reported skeletal abnormality is postaxial polydactyly with a frequency of about 8-16% [4,7]. With age, scoliosis may appear, which is likely to correlate with the degree of hypotonia and require monitoring during puberty.

Neuroimaging studies

'Molar tooth sign' (on axial magnetic resonance imaging of the pons) depends on a specific malformation of the brainstem and cerebellum, characterized by deepened interpeduncular fossa, hypoplasia of the vermis and thickened and elongated superior cerebellar peduncles [3-9]. Such abnormalities correspond with severe hypoplasia/dysplasia of the cerebellar vermis with midline clefting, fragmentation of cerebellar nuclei and heterotopias of Purkinje-like neurons, along with dysplasia of pontine and medullary structures such as the basis pontis, reticular formation, inferior olivary, dorsal column and solitary tract nuclei [17,18].

Other central nervous system malformations affecting the outcome and prognosis have been described. Hydrocephalus, abnormalities of the corpus callosum, white matter cysts, hypothalamic hamartomas, absence of the pituitary gland, migration defects, cortical organization defects (polymicrogyria), and meningoencephalocele have been reported [16,17]. Approximately 10% of individuals with Joubert syndrome have abnor-

mal collections of cerebrospinal fluid in the posterior fossa that may resemble Dandy-Walker malformation [4,5,7]. According to Doherty *et al.*, the brain malformation in Joubert syndrome comprises at least several components: decreased vermis size with probably decreased cell numbers, aberrant axonal path finding (disrupted decussation of the superior cerebellar peduncles and pyramids), possible abnormal neuronal migration (fragmented dentate nuclei, cerebellar and cortical heterotopias, pachygyric inferior olives) [5,6].

Genetic backgrounds

The genes recognized in JSRD encode mediators of signal transduction pathways at the primary cilium. In the cerebellum, primary cilia have been identified in both Purkinje cell and granule cell progenitors. There are two theories explaining the vermis hypoplasia in Joubert syndrome [8-12]. Decreased granule cell proliferation results in vermis hypoplasia, possibly due to aberrant sonic hedgehog (SHH) signaling through defective cilia. According to the second one, there are subtle alterations in specification of the mid-hindbrain boundary and rhombomere identities.

Recent advances in genetic testing have revealed that approximately 25% of patients with either classic Joubert syndrome or JSRD have a mutation in the *AHI1* or the *CEP290/NPHP6* genes [8-12]. All of the genes involved in JSRD pathology have been associated with the primary cilium and basal body, which allows Joubert syndrome to be included in the group of disorders named ciliopathies [18-21]. Genetic testing for JSRD is based on genotype-phenotype correlations and can be prioritized based on clinical features. According to Doherty *et al.*, patients with Joubert syndrome and liver disease should be tested for *TMEM6* mutations followed by *CC2D2A* and *RPGRIP1L* [5,6]. Retinal and renal abnormalities should be checked for *CEP290* mutations. Isolated renal disease should prompt *RPGRIP1L* testing and isolated retinal abnormalities should prompt testing for *AHI1* followed by *CEP290* [9-12].

Differential diagnosis

Molar tooth sign may also be seen in cerebello-oculo-renal syndrome, Dekaban-Arima syndrome, COACH syndrome (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, hepatic fibrosis), Varadi-Papp syndrome (cerebellar vermis hypoplasia, oral frenula, tongue hamar-

Table 2. Differential diagnosis of JS and JSRD

Disease	Clinical presentation	Molecular basis
Dandy-Walker malformation	cerebellar hypoplasia of the vermis and/or hemispheres with an enlarged retrocerebellar cerebrospinal fluid collection continuous with the fourth ventricle, agenesis or hypoplasia of the corpus callosum and hydrocephalus; delayed motor development, hypotonia, and ataxia	3q24
X-linked cerebellar hypoplasia	hypotonia at birth and moderate mental retardation, ataxia, macrocephaly, seizures, strabismus and genital hypoplasia	Xp11.21-q21.3
ataxia and oculomotor apraxia type 1 (AOA1) ataxia and oculomotor apraxia type 2 (AOA2)	childhood-onset progressive cerebellar ataxia, cerebellar atrophy, oculomotor apraxia, peripheral neuropathy, mental retardation	9p13.3
congenital disorders of glycosylation	delays in development, hypotonia, ataxia, and strabismus	different genetic loci
3-C syndrome (cranio-cerebello-cardiac syndrome, Ritscher-Schinzel syndrome)	cardiac malformation, cerebellar malformation, cleft palate or ocular coloboma or four of the following seven findings: prominent forehead, prominent occiput, hypertelorism, down-slanting palpebral fissures, low-set ears, depressed nasal bridge, and micrognathia	unidentified gene locus
pontocerebellar hypoplasias/atrophies type 1, 2A-C,3,4,5,6	cerebellar vermis hypoplasia, hypoplasia of the pons	1 – 14q32 2 – 17q25.1; 3p25.1; 19q13.4 3 – 7q11-q21 4 – 17q25.1 6 – 6q16.1
oro-facio-digital (OFD) syndromes: II (Mohr syndrome) and III	OFD II: tongue tumors with abnormal frenula, midline facial clefts, polydactyly, cerebellar vermis agenesis OFD III: mental retardation and postaxial polydactyly	unidentified gene locus
Meckel-Gruber syndrome	occipital encephalocele, polydactyly, polycystic kidneys, liver developmental defects (hepatic fibrosis, bile duct proliferation, ductal plate malformation)	

tomas, and midline cleft lip, as well as the distinctive feature of central polydactyly with a Y-shaped metacarpal), Malta syndrome, Senior-Loken syndrome (retinopathy and juvenile-onset nephronophthisis), and Bardet-Biedl syndrome [3-5,7,15,16].

Other conditions to consider in the differential diagnosis of Joubert syndrome are those with cerebellar vermis hypoplasia or dysgenesis without the molar tooth sign on MRI: Dandy-Walker malformation, X-linked cerebellar hypoplasia, ataxia and oculomotor apraxia type 1 (AOA1) and ataxia and oculomotor apraxia type 2 (AOA2), congenital disorders of glycosylation (CDG), 3-C syndrome (cranio-cerebello-cardiac syndrome, Ritscher-Schinzel syndrome), the pontocerebellar hypoplasias/atrophies, oral-facio-digital (OFD) syndromes II and III, and Meckel-Gruber syndrome [15,16] (Table 2).

Prognosis

The prognosis of Joubert syndrome is poor. The 5-year survival is about 50% [3-7,15]. Once the diagnosis of Joubert syndrome is made, it is recommended to perform a comprehensive functional and morphological examination of the liver and kidney. Ophthalmologic evaluation for visual acuity, tracking ability, and development of retinal dystrophy should be performed in all patients with JSRD, especially in individuals with *AHI1* or *CEP290* mutations, because they are at high risk for retinal dystrophy [9-12]. It is well known that clinical features may vary between and within the same family due to genetic heterogeneity and phenotype diversity. Despite the remarkable advances in the genetics of Joubert syndrome and related disorders, little is known about how the gene defects may influence brain function, development and structures [18,19,21].

Disclosure

Authors report no conflict of interest.

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