Joubert Syndrome: Clinical and Radiological Characteristics of Nine Patients

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Abstract: Background: Joubert Syndrome (JS) is a rare genetic developmental disorder, first identified in 1969. In patients with JS, certain regions of the brain (mainly cerebellar vermis and brainstem) are underdeveloped or malformed. This can lead to impaired attention, visual, spatial, motor, language and social functional skills. JS is characterized by a host of features, many of which do not occur in every patient. **Aim of the study:** To spotlight and increase awareness of clinical profile and neuroimaging findings of children with Joubert syndrome. **Methods:** This is a retrospective case series study of patients with JS who attended the Pediatric Neurology Clinic in Aladan and Alfarawanya Hospitals in Kuwait, from September 2007 to September 2012. Clinical and radiological data were obtained from the patient medical records. **Results:** Cerebellar vermis hypoplasia/aplasia and apnea were present in all patients, polydactyl in 3 of 16; renal problems with cysts in 5 patients and 11 of 16 had abnormal electroretinograms (ERGs). Blood investigations of organic acids, amino acids and very-long-chain fatty acid, were normal in the all the nine patients. **Conclusion:** JS is a rare genetic brain malformation with association of retinal dystrophy and renal abnormalities. The retinal dystrophy may be progressive. The prognosis of patients depends mainly on the degree of brain malformation.

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1. Introduction

JS is a rare autosomal recessive disorder, first identified in 1969 by Marie Joubert **(Joubert, 1969)**, with agenesis of the cerebellar vermis presenting episodic hyperpnoea, abnormal eye movements, ataxia and intellectual disability. Several years later, a pathognomonic midbrain-hindbrain malformation, the "molar tooth sign" (MTS) (distinctive cerebellar and brainstem malformation) on magnetic resonance imaging, was detected first in JS. The term Joubert Syndrome and Related Disorders (JSRD) has been recently adopted to describe disorders presenting the MTS. JSRD include Joubert syndrome (JS), as well as other related conditions showing the MTS, such as the cerebello-oculo-renal syndrome, Dekaban-Arima syndrome, COACH syndrome, Varadi-Papp syndrome and a minority of cases with Senior-Loken syndrome **(Maria *et al.,* 1997; Satran *et al.,* 1999; Gleeson *et al.,* 2004; Francesco Brancati *et al.,* 2011; Sattar & Gleeson, 2011)**.

Most cases of Joubert syndrome are sporadic but in some families, JS appears to be inherited via a recessive gene. The specific gene was recently located on chromosome 6q23.2-q23.3 (AHI1 gene) **(Ferland *et al.,* 2004; Valente *et al.,* 2008)**.

Other physical deformities may be present in JS are polydactyl, cleft lip or palate, tongue abnormalities, hypotonia, encephalocele, meningocele, hydrocephalus, kidney problems, pituitary abnormality and autistic-like behavior. Seizures may also occur. Some children have a mild form of the disorder, with minimal motor disability and good mental development, while others may have severe motor disability and moderate mental retardation **(Maria *et al.,* 1999; Merritt, 2003; Braddock *et al.,* 2006; Khan *et al.,* 2008; Weiss *et al.,* 2009)**. Treatment for JS is symptomatic and supportive. The prognosis depends on whether or not the cerebellar vermis is entirely absent or partially developed.

Joubert syndrome is often missed clinically and radiologically if no enough attention is paid to its subtle and variable clinical presentation. So the objective of the present study is to clarify the clinical and radiological features of JS and to increase awareness of this rare congenital malformation.

2. Subjects and Methods

The study was performed on the patients diagnosed as JS who attended the Pediatric Neurology clinic in Aladan and Alfarawanya Hospitals in Kuwait, from September 2007 to September 2012. Ethical approval was obtained from the hospital's ethics committee, and informed

consent was obtained from the parents of each patient.

Nineteen patients were diagnosed as JS. The diagnosis of JS was based on history (abnormal neonatal breathing), physical and neurological examination (abnormal eye movements, developmental delay, and ataxia) and MRI findings (MTS).

