Joubert syndrome: a case report

Carolina Araújo Faber da Silva Machado¹, Ana Carolina Gaudard²-³, Rodrigo David Pereira¹, Ana Lucia Hanke Kaiel Nassif¹

Abstract

Joubert Syndrome is an autosomal recessive disorder characterized by cerebellar venous hypoplasia with prominent superior cerebellar peduncle, which leads to the “molar tooth signal” in axial sections on the cranial magnetic resonance. It’s a very important criterion for the diagnosis of the syndrome. This entity shows an association of neurological disorder with variable involvement of multiple systems, like ocular, renal and skeletal systems, for example. Among the clinical manifestations, there is muscular hypotonia still in the neonatal period or in infancy; gait ataxia and instability are also frequently found; episodes of hyperpnea alternated with apnea, delays in motor and language development. Among the multiple systems that are involved, renal disease is described on 25-30% of the individuals that are affected by Joubert syndrome; and it can be like juvenile cystic dysplasia and nephron phthisis. This work aims to describe a clinical case of Joubert syndrome with clinical manifestations, principally renal, on a 1 year and 4 months old female lactating with multicystic dysplastic kidney, visualized on morphological ultrasonography. After birth, at 3 months old, generalized hypotonia of the child, with delay of the neuropsychomotor development, alteration of the field of vision and uncoordinated ocular movements have suggested the diagnostic. In the magnetic resonance imaging of the skull, there was a prominent thickening of the molar tooth sign associated to the morphological disorder of the fourth ventricle (“bat wing”) and agenesis of the cerebellar vermis.

Keywords:
Multicystic Dysplastic Kidney, Muscle Hypotonia, Eye Manifestations, Neurologic Manifestations, Cerebellar Vermis.

CASE REPORT

1 Macaé Municipal Hospital Foundation, Pediatric Resident Physician - Macaé - State of Rio de Janeiro - Brazil.
2 Macaé City Administration, Assistant Pediatrician — Macaé - State of Rio de Janeiro - Brazil.
3 Sírio-Libanês Teaching and Research Institute, Specialist in Medical Residency Preceptorship - São Paulo - State of São Paulo - Brazil.

Correspondence to:
Carolina Araújo Faber da Silva Machado.
Prefeitura Municipal de Macaé. AV. Presidente Sodré, 534, Centro. CEP: 27913-080. Macaé. RJ, Brazil.
E-mail: carolinaafs@yahoo.com.br
INTRODUCTION

Joubert syndrome and related disorders (JSRD) are autosomal recessive genetic diseases characterized by malformation of the brainstem and hypoplasia or agenesis of the cerebellar vermis. Radiologically, the “molar tooth sign” is observed in all patients with this syndrome. The clinical presentation of this disorder has high phenotypic variability and affects several systems, such as the neuromotor, ocular, renal, and skeletal systems, the latter manifesting with polydactyly, cleft lip, and scoliosis.

The aim of this paper is to report a case of JSRD that presented with renal, ocular, and neuropsychomotor changes that should prompt suspicion of the syndrome, and to demonstrate the importance of early diagnosis preceded by adequate screening and childcare for proper management and follow-up of the child.

CASE REPORT

A 1-year-and-4-month-old female was admitted to the emergency service with a 5-day fever (spikes of 38.4ºC) associated with unpleasant smelling urine. On physical examination, the patient exhibited general health deterioration, was eupneic, and had regular heart rate; the neurological examination was characterized as abnormal due to hypotonia and abnormal eye movements. The mother denied any previous history of urinary tract infection.

The initial laboratory tests showed leukocytosis with neutrophilia (26,730 leukocytes/cc with 5% band and 65% segmented neutrophils); C-reactive protein was 28.1 mg/L. The test of abnormal elements and sediments in urine showed proteinuria (+++), hematuria (+++), presence of leukocytes, and absence of nitrite, with numerous pyocytes and increased bacterial flora. Urine culture was negative, but the urine was collected after the start of antibiotics. Antibiotic therapy with ceftriaxone (100 mg/kg/day) was initiated for febrile urinary tract infection and was maintained for 7 days. During hospitalization, an ultrasound of the urinary tract showed the right kidney with normal echographic appearance and the left kidney with several smooth-walled cysts, and the renal cortex was not visualized (Figure 1). The mother reported that the child was being followed as an outpatient by a pediatric nephrologist and a pediatric neurologist. Pre- and post-natal exams were requested and recorded.

The patient was the second child of parents without consanguinity and was delivered by C-section at 40 weeks and 1 day of gestation. She weighed 3,875 g at birth, which was considered large for gestational age; she measured 51 cm, and her head circumference was 36 cm. The Apgar scores at 1 and 5 minutes of life were 8 and 9, respectively, and there were no complications during birth. An obstetric ultrasound performed at 31 weeks and 3 days of gestation showed the fetal left kidney with increased volume, without corticomedullary differentiation, and several noncommunicating anechoic images, measuring between 9 mm and 14 mm (suggestive of a multicystic dysplastic kidney). Renal monitoring was conducted up to 40 weeks with additional obstetric ultrasound examinations. After being discharged from maternity, the infant was referred to outpatient follow-up with a pediatric nephrologist, and a renal scintigraphy with Tc-DTPA and DMSA was requested, showing a normal functioning right kidney and a nonfunctioning left kidney. Continuous use of sulfamethoxazole–trimethoprim was prescribed as prophylaxis for urinary tract infection.

