JOUBERT SYNDROME IN TWO SIBS AND THE DIFFERENTIAL DIAGNOSIS OF CEREBELLAR VERMIAN DYSGENESIS

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ABSTRACT

We present two siblings with Joubert syndrome. Malformation of the cerebellar vermis, abnormal eye movements, developmental delay and retinitis pigmentosa are described. The differential diagnosis of vermian dysgenesis is discussed. At present the genes for Joubert syndrome and the overlap syndromes are not identified and the differential diagnosis of these syndromes is not possible by molecular genetic methods. Therefore the clinical and neuroradiological overlap with other syndromes should be recognized.

Key Words: Hypo/aplasia of cerebellar vermis, Joubert syndrome, Overlap syndromes

INTRODUCTION

Joubert syndrome (JS) was first described by Joubert et al in 1969(1). The characteristic features of this syndrome are neonatal respiratory problems, abnormal eye movements, ataxia, retinitis pigmentosa and mental retardation. Subsequent reports of Joubert syndrome described additional cerebral and extracerebral malformations. Chorioretinal coloboma, occipital meningocel, agenesis of corpus callosum, polydactyly, tongue nodules and renal cysts have been reported in association with JS (1-5). Joubert syndrome is inherited as an autosomal recessive trait. Males predominate by more than 2:1(6).

Joubert patients usually present as neonates with breathing abnormalities that improve with age. 44% of children had respiratory abnormalities in Kendall's series (2). Nystagmus or supranuclear abnormalities of eye movements are common. Retinal dystrophies are reported in 44% of children with JS (2).

We report two siblings with Joubert syndrome. The review of the related literature demonstrates that various syndromes overlap with Joubert syndrome. Because of the difficulty in establishing the boundaries of this syndrome it was necessary to recognize the other syndromes with similar features. The cardial diagnostic criteria for Joubert syndrome was referenced from Saraiva et al (4).

Case 1

A 4 month-old-baby was referred to neurologist for poor head control. His older brother (case 2) was developmentally delayed and the etiology was undetermined. The baby was delivered fullterm after a normal pregnancy. He had respiratory problems during neonatal period. Tachypnea was first noted 12 hours after birth with episodes up to 80/minute. He had been diagnosed as""transient tachypnea of newborn" (TTN). Blood gases demonstrated respiratory alkalosis and investigations including sepsis work-up, echocardiography, cerebral, renal ultrasonograhy were all negative. The respiratory abnormalities improved but the baby was noted to have some regression of head control and jerky eye movements at three months of age. Neurological examination showed truncal hypotonia, poor head control and horizontal jerky nystagmus. Retinal examination did not show dystrophic changes, electroretinography (ERG) was not performed. MRI was remarkable for agenesis of cerebellar vermis (Fig. 1).

Case 2

A 9 year-old-boy (the older brother of first case) was examined and previous extensive investigation for his developmental delay was reviewed. He was also product of uneventful pregnancy and uncomplicated delivery. He did not have respiratory problems at birth, however, he was extremely hypotonic through the infancy. His head circumference was recorded at 97th percentile when he was 5 months old. He did not have visual fixation until 2 years of age. He was developmentally delayed but made slow, steady progress throughout childhood. He sat unsupported at 2 years and walked at 6 years old.

On neurological examination, he executed some simple commands but he had difficulty in paying attention to what he was doing. He was unable to express himself in speech. He used a few single words but it was very hard to understand. He had abnormal saccadic eye movements and had hyperdeviation on abduction. He preferred to move his head when changing fixation. Retinal examination showed retinitis pigmentosa. Motor examination demonstrated severe truncal ataxia. Telengiectasis or other cutaneous markers for neurological disorders were not present.

Patient was evaluated for ataxia and developmental delay in the past and all work-up were negative including lysosomal enzyme studies performed in Germany, An MRI study at age 3 was mistakenly reported as normal. In fact, this MRI study demonstrated hypoplasia of cerebellar vermis (Fig. 2). Additional studies for serum lactate, ammonia and alpha-feto protein level were normal.

Both children are thought to have the diagnosis of Joubert syndrome. The parants are not related. There was one older brother unaffected.