Clinical, radiological and laboratory data were obtained from the patient medical records. The following data were extracted and reviewed; perinatal history, age of onset of symptoms, presenting complaint (apnea, ataxia, visual symptoms, and seizures), laboratory investigations results, urinary tract investigations, and brain computerized tomography (CT), brain magnetic resonance imaging (MRI) scans and EEG. Arrangements were made to recall the patients. Each recalled patient underwent a renal ultrasound and ophthalmological review including slit lamp microscopy of the anterior segment, fundus examination, studying of eye movement, electroretinograms (ERGs) and visual evoked potentials (VEPs). If any of the biochemical studies was inadequate, it was also performed. These included liver function tests, urea and electrolytes, very- long-chain fatty acids, serum amino acids and urine for amino acids and organic acids.

Statistical analysis

SPSS program version 18 was used to analyze the demographic data, neurological, ophthalmological, and renal manifestations, EEG, brain CT and MRI findings and results of renal ultrasound.

3.Results

The results are summarized in table1. Nineteen children (8 males and 11 females) were identified as having JS; as their final diagnosis. This included two pair of siblings from the same family. Three of our patients died; Two from respiratory failure (at the age of 3 and 6 months) and the third one from aspiration pneumonia secondary to a cleft palate (at the age of 11 months). Therefore, 16 patients (6 males and 10 females) were reviewed in this study. Their age ranged from 6 to 63 months (mean 31 months). One child was delivered with meconium stained amniotic fluid. Consanguinity was observed in 14 patients and the other 2 patients` parents were from the same tribe. The onset of symptoms which were usually in the form of respiratory symptoms or hypotonia was between 10 days to 5.5 months (mean in 48 days).

Apnoeic episodes occurred in 14 of 16 patients, and 13 of them had transient phenomenon lasting up to 6 months and one patient continued to have hyperepnic attacks with transient apnoeic episode required oxygen and apnea monitor at home up to the age of 10 months.

Neurologically, general hypotonia was an early observation in all 16 patients. All patients also demonstrated some degree of motor and developmental delay, although this varied from mild to very severe. Three patients had walked unaided with a broad-based gait at the age of 3.5, 4 and 5 years. No IQ assessment was performed during the study, but the speech was a problem in all our patients and 8 of them were attending or had attended speech therapy. Of the 8 children, one had developed intelligible speech. Those 8 patients had mild to moderate disability although they had achieved toilet training and self- feeding. Two had severe disability, with failure to develop even those basic skills. Two patients had seizures and five patients had ataxia.

Other systemic features; chorioretinal coloboma were seen in 2 patient, postaxial polydactyl was present in 3 patients (one of them was bilateral), general joint laxity in 4 patients, keratoconus in one patient, bilateral tight Achilles tendons in 5 patients, and thoracic scoliosis in 6 patients.

Five patients had ultrasound evidence of multiple renal cysts but they had normal renal function. Renal and liver function tests, urine for organic acids, serum, amino acids, very-long-chain fatty acids and routine karyotype were normal in all the patients. Nerve conduction velocity (NCV) and electromyography (EMG) were performed for all patients and were normal. EEG was recorded in all our patients and was abnormal in five: three had seizures; four had sharp discharges over focal areas and two had multifocal distribution consistent with the MRI of multifocal white matter intensities.

MRI and CT were reviewed in all patients. Cerebellar vermis aplasia/hypoplasia was present in all our patients. The vermis was aplastic in 5 patients and hypoplastic in 11 patients, affecting mainly the postero-inferior part. In all patients, the midbrain and superior cerebellar peduncles displayed the molar tooth sign (MTS). Associated features were noted on the MRI and/or CT scans in six patients. These were brainstem hypoplasia in

three patients, white matter cyst in one patient, corpus callosum dysgenesis in one, moderate dilation of the ventricular system in one, and nonspecific high signal lesions in the white matter in a patient who also had seizures.