At 3 months of life, the mother noticed that the child kept an upward gaze and had muscular flaccidity, not being able to hold her head. She sought the assistance of a pediatrician who, on physical examination, confirmed ocular changes suggestive of a reduced visual field, generalized hypotonia, and inability to sustain trunk posture, which are characteristic of delayed neuropsychomotor development. The infant was referred to a neuropsychiatrist who requested a transfontanel ultrasound, which showed no changes. At 1 year and 3 days, the infant continued to show delayed neuropsychomotor development; she was only able to sit with support and exhibited uncoordinated movements and limb hypotonia, no speech development, and still had visual changes. The neuropsychiatrist ordered a magnetic resonance examination of the head, which showed a prominent thickening of the superior cerebellar peduncles (“molar tooth sign”) associated with a morphological alteration of the fourth ventricle (“bat wing”) and agenesis of the cerebellar vermis (Figure 2). She was referred to the genetic service for genetic study and confirmation of the diagnosis of Joubert syndrome.

Electroencephalography performed at 14 months of age was normal for the patient’s age. Echocardiography also did not show heart changes and was scheduled to be repeated at the age of 3–4 years.
Residência Pediátrica 2018;8(3):137-140.

Figure 2. Magnetic resonance of the head showing thickening of the posterior cerebellar peduncles ("molar tooth sign").

This study did not require the approval of an ethics committee because it was an isolated case, and the mother, who was the adult responsible for the child, signed an informed consent form.

COMMENTS

JSRD is a recessive autosomal set of disorders characterized by hypoplasia of the cerebellar vermis, with prominent superior cerebellar peduncle, which leads to the "molar tooth sign" in an axial section of magnetic resonance imaging of the head. This is manifested clinically as hypotonia, delayed neuropsychomotor development, abnormal eye movements, and an irregular breathing pattern with hyperpnea/apnea, which may be noticeable since the neonatal period. The "molar tooth sign" in a neurological image is a mandatory criterion for the diagnosis of JSRD. Joubert syndrome is an entity composed of clinically and genetically heterogeneous diseases, associated with neurological changes and varying involvement of multiple systems such as the ocular, renal, and skeletal systems. According to studies, at least seven mutations are known to be related to the syndrome, namely AHI1 in 6q23, NPHP1 in 2q13, CEP290 (NPHP6) in 12q21.32, TMEM67 in 8q21, and RPGRIP1L in 16q12.2 and in two other genes 9q34 and 11p12-q13. These mutations may be associated with the distinct types of the syndrome, resulting in phenotypic variability. Some of these genes are known for playing essential roles in the development and functioning of several types of cells, including photoreceptors, neurons, and renal tubule and biliary duct cells.

Disorders defined as variants are associated with variations in the classic clinical presentation, such as other abnormalities of the central nervous system (encephalocele and other posterior fossa abnormalities), Meckel syndrome, skeletal defects with polydactyly being prevalent and orofacial changes occurring more rarely, and scoliosis as a complication. Coloboma and retinal dystrophy are also reported, as well as renal disease, including cystic dysplasia and nephronophthisis.

Hypotonia occurs early in the life of almost all patients with this syndrome, during the neonatal period or during infancy; gait ataxia and loss of balance are also frequent findings. Thus, patients who exhibit these changes should undergo magnetic resonance imaging of the head, bearing in mind this diagnostic hypothesis. Among the respiratory anomalies found in JSRD are episodes of hyperpnea, alternating or not with apnea, which normally disappear at 6 months of life. A severe respiratory form is characterized by prolonged periods of apnea, which indicate the need for intensive treatment and ventilation support.

Neuropsychomotor development may become compromised, primarily with delayed motor and language development; however, this is not a mandatory criterion for diagnosing the syndrome. There are reports of siblings with Joubert syndrome who have different degrees of motor and intellectual development delay. Therefore, it is possible for patients to have a normal intellect.

The retina is one of the most affected organs in JSRD, especially in the form of retinal dystrophy, because of the gradual degeneration of the photoreceptor cells. Ocular disorders include eye movement abnormalities, including horizontal, vertical, or pendular nystagmus, strabismus, oculomotor apraxia, eyelid ptosis, and in more severe cases, compromised visual acuity or even blindness (Leber’s congenital amaurosis).

Renal disease is described in 25%–30% of individuals affected by Joubert syndrome and may be divided into two subtypes: cystic dysplasia and juvenile nephronophthisis. Cystic dysplasia is characterized by the presence of multiple cysts of varying size, visualized on ultrasound of the kidney and urinary tract. The cysts may be present since birth. The finding of cystic dysplasia is characteristic of the JSRD variant known as Dekaban–Arima syndrome.

Juvenile nephronophthisis is characterized by a tubulointerstitial structural disorder, with microcysts in the renal tubules that lead to abnormal urine concentration. It manifests with polydipsia, polyuria, anemia, and growth impairment. It may progress to renal failure, usually in the second decade of life, which requires dialysis or renal transplantation. Ultrasound through the course of the disease shows a decrease in kidney dimensions, as well as scarring of the kidney parenchyma.

The patient in this case had findings typical of Joubert syndrome, which include the "molar tooth size" on magnetic resonance imaging of the head, delayed neurological development, and renal malformations, which characterize the
Dekaban–Arima syndrome, and ocular changes suggestive of reduced visual field and strabismus.

CONCLUSIONS

Considering the heterogeneous and multisystemic nature of JSRD, neuropsychomotor changes, some noticeable since birth, associated with visual and skeletal changes, in combination with findings of renal changes on ultrasound, should be indicative of a diagnosis for JSRD. Magnetic resonance imaging of the head should be requested, which shows aplasia of the cerebellar vermis with the “molar tooth sign,” a mandatory criterion for diagnosing the syndrome. Some patients progress with end-stage renal disease, and therefore, it is recommended to thoroughly investigate renal malformations and to evaluate renal function whenever this syndrome is suspected, aiming for adequate patient management and improved prognosis.

REFERENCES

7. Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the "molar tooth". Lancet Neurol. Author manuscript; available in PMC 2014 September 01.