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CLINICAL CASE

Joubert syndrome: a case report of neonatal presentation and early diagnosis

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Abstract

Background: *Joubert syndrome is a rare genetic condition with a prevalence of 1:80,000–1:100,000. In most cases, it shows an autosomal autosomal recessive hereditary pattern, although X-linked and autosomal dominant cases have been described. The distinctive characteristic of this syndrome is the malformation at cerebral and cerebellar levels, known as the "molar tooth sign," hypotonia, and delayed neurodevelopment.* **Case report:** *We describe the case of a newborn with transient tachypnea. However, during hospital stay, he showed other clinical signs not corresponding to the admission diagnosis, such as bradycardia, apneas, hypotonia, and alteration in swallowing mechanics. To rule out etiologies of central origin, we conducted a magnetic resonance of the brain and identified the "molar tooth sign," where the pathognomonic sign of Joubert syndrome.* **Conclusions:** *Rare genetic diseases may manifest as early as the neonatal period with non-specific signs. The early diagnosis of Joubert syndrome is reflected in better pediatric follow-up, which impacts its prognosis and the possibility of improving the patient's quality of life with a multidisciplinary management and genetic counseling.*

Keywords: *Tachypnea. Apnea. Joubert syndrome. Genetic diseases.*

Síndrome de Joubert: reporte de caso de presentación neonatal y diagnóstico temprano

Resumen

Introducción: *El síndrome de Joubert es una rara condición genética con una prevalencia de 1:80,000 a 1:100,000. En la mayoría de los casos se presenta con un patrón de herencia autosómica recesiva, aunque se han reporatdo casos ligados al cromosoma X y autosómicos dominantes. La característica distintiva de este síndrome es la malformación a nivel cerebral y del cerebelo conocido como el "signo del molar", hipotonía y retraso en el neurodesarrollo.* **Caso clínico:** *Se describe el caso de un recién nacido con taquipnea transitoria del recién nacido; sin embargo, durante su estancia manifestó otros signos que no correspondían con el diagnóstico de ingreso, como bradicardia, apneas, hipotonía y alteración en la mecánica de la deglución. Para descartar etiologías de origen central, se realizó una resonancia magnética cerebral en la que se detectó el "signo del molar", patognomónico del síndrome de Joubert.* **Conclusiones:** *Las enfermedades genéticas raras pueden manifestarse desde el periodo neonatal con signos muy inespecíficos. El diagnóstico precoz del Síndrome de Joubert permite un mejor seguimiento pediátrico que impacta en su pronóstico y en la posibilidad de mejorar la calidad de vida del paciente con un manejo multidisciplinario, así como brindar asesoramiento genético.*

Palabras clave: *Taquipnea. Apnea. Síndrome de Joubert. Enfermedad genética.*

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Introduction

Joubert syndrome is a rare genetic condition with a 1:80,000–1:100,000 prevalence[1]. This syndrome was described in 1968 by Dr. Marie Joubert in a family presenting with respiratory pattern abnormality (hyperventilation), abnormal eye movements, ataxia, intellectual disability, and cerebellar vermis agenesis[2].

Joubert syndrome has often been described with an autosomal recessive inheritance pattern, although heterozygous variants in the *ZNF423* and *OFD1* genes indicate dominant and X-linked inheritance, respectively[3]. It is classified within the group of diseases known as ciliopathies[4]. The hallmark of this syndrome is the malformation of the brain and cerebellum known as the "molar tooth sign," hypotonia, and neurodevelopmental delay[5].

This disease manifests initially in the neonatal period with alterations of the respiratory pattern (tachypnea or neonatal episodic apnea). Subsequently, this pattern improves, and new neurological symptoms appear, such as hypotonia or delayed psychomotor development. It has a clinically heterogeneous picture, which may be associated with renal, hepatic, or ocular alterations. Periodic complementary tests should be performed as part of the active search for these alterations[6].