Ophthalmological examination: Anterior segment examinations were normal in all the 16 patients but fundus examination revealed retinal pigment epithelium mottling in 3 patients who had abnormal ERG. There were 4 patients with squint (one with convergent squint and 3 with divergent squints). 6 patients were associated with nystigmus (four with horizontal pendular nystigmus and two with upbeat nystigmus). In eye movement study; limited eye movement (ocular motor apraxia) was evident in 9 of 16 patients. ERG and VEPs were abnormal in 11 of our 16 patients indicating that visual acuity was affected and at a rudimentary level.

Table (1): Clinical and radiological features of studied patients

Features			Findings
Age (months)			6-63 months (31 months)
Sex	Male		6
	Female		10
Age at onset (days)			10-166 (48)
Family and perinatal history	Consanguinity		14 (87.5%)
	FH of similar conditions		3 (18.8%)
	Perinatal problems		1 (6.25%)
Neurological manifestations	Hypotonia		9 (100%)
	Speech problems		9 (100%)
	Apnea or hyperapnea		14 (87.5%)
	Seizures		2 (12.5%)
	Abnormal EEG		5 (31.25%)
Ophthalmological manifestations	Anterior segment abnormalities		0 (0)
	Fundoscopy abnormalities		3 (18.75%)
	Squint	Convergent	1 (6.25%)
		Divergent	3 (18.75%)
	Nystigmus	Horizontal	4 (25%)
		Upbeat	2 (12.5%)
	Ocular motor aprexia		9 (56.25%)
	ERG & VEPs	Abnormal	11 (68.75%)
		Normal	5 (31.25%)
Other features	Chorioretinal coloboma		2 (12.5%)
	Polydactyl		3 (18.75%)
	Joint laxity		4 (25%)
	Keratoconus		1 (6.25%)
	Tight tendon achillis		5 (31.25%)
	Thoracic scoliosis		6 (37.5%)
	Renal cysts		5 (31.25%)
CT & MRI findings	Cerebellar vermis anomalies	Aplasia	5 (31.25%)
		Hypoplasia	11 (68.75%)
	Brain stem hypoplasia		3 (18.75%)
	White matter cyst		1 (5.6%)
	Corpus callosum dysgenesis		1 (5.6%)
	Dilatation of ventricular system		1 (5.6%)
	Non-specific high signal lesions in white matter		1 (5.6%)

Data are presented as ranges & numbers; mean & percentages are in parenthesis

Table 2: Clinical Features of Joubert Syndrome and JSRD

Feature	Classic Joubert	Dekaban-Arima	Joubert-LCA-Like	COACH	Senior-Løken	OFD VI Varadi	Juvenile Nephronophthisis	Cogan OMA
Neurological features								
Cerebellar vermis hypoplasia and ataxia	+	+	+	+	(+)	+	(+)	(+)
Molar tooth sign on MRI	+	(+)	+	(+)	(+)	(+)	(+)	(+)
Developmental delay/mental retardation	+	+	+	+	(+)	+	(+)	(+)
Episodic tachypnea ± apnea	+	+	+	(+)	(+)	(+)	?	?
Dandy-Walker-like malformation	(+)	?	?	?	?	?	(+)	?
Occipital cephalocele	(+)	(+)	(+)	(+)	(+)	(+)	–	–
Eye								
Retinal dystrophy	(+)	+	+	+	+	–	(+)	?
Severe visual impairment/LCA	–	+	+	(+)	(+)	–	?	?
Oculomotor apraxia	+	(+)	(+)	(+)	(+)	(+)	(+)	+
Coloboma	–	?	?	+	?	?	–	–
Retinal dystrophy	(+)	+	+	+	+	–	(+)	?
Kidney								
Cystic dysplasia	–	+	–	–	–	(+)	–	–
Nephronophthisis	(+)	–	–	(+)	+	–	+	(+)
Others								
Facial dysmorphism	(+)	?	(+)	?	(+)	(+)	?	?
Hepatic fibrosis-cirrhosis	–	(+)	–	+	?	–	–	–
Polydactyly	(+)	?	(+)	?	?	+ [1]	–	–
Early death	(+)	+	(+)	(+)	(+)	(+)	?	?

