Exploring Joubert Syndrome: A Rare Case Study from Indonesia

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Abstract

Background: Joubert Syndrome is a rare autosomal recessive disorder characterized by midbrain-hindbrain malformation and multisystem involvement. This study aims to present a detailed case of Joubert Syndrome from Indonesia, emphasizing clinical presentation, diagnostic challenges, and management strategies in a resource-limited setting.

Methods: This descriptive case study examines a newborn female referred for breathing difficulties and a skull tumor present since birth. Data were collected through clinical evaluations, imaging studies, laboratory tests, genetic analysis, and multidisciplinary consultations. A literature review was conducted to compare the findings with global data.

Result: The first case involved a female infant with hydrocephalus, a posterior skull mass, and microcornea. Echocardiography showed a patent foramen ovale, while genetic analysis confirmed a normal 46,XX karyotype. The second case featured a male infant with posterior meningocele, seizures, and retinal dystrophy. EEG confirmed subclinical seizures, and genetic testing identified pathogenic TMEM237 mutations consistent with Joubert Syndrome type 14. Both infants received respiratory support, antibiotics, and targeted treatments, resulting in significant clinical improvement.

Conclusions: These cases highlight the importance of multidisciplinary care and genetic testing in Joubert Syndrome diagnosis and management. Early recognition, advanced diagnostics, and consistent follow-up are crucial for optimizing outcomes, particularly in resource-limited settings.

Introduction

Joubert syndrome is a rare genetic disorder that affects a small segment of the population. Its occurrence is estimated to be between 1 in 80,000 and 1 in 10,000 individuals. Dr. Marie Joubert made the initial identification of it in 1968. Individuals with undeveloped cerebellar vermis, ataxia, aberrant eye movements, and a family history of respiratory disorders are more likely to exhibit this syndrome. Joubert syndrome frequently has an autosomal recessive mode of inheritance. Heterozygous variants in the AHI1 and OFD1 genes, on the other hand, can occasionally show dominant and X-linked inheritance, respectively.[1] This disease, which is categorized as a ciliopathy, is identified by unique brain and cerebellar abnormalities that are referred to as the "molar tooth sign," in addition to low muscle tone and delayed neurodevelopment.[2]

Joubert syndrome symptoms might include abnormal breathing patterns in neonates, such as fast breathing or periods of cessation of breathing. These symptoms usually manifest during the neonatal period. Further neurological symptoms, such as decreased muscle tone or delayed cognitive and motor skill development, may result from these patterns. Different clinical symptoms may be present with the illness, and these symptoms may be linked to problems in the kidneys, liver, or eyes. Regular supplementary testing is essential as part of proactive measures to find and treat any possible issues.[3]

Material And Methods

This descriptive case study analyzed clinical, radiological, genetic, and ophthalmologic findings in two term infants presenting with cranial anomalies and respiratory distress. Diagnostic tools included MRI, echocardiography, genetic testing, and electroencephalography (EEG).

Result

Case I

The patient was referred from another hospital due to breathing difficulties and a tumor located on the back of the skull, which had been present since birth. She weighed 2500 grams at birth and received an Apgar score of 8/9. The delivery was conducted via cesarean section. The initial diagnoses included meningoencephalocele, respiratory discomfort, potential Dandy-Walker Syndrome, and suspected hydrocephalus.

Upon examination, the patient exhibited a solid, immobile, and painless mass measuring 1.5 x 1 x 1.5 cm. On the first day, her oxygen saturation (SpO2) levels ranged from 93% to 96%, and she was breathing spontaneously while on

CPAP with settings of 7/25%. The patient demonstrated normal urine output and bowel movements and tolerated feedings well. Subsequent diagnoses included encephalocele, hydrocephalus, sepsis, dehydration, hypernatremia, and microcephaly. A comprehensive series of tests were ordered, comprising a complete blood count, CRP, sodium, potassium, calcium, blood glucose, blood gas analysis, blood culture, an anteroposterior thoracoabdominal X-ray, head ultrasound, and a consultation with neurosurgery. The treatment plan encompassed CPAP with PEEP at 7 and FiO2 at 25%, as well as administration of amoxicillin, gentamicin, and parenteral nutrition.

