

Case Report

A Single Institutional Experience with Joubert Syndrome: The Past and Present

Osama Shukir Muhammed Amin*

Department of Neurology, Sulaimaniya General Teaching Hospital, Sulaimaniya City, Kurdistan Region, Iraq

*Corresponding author

Osama S.M. Amin, Department of Neurology, Sulaimaniya General Teaching Hospital, Sulaimaniya City, Kurdistan Region, Iraq; Tel: +9647703515964; Fax: +14133047585; E-mail: dr.osama.amin@gmail.com

Submitted: 24 July 2013

Accepted: 31 July 2013

Published: 02 August 2013

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Keywords

- Joubert syndrome
- Molar tooth sign
- Mental retardation
- Episodic hyperpnea
- Ataxia

Abstract

Joubert syndrome is an autosomal recessive disorder characterized by a variable combination of mental retardation, cerebellar ataxia, episodic hyperpnea, eye movement abnormalities, generalized hypotonia, and the molar-tooth sign visible on brain imaging. The number of reported cases has been escalating all over the world since the description of the syndrome by the late French neurologist Marie Joubert in 1969, but the syndrome remains under-diagnosed; failure to recognize its core features and unfamiliarity with the brain imaging findings are the main culprits. In 2011, we reported on three Iraqi children who had been diagnosed with Joubert syndrome and it was the first-ever published case series from Iraq. Two of them were already misdiagnosed as ataxic cerebral palsy and hereditary spinocerebellar ataxia. The third child presented with delayed milestones. During the past 2 years, we have been regularly following-up those children on an outpatient basis, every 6 months. The first child's epilepsy has been well-controlled and no breakthrough seizures have been reported while the second child's diffuse ichthyosis has been more or less the same; their moderate intellectual disability and cerebellar ataxia have been plateaued. The third child's Leber's congenital amaurosis and poor vision hasn't progressed further and he is unable to sit or stand without major assistance; his age is 2 years and 7 months. None of the children has a family history of the same illness. No renal or hepatic involvements have been found during the past 2 years of follow-up.

INTRODUCTION

Joubert syndrome is a rare autosomal recessive disorder characterized by aplasia/hypoplasia of the midline cerebellar vermis in addition to several brainstem and extra-cranial anomalies. Many genetic abnormalities have been identified in Joubert syndrome patients. The long-term prognosis is still unknown and the outlook differs from patient to patient [1,2].

Cases' presentation

Patient 1 was a 7-year-old Arabic male. He developed recurrent generalized tonic-clonic seizures during the year 2009, which were not responding to oral phenytoin. A pediatrician had diagnosed him with ataxic cerebral palsy. The family history was unremarkable and his parents were non-consanguineous. He had short-lived episodes of shortness of breath during the neonatal periods, which were ascribed to acute asthma. His blood tests and CT brain scanning were unremarkable as the pediatrician's referral letter had stated. The boy demonstrated poor language development, bidirectional horizontal gaze-evoked nystagmus,

instability of stance, and wide-based ataxic gait; he was unable to stand and walk without major assistance. There were no involuntary movements, pyramidal signs, facial dysmorphism, or hand anomalies and his fundal examination was normal-looking. He underwent a battery of blood and urine testing (including for inborn error of metabolism) as well abdominal ultrasound examination, which turned out to be normal. Brain MRI without gadolinium revealed absence of the midline cerebellar vermis and the molar-tooth sign (Figures 1 and 2). Escalating doses of oral lamotrigine was prescribed and he has been seizure-free since then. He is now 11 years old. He demonstrates moderate mental retardation and severe cerebellar ataxia; both of these have been more or less the same since 2009. Apart from "mama and papa," he utters few incompressible words. Abdominal and pelvic CT scanning revealed no abnormalities.