Adapted from Satran *et al.* (1999) and Gleeson *et al.* (2004); Present, (+) = Sometimes present, – = Absent, ? = Unknown; LCA-like = Leber congenital amaurosis-like, OMA = Oculomotor apraxia

4.Discussion

Joubert Syndrome (JS) is a rare genetic developmental disorder, first identified in 1969. The diagnosis of Joubert syndrome as a definite diagnosis from other similar clinical conditions is difficult due to absence of a specific test or genetic marker **(Blair *et al.*, 2002)**.

The term "Joubert syndrome" is reserved for those individuals fulfilling the diagnostic criteria that require the presence of developmental delay, abnormal ocular movements, and radiological evidence of marked cerebellar vermis abnormalities leading to the presence of the 'molar tooth sign on MRI **(McGraw, 2003; Maria *et al.*, 2003)**. This may also be termed "classic Joubert syndrome. The term "Joubert syndrome and related disorders" (JSRD) describes conditions that share the molar tooth sign and the some clinical features of Joubert syndrome, but that also have other manifestations that may represent a distinct syndrome. At least eight conditions in which a subset of affected individuals demonstrates the molar tooth sign have been identified **(Satran *et al.*, 1999; Gleeson *et al.*, 2004)** (Table 2). There is debate whether these represent subtypes of Joubert syndrome or distinct syndromes. In the present study, only patients fulfilling the criteria mentioned before for diagnosis of JS were chosen

and included in the study. Other features sometimes identified in JS include retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyl, oral hamartomas, and endocrine abnormalities.

The prevalence of Joubert syndrome has been estimated from to be 1:258,000 **(Flannery & Hudson, 1994; Badhwar *et al.,* 2000)**. In our study, 19 cases were reported in 2 general hospitals draining about 750.000 people within 5 years of study, so the prevalence is a little higher. This can be explained by consanguineous marriage which is famous in the gulf area (multigenerational consanguinity) and this was present in all our patients.

A reported male: female ratio of approximately 2:1 **(Badhwar *et al.,* 2000)** was not confirmed in other surveys **(Saraiva *et al.,* 2000)**. In our study, male to female ratio was 6: 10.

Possible prenatal diagnosis of Joubert syndrome can be achieved by serial prenatal ultrasound imaging starting at 11-12 weeks' gestation, with detailed evaluation of cerebellar and other fetal anatomy through 20 weeks' gestation, followed by fetal MRI imaging at 20-22 weeks' gestation **(Aslan *et al.,* 2002; Doherty *et al.,* 2005)**. However in our study, no patient diagnosed in utero inspire of good follow up for the mothers during pregnancy. Only one patient had a perinatal problem (meconium stained amniotic fluid).

Many of the clinical features of Joubert syndrome are evident in infancy **(Joubert, 1969; Boltshauser & Isler, 1977)**. In our study, the onset of symptoms which were usually apnea or hyperapnoea in the first 48 days (range 10 days to 5.5 months)

Typical respiratory abnormalities in JS are represented by short alternate episodes of apnea and hyperpnoea or episodic hyperpnoea alone, which tend to occur shortly after birth, and progressively improve with age, usually disappearing around the sixth month of life. Their severity can range from occasional short-lasting episodes manifesting every few days to extremely frequent (up to several per day) and prolonged attacks of apnea **(Boltshauser *et al.,* 1981; Brancati *et al.,* 2010)**. In our study 14 out of 16 patients had respiratory symptoms occurred in early infancy, 13 of them improved within 3 months and the fourth one improved at the age of 10 months.

Early hypotonia is observed in nearly all JS patients and can be recognized in the neonatal period or in infancy **(Braddock *et al.,* 2006; Brancati *et al.,* 2010)**. This is also observed in all our 16 patients. All patients also demonstrated some degree of motor and developmental delay, although this varied from mild to very severe. There are many reports about the developmental disabilities in JS, in particular language and motor skills, with variable degrees of severity **(Gitten *et al.,* 1998; Fennell *et al.,* 1999; Braddock *et al.,* 2006)**. However, it must be stressed that intellectual deficit is not a mandatory feature of JS and exceptional cases may have borderline or even normal intellect. One of our patients had developed intelligible speech. There is a strong relationship between articulatory deficits and abnormal eye movement, and this might be attributable to vermis malformation **(Hodgkins *et al.,* 2004)**.