DISCUSSION

Various syndromes show a similarity to Joubert syndrome and it is difficult to define the boundaries of this syndrome. The syndromes with vermal dysgenesis and common phenotypic features with JS were summarized in Table I (2,4,7-9). Joubert syndrome shows some phenotypic overlap with orofaciodigital (OFD) syndrome type II. The principal features of OFD type II are lingual hamartomas/fibromas, postaxial polydactyly, malformation of the cerebellar vermis, abnormal eye movements, prominent forehead with large anterior fontanel, polycystic kidneys and dublicated hallux (8).

Some cases of Joubert syndrome had been diagnosed as Dandy-Walker syndrome or Dandy-Walker variant. It is important to recognize the distinguishing neuroradiological abnormalities of posterior fossa malformations (6,10). In Joubert syndrome the fourth ventricle is normal or modestly enlarged but there is no hydrocephalus or posterior fossa cyst, so the posterior fossa is not expanded (6). The association between malformation of cerebellar vermis and renal and hepatic disease has also been

Table I. Joubert Syndrome: Differential Diagnosis

	JS	DWS	OFD	LA	COACH	Arima	MGS
Agenesis/Hypoplasia of vermis	+	+	+	?	+	+	+
Cystic enlarged fourth ventricle	-	+					+
hydrocephalus		+					+
occipital meningoencephalocele	±						+
craniofacial anomalies	±	±	+				+
tongue nodules (lingual hamartomas/fibromas)	±		+				
cleft plate		±	±				±
hepatic fibrosis	2 cases				±	±	±
polycystic kidneys	±	±	±			+	±
polydactyly/syndactyly	+	±	+				+
mental retardation	+	±	+				
hypotonia	+		+				
respiratory anomalies	+	±	±				
abnormal eye movements	+		+				
retinal dystrophy	+			+		+	
retinal coloboma	+				+		

JS: Joubert syndrome; **DWS:** Dandy-Walker syndrome; **OFD:** Oro-facio-digital syndrome;

LA: Leber congenital amaurosis; **COACH:** Cerebellar vermis hypo/aplasia, oligophrenia, ataxia, coloboma, hepatic fibrocirrhosis; **MGS:** Meckel-Gruber syndrome

evaluated in the spectrum of cerebello-occulo-hepato-renal syndrome (3).

Pathological examination demonstrates a variable degree of dysplasia of cerebellar vermis in JS. The vermis may be completely absent or show partial agenesis/hypoplasia that affects either the superior or the inferior vermis predominantly (2). Multiple heteropic foci are found in the cerebellar cortex. Associated abnormalities of the cervicomedullary junction include complete absence of the pyramidal decussation, dysplasia of the olivary and paraolivary nucleus, and hypoplasia of the nucleus gracilis, solitary fascicle and descending trigeminal tracts (2). The episodic tachypnea and apnea are most likely due to abnormalities in the solitary fascicle and the nuclei gracili of the brainstem that control afferent respiratory impulses (2). Joubert syndrome appears to be one of a spectrum of congenital malformation syndromes involving the central nervous system, eye, kidneys and may be liver. The embryological defect has not been determined. The complex anomalies may be all due to a disturbance in the normal epithelio-mezenchymal interactions (3). From an embryological standpoint, some other authors have pointed out that the association of the anomalies