Patient 2 was referred by an orthopedic surgeon. The patient was a 12-year-old mentally retarded Arabic girl. She was wearing a foot orthosis because of bilateral flaccid ankles and foot drops. A diagnosis of spinocerebellar ataxia was made at the age of 5

years because of delayed milestones and gross gait ataxia. The patient's mother said that her girl had recurrent rapid and shallow breathings during her first month of life; a diagnosis of recurrent pulmonary aspirations was done but her chest films were always normal-looking. The girl's parents were cousins but they denied any history of a neurological or degenerative disease in the family. The girl had dysarthria and demonstrated ocular apraxia, wide-based cerebellar gait ataxia, generalized hypotonia, and diffuse skin ichthyosis. Her face was broad and there was hypertelorism. Fundoscopic examination revealed a normal-looking retina. Pes cavus was absent. Her blood tests and abdominal ultrasound were unremarkable. The patient's brain MRI uncovered the presence of the molar-tooth sign (Figure 3).

Patient 3 presented to our neurology outpatients' clinic because of difficulty suckling and inability to sit unaided. He was a 7-month-old Kurdish male. His mother said that her baby always coughs during breastfeeding. The baby had generalized hypotonia

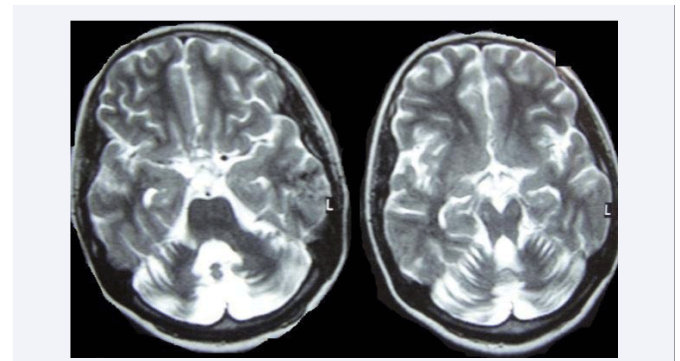


Figure 3 Axial T2-weighted MRI of patient 2 at the level of mesencephalon (right) and mid-pons (left). The midline vermis is severely hypoplastic and the molar tooth sign is obvious at the level of the mesencephalon. Note the deep inter-peduncular fossa, large 4th ventricle, and the thin and slender superior cerebellar peduncles.

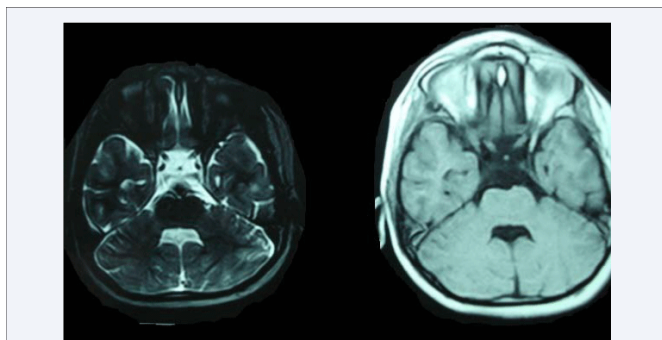


Figure 1 Non-contrast axial T1-weighted (right) and T2-weighted (left) MRI of patient 1 at the level of the mid-pons. Note the absence of the midline cerebellar vermis and how the cerebellar hemispheres meet in a bat-wing configuration.

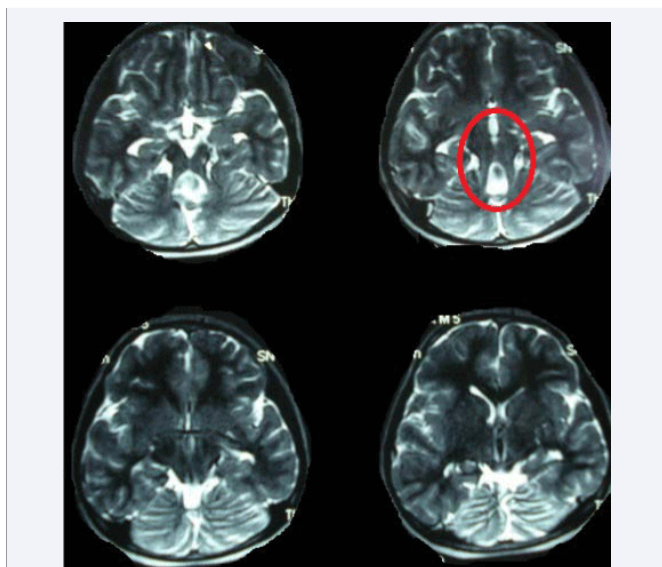


Figure 2 Non-contrast axial T2-weighted MRI of patient 1 at the level of mesencephalon. Note the deep inter-peduncular fossa, elongated and slender superior cerebellar peduncles, and enlarged 4th ventricle. This constellation forms the molar tooth sign (surrounded by the red circle). The vermis is severely hypoplastic. The cerebral hemispheres appear normal.