Table 1. Summary of the laboratory results (Case I)

	Day 1	Day 3	Day 5	Day 12	Day 17
Hb	15,8	14,9		12,7	11,2
Hct	47,3	41,1		36,5	33,2
WBC	5.230	5.52		10.120	10.610
PLT	382.000	266.000		405.000	418.000
CRP	0,2	0,0		0,9	3.1
Bilirubin Total/ Direct/ Indirect	8,7/0,14/ 8,06		2,85/0,15/2,4		0,29/0,14/ 0,15
PT/APTT	11,9/ 39,0				
Blood Glucose	74				81
Natrium/Kalium/Chloride/ Calcium	153/4,5/ 12,9/1,33			142/5,4/ 109/1,29	138/5.6/106/ 1.32
Echocardiography	Patent Foramen ovale				
Protein Total/Albumin					5.40/3.45
Ureum/Creatinine /e-GFR	16/0.4/ 173.1				
IgG/IgM TORCH	Positive (25,0) Negative (0,5)				

On the second day, the patient showed a reduction in retractions, diminished shortness of breath, and no signs of enteral intrusion. The enteral nutrition was increased to eight doses of 20 ml each via an orogastric tube, while parenteral nutrition was provided without sodium.

Antibiotics were continued. By day four, retractions were minimal, there was no tightness, although occasional desaturation was observed. The patient was then transitioned to a nasal cannula with 0.25% FiO2 at 23-25%. Full enteral nutrition was established, and antibiotics were discontinued.

An ophthalmology consultation assessed the patient, revealing the following: Corneal diameter was 9-10 mm in the right eye (OD) and 7-8 mm in the left eye (OS), with clear lenses. Fundoscopic examination showed oval papillae with clear boundaries, a cup-to-disc ratio of 0.3, and normal retinal appearance, leading to a diagnosis of microcornea in the left eye (OS < OD) and optic nerve head anomalies (OD > OS). A re-evaluation was planned in 1-2 weeks.

A genetic examination was performed using the peripheral blood culture method with G-banding, which confirmed a female karyotype (XX) with 46 chromosomes present in all 20 analyzed metaphases. No structural chromosomal abnormalities or mosaicism were detected. There were

also no mutation or microdeletion points found at the examined band resolution. Whole Exome Sequencing is highly recommended for this patient based on significant clinical findings that may indicate Joubert syndrome.

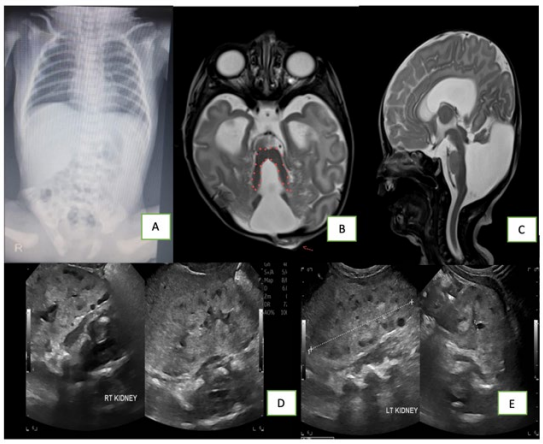

Figure 1. (A) Babygrams: No abnormalities detected in thorax and abdomen X-rays. (B) MRI axial slice showing the "molar tooth sign" (highlighted area with red dots): indicates expansion of the interpeduncular fossa and the superior cerebellar peduncles. The red arrow in the occipital region points to an atretic encephalocele. (C) MRI sagittal slice illustrating Dandy-Walker Malformation: features vermian hypoplasia with cephalad rotation and an IV ventricle associated with cystic lesions in the posterior fossa. (D)(E) Bilateral diffuse parenchymal kidney disease characterized by small, multiple cystic lesions.

Echocardiography results showed atrial situs solitus and atrioventricular and ventriculo-arterial concordance, with normal pulmonary venous drainage. The foramen ovale remained open, resulting in a left-to-right shunt. The interventricular septum was intact, with mildly dilated right atrium and right ventricle. The left aortic arch was normal, with no coarctation of the aorta (CoA) or patent ductus arteriosus (PDA). There was no pericardial effusion, and the ventricles were contracting well without paradoxical movement. It was suggested to repeat the echocardiogram at 6 to 12 months of age.