Clinical case

We describe the case of a male newborn whose mother was 25 years old, second gestation with adequate prenatal control. Two structural ultrasounds were performed, which reported the measurement of cisterna magna in the 95th percentile. It was decided to terminate the pregnancy by the abdominal route at week 37 due to cholestasis associated with gestation.

The newborn with an irregular respiratory effort required a cycle of positive pressure ventilation: APGAR at 1 min was 8 and 9 at 5 min. At the nursery, the patient presented persistent tachypnea, so an oxygen hood was placed. At 6 h of life, he was admitted to intermediate therapy with high-flow nasal prongs and a diagnosis of transient tachypnea of the newborn. Capillary blood gas showed compensated respiratory acidosis with normoxemia, and a chest X-ray showed lung volume of nine intercostal spaces.

On physical examination, the patient showed decreased muscle tone, weak sucking reflex, hypertelorism, blepharoptosis of the right eye, a flat nasal bridge with a short nose, and postaxial polydactyly of the left hand. He presented no other pathologic data.

The patient was on fasting during the first 48 h of life due to persistent tachypnea > 80/min. When the enteral feeding was restarted, he presented stridor and increased respiratory rate > 100/min. In addition to tachypnea, he presented abundant secretions since birth and polydactyly. An esophagogram was performed, which showed no evidence of a tracheoesophageal fistula, but an alteration in the swallowing mechanics shown by the passage of contrast medium secondary to intermittent dysfunction in the closure of the larynx.

Given the persistence of bradycardia, an electrocardiogram showed sinus bradycardia, and an echocardiogram reported a structurally healthy heart. In addition to the bradycardia, episodes of apneas were identified, so caffeine management was initiated.

The combination of clinical data (sinus bradycardia, swallowing mechanics disorder, hypotonia, apneas, and blepharoptosis) lead to an investigation for a central hypotonic syndrome.

A brain magnetic resonance imaging (MRI) showed a spectrum of midbrain and hindbrain malformations characterized by symmetrical thickening and elongation of the upper cerebellar peduncles with a vertical arrangement, giving the midbrain a molar tooth appearence (Figure 1). The cerebellar hemispheres showed reduced volume and alteration (disorganization) in their folial pattern. The vermis was also hypoplastic and dysplastic, mainly toward its superior portion. The cisterna magna was wide (Figure 2). It was concluded as a Joubert's syndrome diagnosis.

A polysomnography showed apneas of central origin. In addition, the patient presented normal auditory-evoked potentials and visual potentials with delayed response. Electroencephalogram showed no abnormal activity.

As part of the evaluation of Joubert syndrome, we performed a renal ultrasound, in which bilateral nephronophthisis was reported, and a Schwartz glomerular filtration rate of 37.2 mL/min was calculated. Additionally, the hepatic ultrasound showed no alterations. The ophthalmology evaluation reported aponeurotic ptosis of the right eye and normal fundus in both eyes.

A genetic panel analysis based on next-generation sequencing technology (Invitae, Corp.) and deletion/duplication analysis of 102 genes related to ciliopathies was performed. We found a heterozygous variant c.719T>C (p.Ile240Thr) in the *CEP104* gene, and a heterozygous variant c.481G>A (p.Asp161Asn) in the *TMEM231* gene. Both variants were classified as variants of uncertain significance. Homozygous or compound heterozygous variants in these genes cause Joubert syndrome, and digenic inheritance has been