and was unable to sit on his buttocks unaided. He couldn't follow-up visual cues. His parents were non-consanguineous. Both pupils were dilated and did not react to light, both directly and indirectly. A pendular horizontal type of nystagmus was present. His fundoscopic examination was unremarkable. There was neither a history of perinatal insult nor a history of abnormal neonatal respiratory pattern. His older brother died at the age of 3 years and 2 months because of "cerebral palsy" and mental retardation. His blood tests and abdominal ultrasonography were unremarkable. An MRI of the brain showed the molar tooth sign (Figure 4).

DISCUSSION

Thanks to the work of the late French neurologist Marie Joubert and her colleagues; they published a landmark paper in the year 1969 reporting on hypoplasia of the midline cerebellar vermis in five children [3]. Four out of those children were siblings and the fifth one was sporadic. All of those children had a combination of developmental delay and intellectual disability, gait ataxia, episodic hyperpnea and breathing dysregulation during the neonatal period, generalized hypotonia, and a multitude of eye movement abnormalities. The hallmark was the presence of the molar tooth sign, a complex hindbrain/midbrain malformation, which is visible on brain imaging; this was discovered several years later [4]. Joubert designated this constellation as "familial agenesis of the cerebellar vermis." Since then, many investigators have worked on this subject, expanded the clinical features of this constellation, and contributed a lot to our current understanding of the now so-called Joubert syndrome. A multitude of other conditions which were previously considered as distinct entities have been coined by the term Joubert syndrome and related disorders; all of them demonstrate the molar tooth sign [5].

The incidence of this syndrome is unknown world-wide; in the United States, a figure of 1/80000 to 1/100000 has been found [6]. However, many neurologists think that the syndrome is under-diagnosed and the precise number is much larger; failure to recognize the clinical features and/or the brain imaging findings can explain this underestimation [7,8].

Saraiva and Baraitser [9] concluded that Joubert syndrome

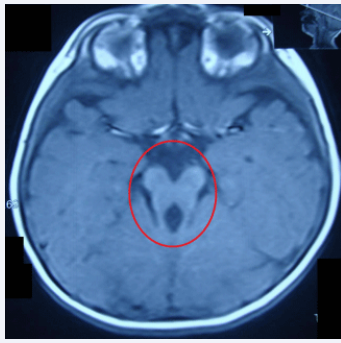


Figure 4 This axial non-contrast T1-weighted MRI image belongs to patient 3. He was 7 months old at the time of diagnosis. Note the molar tooth sign (within the red circle) and the partial absence of midline vermis. In addition, he has Leber's congenital amaurosis. He is now 2 years and 7 months and is unable to sit or stand without major assistance.

is an autosomal recessive disease after reviewing 101 patients. Approximately half of Joubert syndrome patients lack a relevant family of the same condition, however. About 50% of the cases have a mutation in one of the following 10 ciliary/basal body genes: *INPP5E*, *TMEM216*, *AHI1*, *NPHP1*, *CEP290*, *TMEM67*, *RPGRIP1L*, *ARL13B*, *CC2D2A*, and *OFD1* [6]. The locus *CORS2* on chromosome 11 is thought to be involved in the pathogenesis but its precise gene is unknown [10]. However, according to Romani and colleagues [11], there are 21 causative genes and the disease may harbor an X-linked recessive inheritance. A single abnormal gene can result in a multitude of clinical features (i.e., allelic heterogeneity). On the other hand, more than one gene can be associated with a single phenotype (i.e., locus heterogeneity) [12]. These phenomena are consistent with the original Joubert's observation of intra-familial variability of the clinical features; i.e., the phenotype of the disease varies among the afflicted siblings within the same family [3].