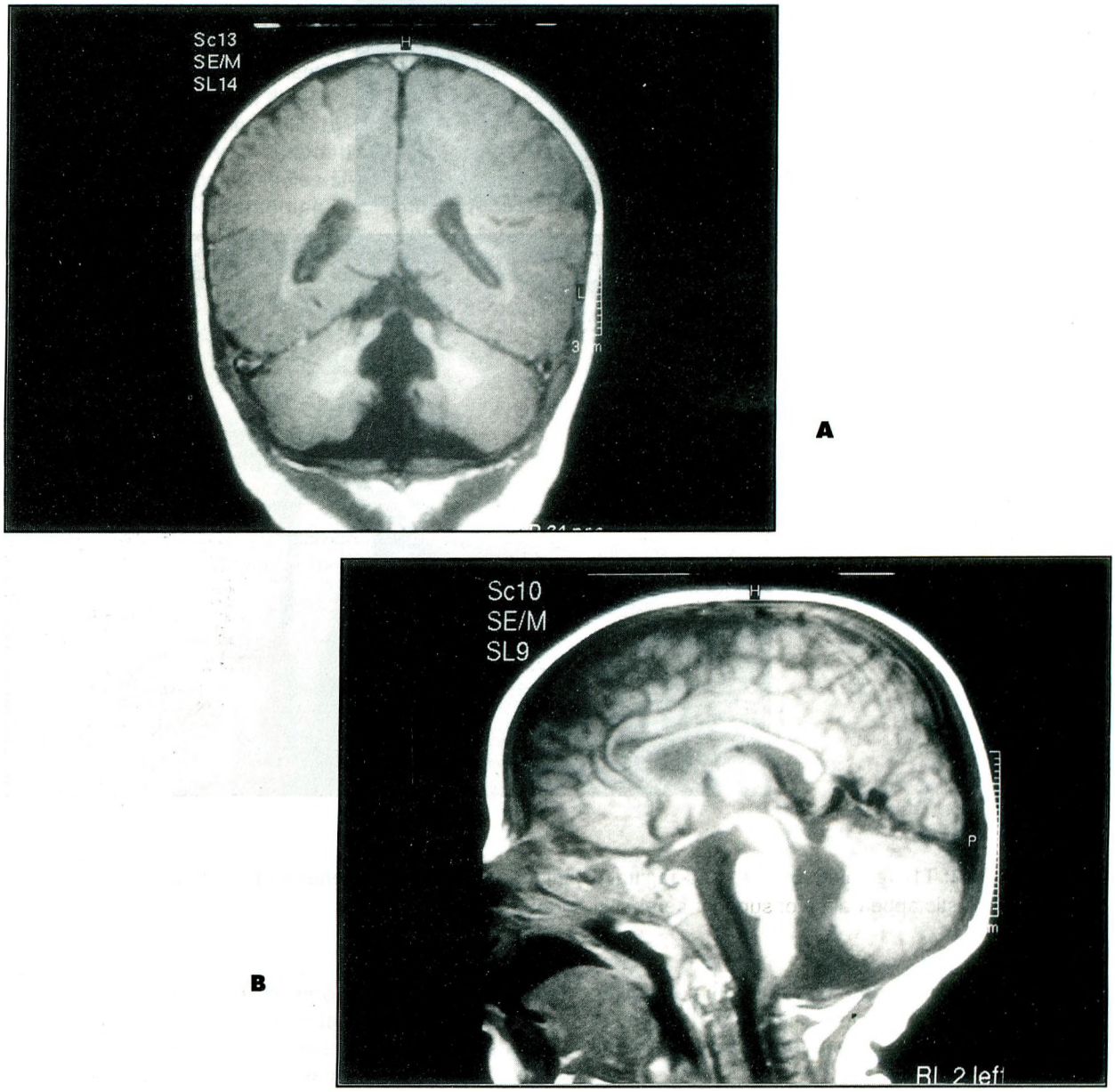
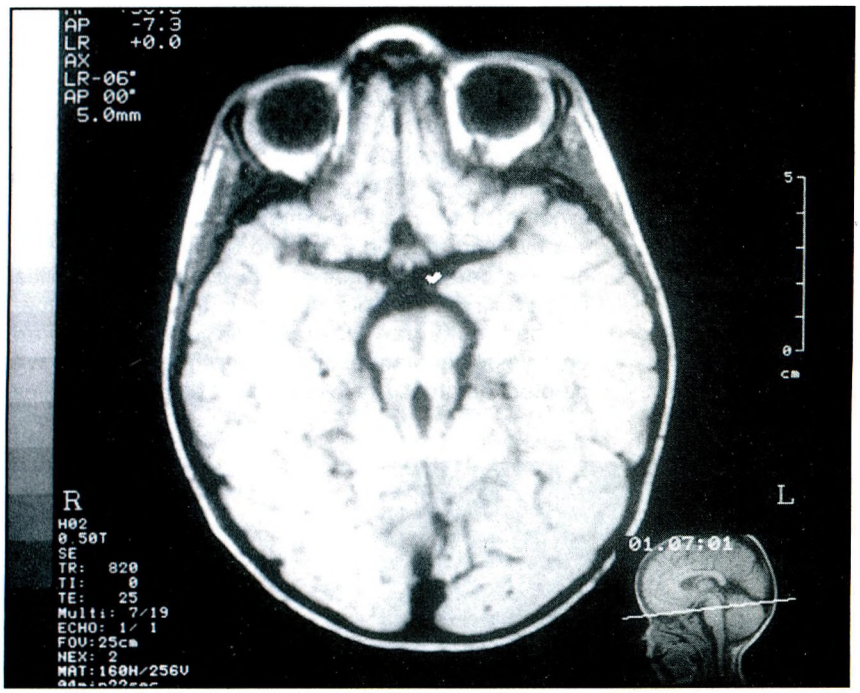
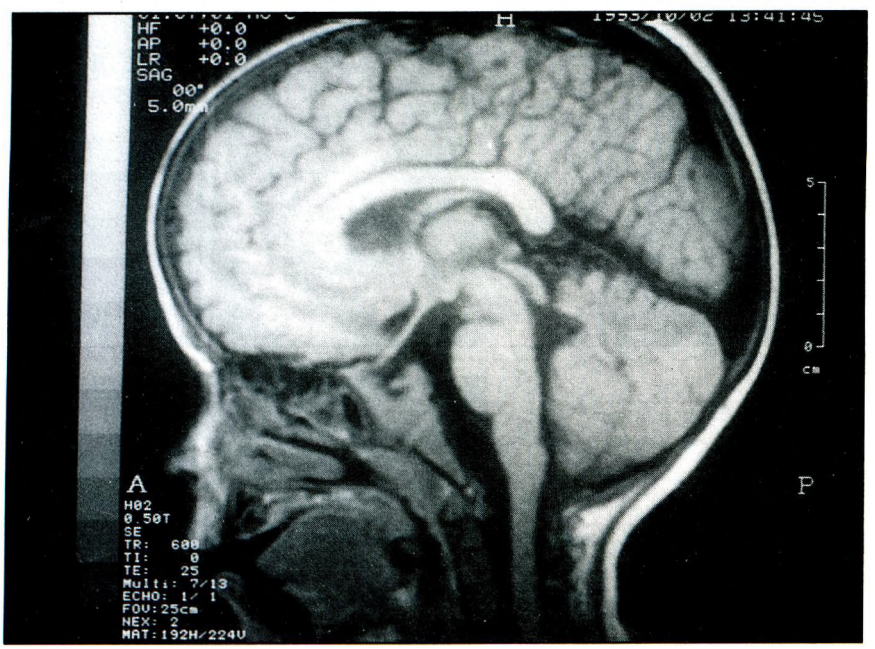