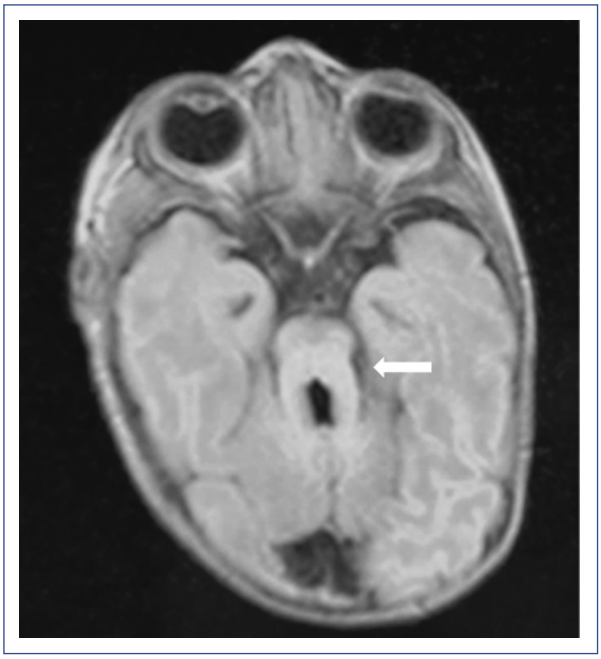

Figure 1. Brain MRI, axial plane, T1-weighted. There is a classic aspect of molar tooth of the midbrain secondary to thickening and elongation of the superior cerebellar peduncles.

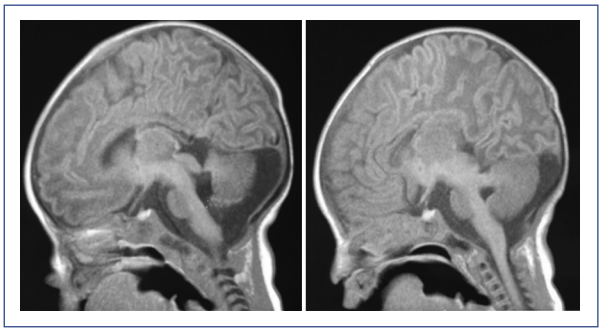

Figure 2. Brain MRI, T1, sagittal and parasagittal planes, showing hypoplasia and dysplastic aspect of the superior cerebellar vermis and cerebral hemispheres, associated with folial disorganization and wide cisterna magna, in addition to thinning of the corpus callosum.

identified at gene *loci* related to the etiology of Joubert syndrome[7].

Discussion

Transient tachypnea of the newborn is the first cause of admission to neonatal care therapy. We present the clinical case of a newborn with initial clinical manifestations and risk factors for this diagnosis (male, early term, and cesarean birth). However, during his stay, the patient had an atypical evolution, showing neurological signs and minor dysmorphias that led us to rule out causes of central origin. The "molar tooth sign," pathognomonic of Joubert's syndrome, was detected on MRI. Once recognized, no other differential diagnosis was established. This radiological finding is caused by the lack of fiber decussation of the superior cerebellar peduncle, leading to the elongation of the peduncles; additionally, the peduncles have a more horizontal course, and there is an enlargement of the interpeduncular cistern. Other primary imaging features of Joubert syndrome are the absence of the cerebellar vermis and deformity of the fourth ventricle[8].

Currently, more than 35 genes have been associated with Joubert syndrome[8]; in our case, alterations in the *TMEM231* and *CEP104* genes were reported. Although the variants found in this patient have been reported to be of "uncertain significance," variant prediction programs (SIFT, PolyPhen-2, and Align-GVGD) were used. In the case of the c.719T>C (p.Ile240Thr) variant in *CEP104*, all programs suggested that it could be a disruptive variant. In contrast, in the c.481G>A (p.Asp161Asn) mutation in *TMEM231*, the prediction algorithms were inconsistent, or the information about structure and function was unavailable.

CEP104 is located on 1p36.31 and encodes the 104kDa centrosomal protein, required for ciliogenesis and for the structural integrity of the cilia endings[9]. *TMEM231* is located on 16q23.1 and encodes the transmembrane protein 231, which is part of a protein complex at the base of the cilium that acts as a barrier to restrict protein diffusion between the plasma and ciliary membranes[10].

Considering the patient's phenotype and the importance of *CEP104* and *TMEM231* in ciliary formation and function, and reports of digenic inheritance, the molecular findings were used for follow-up, prognosis, and genetic counseling. In our case, the variants were not candidates for segregation in the parents due to their uncertain significance. However, a 25% recurrence risk was provided to the parents, informing them of the limitations of the result. The mutations should be reanalyzed, as they may be reclassified as pathogenic in the future.