Both genders are equally afflicted and there is no gender preponderance. Hundreds of cases have been reported worldwide since the establishment of the syndrome by Joubert [2]. In addition, some cases have been successfully diagnosed prenatally using ultrasonography [13,14] and according to Valent and coworkers, the identification of mutations allows early prenatal diagnosis in couples at risk, while fetal neuroimaging may remain uninformative until the late second trimester of pregnancy [15].

The syndrome was thought to be caused by hypoplasia or aplasia of the midline cerebellar vermis [1,2]. Yachnis [16], did a comprehensive post-mortem neuropathologic examination of patients with Joubert syndrome; all of his cases were clinically and radiographically well-documented. He found, in addition to vermian aplasia/hypoplasia, malformations in multiple brainstem structures. There were prominent dysplastic changes of structures at the pontomesencephalic junction and caudal medulla. The superior cerebellar peduncles displayed abnormal decussation while pyramidal decussation was absent. The dentate nuclei were fragmented, the inferior olivary nuclear complex was hypoplastic, and the basis pontis and reticular formation neurons appeared reduced in number. The abnormalities of ciliary/basal bodies' genes suggest that the syndrome may result from inability

of posterior fossa structures to cross the midline at a critical step in brain development early in gestation [1,2].

There has been no consensus about the diagnostic criteria of the syndrome since the publication of Joubert's paper in 1969 and the diagnosis of Joubert syndrome has been revised several times by many researchers [17-20]. Furthermore, there is an overlap with other brainstem malformations, both clinically and radiologically, such as Dandy-Walker syndrome and Arima syndrome [21,22].

Twelve children with Joubert syndrome were reviewed by Barreirinho and coworkers, both clinically and radiologically [23]. They tried to correlate the clinical features with the imaging findings. Some features were found in all cases while other well-documented ones, such as breathing dysregulation, were variable. Accordingly, Barreirinho and coworkers [23] believed that the following should be considered as "major diagnostic criteria" for Joubert syndrome: hypotonia, ataxia, mental retardation, oculomotor apraxia, and the radiological molar tooth sign. However, they considered the presence of abnormal respiratory pattern, retinal pigmentation, renal abnormalities, and facial dysmorphism as "supportive" features (i.e., not absolutely required). They suggested that the application of these criteria in making the diagnosis of "classic Joubert syndrome" will avoid overlap with other syndromes.

Maria and colleagues [7] and Andermann and colleagues [8] found that the most striking feature during neonatal period was the episodic hyperpea, sometimes intermixed with central apnea. Transient tachypnea of the newborn is the most important differential diagnosis. However, Wolfe and coworkers [24] reported on a Joubert syndrome child who had severe central apnea rather than attacks of hyperventilation. The other constituents of the syndrome are usually not obvious at this neonatal stage; this makes the syndrome difficult to recognize clinically.

Hypotonia is striking feature during the first year of life and is found in all cases [25,26]. The child appears flabby and is unable to support his head or sit unaided on his buttocks at the appropriate age. Maria and colleagues [7] found that the average age of independent sitting was 19 months and the average age of walking was 4 years for those who developed these skills. When the child starts standing and walking, cerebellar ataxia starts to appear in 100% of cases [25]. Therefore, delayed milestones are common presenters in "toddlers" and cerebral palsy (usually ataxic one) comes into mind [2].

Intellectual disability and mental retardation are core features of the syndrome and are found in all patients but differ in severity. Most children demonstrate moderately severe degree of mental retardation, according to Steinlin and coworkers [27]. Eleven children with Joubert syndrome were examined by Ozonoff and colleagues [28], looking for autistic features. Three out of those 11 patients met the DMS-IV criteria for autistic disorder, and a further child had pervasive developmental disorder not otherwise specified. Few years later, Takahashi and coworkers [29] concluded that Joubert syndrome is a genetically distinct disorder from autism and that different genes with different inheritance patterns that affect neurodevelopment of

the cerebellum could explain the clinical similarities previously reported in Joubert syndrome and autism. Hodgkin et al. [30] found that behavioral problems commonly develop with increasing age. Delayed language development is very common and results from the combination of speech ataxia, oro-motor apraxia, mental subnormality, and autistic and behavioral disorders [12].