Case II

A term infant was referred for evaluation due to a lump in the cranial region. The infant was delivered via cesarean section and had previously been treated in the neonatal intensive care unit (NICU) for respiratory distress. During their NICU stay, the infant received continuous positive airway pressure (CPAP) and antibiotics. On the second day of treatment, the infant exhibited symptoms including dyspnea, rapid breathing, and seizures, which prompted additional interventions in the NICU. To ensure comprehensive care, a variety of diagnostic and management procedures were performed. The infant underwent an MRI to evaluate for a potential posterior meningocele and received appropriate treatment for pneumonia. Furthermore, a bedside Cerebral Function Monitoring (OBM) device was used to continuously monitor subclinical seizures through electroencephalography (EEG), enhancing the overall management of the infant's condition.

Table 2. Summary of Laboratory Results (Case II)

	Day 1	Day 6
Haemoglobin	12,9	13,4
Hematocrit	36,1	38,4
Leucocyte	9.740	8.370
Thrombocyte	278.000	308.000
C-reactive protein	0,0	0,3
Blood Glucose	91	
Natrium/Kalium/Chlorida/ Calcium	137/4,2/1,1/1,25	141/5,7/1,23
Ureum	18	
Creatinine	0,3	
e-GFR	221,5	

A full-term baby was born weighing 3,500 grams and is currently improving, now weighing 4,294 grams. The primary medical issue being addressed is posterior meningocele, with possible pneumonia and seizures occurring early in life. The treatment regimen includes Amoxicillin, gentamicin, and oral Keppra. An echocardiogram showed normal atrial positioning (situs solitus) and proper alignment of the atrioventricular valves and ventricles (AV-VA concordance). The foramen ovale remains patent, leading to a left-to-right shunt. The intraventricular septum is intact, and all four heart chambers are functioning normally. The heart valves are standard, and a left aortic arch is present, with no signs of aortic coarctation (CoA) or patent ductus arteriosus (PDA). The pericardium has no fluid accumulation, and the ventricles contract effectively without any paradoxical movement. A follow-up echocardiogram is scheduled for six months to evaluate the patent foramen ovale (PFO). Additionally, the patient was referred to the ophthalmology department, where they were diagnosed with coloboma, retinal dystrophy, and unequal eye movements. A medical consultation included an Otoacoustic Emission (OAE) test, which showed no abnormalities. Chromosomal analysis revealed two heterozygous pathogenic mutations in the TMEM237 gene, resulting in a genetic diagnosis of autosomal recessive Joubert syndrome type 14.

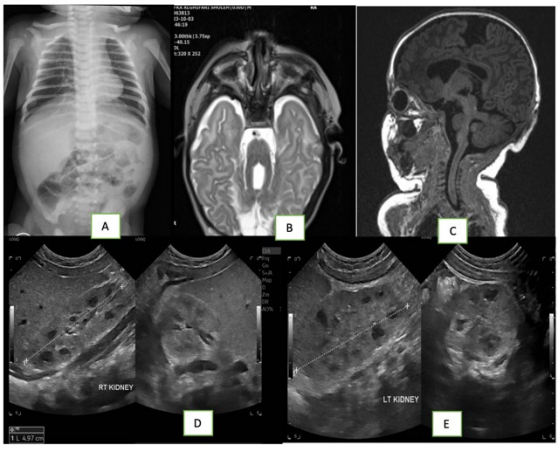

Figure 2. (A) Interstitial infiltrate in the lungs, differential diagnosis: pneumonia. (B) MRI axial slice image supporting a diagnosis of Joubert syndrome, associated with a posterior meningocele in the occipital midline (evident bone defects and the size of the lesions above), along with ventriculomegaly (ex-vacuo), anti-white matter volume loss, and hypotrophy of the corpus callosum. (C) An MRI sagittal slice showed no obvious cortical malformations, cerebral edema, encephalomalacia, bleeding, calcifications, or current intracranial lesions/masses. (D)(E) Findings suggest bilateral parenchymal kidney disease, predominantly on the left side.