Fig. 1: Case 1: T1-weighted coronal (A) and sagittal (B) images show agenesis of cerebellar vermis and the dysplastic appearance of superior cerebellar cortex



A



B

Fig. 2: Case 2: T1-weighted axial (A) and sagittal (B) images show partial agenesis of cerebellar vermis and dysplastic appearance of superior cerebellar cortex

cannot be explained on the basis of common timing; for example occular abnormalities are thought to occur at a much later embryonic stage than the formation of vermis (3).

Wide spectrum of malformations raise the question whether a multisystemic metabolic disorder is responsible for abnormalities or not. Is an abnormal gene coding an abnormal protein and causing different organ involvement? It is known that some metabolic disturbances can cause the developmental abnormalities in central nervous system. Carbonhydrate-deficient glycoprotein (CDG) syndrome was mentioned based on the similarities

with JS (11). In this disease, glycosilation of many glycoproteins is impaired. CDG syndrome is characterized with cerebellar atrophy, psychomotor retardation, abnormal eye movements, retinal dystrophy, stroke-like episodes, progressive weakness of lower extremities, cardiac findings, skeletal abnormalities and in some patients, also renal cysts and liver disease (11,12). Our cases do not show the characteristic features of CDG syndrome. Buisonniere et al discussed the relationship between peroxisomal dysfunction and JS since 3 cases of Joubert syndrome have been reported with pipecolic acidemia (13). The etiology of this syndrome is unknown. Differently named syndromes with overlap features may be resulting from a same mutant gene which exhibits considerable pleiotropy. The genes for JS and for other similar syndromes mentioned above are not yet identified, separation of these syndromes is therefore (at present) not possible by molecular genetic methods. Metabolic investigations such as peroxysomal enzyme studies should be considered. The better understanding of embryogenesis, neuroimaging characteristics, genetics and investiations for possible underlying metabolic derangements would lead to better descriptions and classifications of these wide spectrum clinically overlap syndromes.

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