Nystagmus (horizontal, vertical, or combined vertical and torsional) which is usually pendular, is a common finding at birth and is therefore, a very useful clue to the underlying cerebellar and brainstem dysfunction [31]. Tusa and Hove [32] systematically examined the coulometer systems of 13 Joubert syndrome patients and concluded that the key coulometer features of this syndrome, apart from nystagmus, were decreased smooth pursuit and vestibulo-ocular reflex cancellation, partial to complete coulometer apraxia (both in the horizontal and vertical directions), and hypometric saccades if oculomotor apraxia is not complete. These are usually difficult to be recognized by inexperienced physicians.

The morphologic characteristics of Joubert syndrome were analyzed extensively by Braddock and coworkers [33]. They found that facial dysmorphism is common but not invariable feature. This facial dysmorphism encompasses long face, frontal prominence, bitemporal narrowing, ptosis, prominent nasal bridge and tip, prognathism, eyebrow abnormalities, trapezoid shaped mouth, lower lip eversion, and thick ear lobes. However, the morphologic overlap with other brainstem malformation syndromes renders this boundary blurred.

Cranial/intracranial (microcephaly, encephalocele, agenesis of corpus callosum, eye coloboma, and retinal dystrophy) and extracranial malformations (duodenal atresia, cystic renal disease, hepatic fibrosis, and congenital heart anomalies) may be found in some patients; these additional anomalies usually inflate the syndrome's morbidity and mortality. For example, patients who have retinal dystrophic changes are more likely to have underlying renal dysplasia and cysts and their survival figure is shorter than those who lacks retinal dystrophy [4,5]. The term "Joubert syndrome and related disorders" was therefore coined by some investigators to define those patients' subset [34-39]. Their overall clinical picture is very protean and may result in cerebello-oculo-renal syndrome (combination of ocular abnormalities and nephronophthisis/renal cysts), Senior-Løken syndrome (renal involvement and retinal dystrophy), and COACH (Coloboma, Oligophrenia, Ataxia, Cerebellar vermis hypoplasia, Hepatic fibrosis) syndrome. The molar tooth sign is the imaging hallmark of all those [25].

Cranial MRI is the best imaging modality for the detection of the molar tooth sign in children suspected of having Joubert syndrome. The midline cerebellar vermis can be aplastic or hypoplastic; the superior cerebellar peduncles appear elongated, slender, thickened, and hypoplastic; the ponto-mesencephalic junction is elongated and has a deep interpeduncular fossa; and the fourth ventricle appears enlarged and deformed [1,2]. The aforementioned findings are the constituents of the molar tooth sign, which is seen at the level of mesencephalon and pons. This sign has been found 85% of cases and 13% of those who display this sign have an additional brain malformation (or

malformations) [19,40]. One must stress on the fact that the mere absence of the midline cerebellar vermis does not mean that the patient in question has Joubert syndrome; the vermis can be absent in Down syndrome and Dandy-Walker syndrome [22,41]. Furthermore, up to 10% of Joubert syndrome patients have an excess fluid collection in the posterior fossa; this may prompt the physician to think of Dandy-Walker syndrome instead of Joubert syndrome [22,42].

Andermann and coworkers reported on the original proband case of Joubert syndrome in the year 1999 [8]. At that point, this male patient had reached the age of 30 years. He demonstrated severe dysarthria, moderate ataxia of stance of gait, poor judgment, and borderline intelligence. His abnormal eye movements were less prominent and his hyperpnea had diminished.

For the time being, it has been 44 years since this syndrome had been reported by Marie Joubert. However, the prognosis is still not fully understood and its outlook is not yet documented. The degree of developmental delay in Joubert syndrome and the severity of gross central nervous system malformations appear to be independent from each other, according to Gitten and colleagues [43]. On the other hand, Steinlin and coworkers [27] studied 19 patients with Joubert syndrome children from a single institution. The found that 3 children were dead before the age of 3 years and the rest (n=16) who survived showed variable combination of gross motor and cognitive impairments; walking was typically achieved between 2 and 10 years and 2 children did not learn to walk at all. They also suggested that the ocular and kidney manifestations may change or develop over the years and therefore, all patients should have a careful be followed-up.