Although ataxia and balance difficulties are non-specific findings in JS but they represent a frequent finding. Nine of our patients (56.25%) had either ataxia or broad-based gait. Although epilepsy is a rare feature of JS, abnormal EEG was reported in 5 patients representing 31.25% of our patients but this can be explained by the associated CNS malformations other than MTS as midbrain hypoplasia, white matter cyst, corpus callosum dysgenesis, dilation of the ventricular system, and high signal lesions in the white matter which have higher incidence of epilepsy. Small number of cases presents with occipital (meningo) encephalocele of variable severity **(Shian *et al.,* 1993; Wang *et al.,* 1999)** but this was not reported in our patients.

Abnormal eye movements also represent a recurrent feature in JS. Oculomotor apraxia is one of the most characteristic and frequent abnormalities, that manifests with the inability to follow objects visually with compensatory head movements. Primary position nystigmus is also common. 6 of our patients (37.5%) were associated with nystigmus. The nystigmus was horizontal pendular and upbeat nystigmus. These varieties of nystigmus were not typical of congenital sensory nystigmus even in those with an associated retinal dystrophy, and mostly can be attributed to a neurological cause probably resulting from brainstem malformation **(Khan *et al.,* 2008; Schild *et al.,* 2010)**. A range of eye movement abnormalities (ocular motor apraxia) were present, in 9 of 16 patients (56.25%) reviewed. There is a strong association of eye

movement abnormalities with vermian malformations **(Dekaban *et al.,* 1969; Khan *et al.,* 2008; Malaki *et al.,* 2012)**.

Previous eye manifestations are present independently from the specific defects of the eyes and relate to the underlying midbrain-hindbrain malformation **(Weiss *et al.,* 2008; Sturm *et al.,* 2010)**. This was also observed in our patients who showed normal anterior segment by lit lamp examination. **Dekaban (1969)** was the first to describe association of retinal problems with JS. Many studies have reported association of JS with very attenuated or undetectable rod-mediated ERGs previously **(Khan *et al.,* 2008; Schild *et al.,* 2010)**. Our study supports the reports in the literature through records of ERG and VEPs which showed retinal abnormalities in 68.75% of our patients. We found evidence of progressive retinal damage in one of the patient in VEPs compared with the old one done 2 years back. One of those patients had total visual impairment. Fundus examination of these patients revealed mottling of the retinal pigment epithelium, especially at the macula area in 3 patients with abnormal ERG.

Renal disease often occurs in 25% of individuals with JS. Five patients in our studies showed renal cysts, all of them had abnormal ERG. Many reports showed renal anomalies in JS. Other renal problems may be present in JS as shown in many reports such as renal dysplasia, and juvenile nephronophthisis, a form of chronic tubulointerstitial nephropathy **(Brancati *et al.,* 2010)**. Our patients showed normal renal function tests. **Saraiva & Baraitser (1992)** noted that retinal dystrophy was never absent when renal cysts were observed can no longer be applied as a general rule **(Saraiva & Baraitser 1992)**.

Some individuals with JS have congenital hepatic fibrosis as a result of anomalies of biliary structures and portal tracts during embryonic development **(Brancati *et al.,* 2010)**. Liver function tests with hepatic ultrasound are recommended biannually in children and at diagnosis in adults. None of our patients showed any hepatic fibrosis or abnormal hepatic function.

Other systemic features reported in our patients with JS as chorioretinal coloboma, postaxial polydactyl, general joint laxity, keratoconus, bilateral tight Achilles tendons, and thoracic scoliosis were also reported in other literatures **(Brancati *et al.,* 2010)**.

Conclusion

Joubert Syndrome (JS) is a rare genetic brain malformation characterized by absence or underdevelopment of cerebellar vermis. Retinal dystrophy and renal abnormalities are common associations. The prognosis of patients depends mainly on the degree of brain malformation.

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