Although many genes can be affected, the genetic cause can currently be determined in 62% of individuals with Joubert syndrome[8]. Identifying the underlying genetic defect can help define the prognosis of the disease and guide selective detection of secondary

diseases, and allow accurate genetic counseling, the option of prenatal diagnosis, and preimplantation of genetic diagnosis[11].

Prenatal diagnosis of Joubert syndrome by ultrasound is rare. Medical sonographers can usually observe non-specific features, such as widened posterior fossa and cerebellar vermis dysplasia. However, these signs can also be found in other malformations, such as Dandy–Walker malformation and pontocerebellar hypoplasia, among others[12]. Based on obstetric ultrasound findings and complemented with fetal MRI, prenatal diagnosis of Joubert's syndrome is now possible during the third trimester of gestation[13]. However, in the case of our patient, prenatal diagnosis was not performed since the only abnormal finding reported was the measurement of cisterna magna in the 95th percentile.

An epidemiological study conducted in Italy in 284 patients with Joubert syndrome showed that the mean age at diagnosis was 6.6 years. An early diagnosis is difficult because Joubert syndrome does not have an easily recognizable facial appearance[14].

The clinical spectrum of Joubert syndrome may be accompanied by some alterations of other organs, such as retinal defects, nephronophthisis, and hepatic fibrosis; other infrequent conditions include chorioretinal or optic nerve colobomas, congenital cardiac malformations, *situs inversus*, skeletal dysplasia, and midline defects[15].

Eight subtypes of Joubert syndrome have been described: classic, with retinal disease, renal disease, oculorenal disease, liver disease, oral-facial-digital features, acrocallosal features, and asphyxiating thoracic dystrophy features[16].

A study of 16 patients with Joubert syndrome showed cerebellar vermis hypoplasia/aplasia and apnea present in all patients, polydactyly was present in three patients, renal problems with cysts were present in five, and 11 had abnormal electroretinograms[17]. In the case of our patient, he presented all the previously mentioned findings. However, only the fundus has been explored in the ophthalmologic approach, which was normal; until now, an electroretinogram has not been performed.

Once Joubert syndrome has been diagnosed, it should be complemented with renal and hepatic function tests, hepatic and renal ultrasound, and polysomnography to evaluate apneas of central origin. In addition, evaluation by ophthalmology, pediatric cardiology, genetics, pediatric gastroenterology, rehabilitation, and pediatric neurology should be made[2]. These studies allow to identify the Joubert's syndrome subtype and provide a better follow-up and long-term prognosis.

According to his clinical features, our patient could be classified within the subgroup of Joubert's syndrome with renal disease; however, he has some orofacial-digital features.

Each patient's prognosis is difficult to define since Joubert syndrome has various related conditions and a wide range of intellectual disabilities[11]. At present, the most important risk factor in our patient is nephronophthisis; therefore, close monitoring by pediatric nephrology should be maintained to preserve renal function as much as possible.

Treatment of the disease is mainly symptomatic and should be multidisciplinary. It usually includes physical therapy programs and adaptation of education to the cognitive and behavioral characteristics of the patient, and treatment of complications or associated symptoms that may appear. The primary care pediatrician's role should be one of integration and coordination of the different referrals[18].

Rare genetic diseases can manifest from the neonatal period with non-specific signs that could be confused with common neonatal diseases. In this case, tachypnea is a very frequent sign in the neonatal stage and can be a symptom of multiple origins, including respiratory, hemodynamic, infectious, hematological, and neurological diagnoses. This case should lead us to reflect on the importance of physical examination and clinical judgment to conduct approaches leading to specific diagnoses and, consequently provide a better treatment plan.

Early diagnosis of Joubert syndrome is reflected in better pediatric follow-up, which impacts prognosis and improving the patient's quality of life with multidisciplinary management and providing genetic counseling.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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