Pascual-Castroviejo [44] published a paper in the year 2004 which described two siblings (26 and 22 years old, respectively) with Joubert syndrome that had a relatively normal evolution. Both patients showed normal gait but demonstrated difficulty running. They performed their personal self-care and their contact with other people is good. Torres et al. [45] followed-up a child for 24 months (from the age of 16 to 40 months). The child had received personalized stimulation therapy, concentrating on five areas; socialization, language, self-help, cognition, and motoricity. They concluded that during treatment, greatest progress was made in the areas of cognition and communication. In 2008, Zaki and colleagues [46] found that cognitive therapy is helpful in improving the patient's cognitive and communicative functions.

From February 2009 to April 2011, we encountered three cases of Joubert syndrome [1,2]. Table 1 displays their clinical features. The first patient was an Arabic male from Baghdad, the second one was an Arabic female from Diyala, and the third one was a Kurdish male from Sulaimaniya. Since then, we have been following up them till June 2013. No additional features were encountered and their overall clinical picture was more or less the same.

Only patient 1 had a history of parents' consanguinity while family history of Joubert syndrome was absent in all three patients; however, we wonder whether the deceased older brother of patient 3 had Joubert syndrome or not? The generalized seizures

Table 1: Various patients' characteristics and clinical findings.

	P1	P2	P3
Age (at diagnosis)	7 y	12 y	7 m
Gender	Male	Female	Male
Residence	Baghdad	Diyala	Sulaimaniya
Parents consanguinity	-	+	-
Family history of JS	-	-	Questionable *
Mental retardation	+	+	CBA
Ataxia	+	+	CBA
Episodic hyperpnoea	+	+	-
OMA	Nystagmus	Ocular apraxia	Nystagmus†
Hypotonia	+	+	+
Molar tooth sign	+	+	+
Other malformations‡	None	Broad face, ptosis, and hypertelorism¶	None

P, patient's number; y, year; m, month; -, negative; +, positive; CBA, cannot be assessed; OMA, ocular movements abnormalities.

*The child's older brother died at the age of 3 years and 2 months because cerebral palsy, as the parents had stated; we wonder whether this child had Joubert syndrome or not.

†This patient did not follow visual cues and pupillary reflexes were absent.

‡None of the patients had demonstrated renal cystic disease, retinal dystrophic changes, or hepatic fibrosis.

¶Patient 2 had diffuse skin ichthyosis.

of patient 1 had been well-controlled using lamotrigine tablets (100 mg twice a day). His gait ataxia and mental retardation have not been changed since 2011.

Severe visual loss has been documented in some children. Their electroretinographic traces reveal marked flattening; this has been linked to Leber's congenital amaurosis [32,47]. The visual loss and pupillary reflexes in patient 3 had pointed towards this retinal disease. Early in life, the dystrophic retinal changes of this amaurosis may not be obvious but they appear gradually as the child gets older. Patient 3 is now 2 years and 7 months old. He is mentally retarded, blind, and has poor language development. He is unable to sit unaided and cannot stand or walk with a major assistance.

Patient 2 had extensive skin ichthyosis. We had reviewed the pertinent literature and found that this skin manifestation has never been reported in Joubert syndrome. Whether it is related to Joubert syndrome or it is a mere coincidence, this observation needs further analysis. She also demonstrates facial dysmorphic features; the other two cases do not. Patient 2 has reached the age of 15 years. She has moderate mental retardation and severe instability of stance and gait.

Only patient 3 did not have a clear-cut history of breathing dysregulation during the neonatal period, while patients 1 and 2 had a history of episodic hyperpnea; in patient 1, this had been misdiagnosed as bronchial hyper-responsiveness while repeated pulmonary aspirations were thought to be the culprit in patient 2. The presence of episodic hyperventilation during the neonatal period in the absence of cardio-pulmonary disease should always prompt the physician search for cerebellar dysfunction.

During the past 2 years, none of the patients had demonstrated renal or hepatic involvement. According to Zaki et al. [46], these abnormalities may not become apparent until adolescence;

therefore, annual abdominal ultrasound examination is recommended.

ACKNOWLEDGMENT

Special thanks go to our patients and their families; without their kind cooperation, this paper would have not been published.

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Cite this article

Amin OSM (2013) A Single Institutional Experience with Joubert Syndrome: The Past and Present. *J Neurol Disord Stroke* 1(2): 1010.