Table 3. Two heterozygous pathogenic variants were identified in the TMEM237 gene, consistent with a genetic diagnosis of autosomal

Gene	Variant Coordinates	Amino Acid Change	SNP Identifier	Zygosity	In Silico Parameters*	Allele Frequences**	Type and Classification***
TMEM237	NM_001044385.3:c.550d	p.(Ser184Alafs*12)	N/A	Heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A Mutation Taster: N/A Conservation: Conservation_aa:	Genom AD: - ESP: - 1000 G: - CentoMD: -	Frameshift Pathogenic (class 1)
TMEM237	NM_001044385.2:c.677+1G>A	p.?	N/A	Heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A Mutation Taster: N/A Conservation_nt: high Conservation_aa: 2/2 likely splice effect	Genom AD: 0.0000089 ESP: - 1000 G: - CentoMD: -	Splicing Pathogenic (class 1)

Discussion

Joubert syndrome (JS) is a rare genetic disorder that is inherited in a recessive manner. It is characterized by a distinctive abnormality in the midbrain and hindbrain, known as the "molar tooth sign," along with a variety of neurological and systemic issues. The reported incidence of JS ranges from approximately 1 in 80,000 to 1 in 100,000 live births. However, recent research suggests that these prevalence rates may be higher due to improvements in diagnostic techniques and increased awareness of the condition.[4] JS is found worldwide, though its genetic composition varies significantly across different populations. Mutations linked to the development of JS have been identified in over 30 genes. Specifically, mutations causing JS to have been reported in more than 35 genes, including INPP5E, AHI1, NPHP1, NPHP6 (also known as CEP290), TMEM67 (MKS3), RPGRIP1L, ARL13B, CC2D2A, OFD1, TTC21B, KIF7, TCTN1, TCTN2, TMEM237, CEP41, TMEM138, C5orf42, TCTN3, ZNF423, TMEM231, CSPP1, and PDE6D. These mutations can lead to different phenotypic variations of the syndrome.[5]

To accurately diagnose classic Joubert Syndrome (JBTS), the following criteria must be satisfied: (a) A cranial MRI examination should reveal three specific findings: cerebellar vermis hypoplasia (CVH), a deep interpeduncular fossa, and a thickened and extended superior cerebellar peduncle; (b) There should be clear evidence of cognitive impairment or developmental delay, with varying degrees of severity; (c) Hypotonia must be present during infancy; (d) One or both of the following features, while not mandatory, can support the diagnosis: irregular breathing patterns during infancy (such as episodic apraxia and/or tachypnea, which may alternate) and abnormal eye movements (including nystagmus and/or oculomotor apraxia (OMA)).[2] Furthermore, many children diagnosed with Joubert Syndrome display distinctive facial characteristics. These may include a broad forehead, raised eyebrows, drooping eyelids, widely spaced eyes, an open jaw position, and reduced muscle

tone in the face. Some individuals with JBTS may also present with polydactyly, characterized by the presence of extra fingers and/or toes.[4]

Based on the facts presented, the first patient has multiple illnesses that may be interconnected or merit consideration as potential alternative diagnoses. The patient is demonstrating autonomous respiration using CPAP at a pressure of 7/25% and shows no signs of bradycardia or significant decreases in blood oxygen saturation. Blood oxygen (SpO2) levels have been recorded between 93-96%. The interactions between food and drink appear satisfactory, and the function of the intestines and bladder is within the expected range. However, certain health issues are evident, such as low birth weight and current birth weight, which suggest possible nutritional and developmental challenges. The potential central abnormalities are relevant to the possible occurrence of both encephalocele and hydrocephalus. Additionally, medical disorders such as sepsis, dehydration, and hypernatremia require prompt medical intervention, as they may indicate a severe medical condition that necessitates appropriate fluid administration. Although not explicitly mentioned, the potential presence of microcephaly could further complicate the patient's health. It is essential to examine the symptoms in relation to JS.[6] However, the case description does not report any characteristic signs of JS, such as ataxia or breathing difficulties. Consequently, managing these individuals requires a thorough assessment to establish an accurate diagnosis and develop an effective management strategy, which may include both medical and nutritional therapies as needed. In this case, the patient's ophthalmological assessments and chromosomal examination results did not show the typical symptoms or indicators of JS. While JS can lead to various congenital abnormalities, including ocular anomalies and structural brain defects, there were no signs of JS present in the patient's examination results. Thus, although JS should be considered a potential diagnosis when evaluating patients with eye abnormalities and neurological issues, the observed ophthalmologic findings and chromosomal analysis results do not align with the typical symptom pattern associated with JS.[7] Therefore, it is crucial to continue focusing on identifying the underlying causes of these patients' ophthalmologic observations and optic nerve irregularities, developing appropriate treatment strategies, and ensuring ongoing monitoring. This regular monitoring is vital for the patient's well-being and recovery.

The MRI results of the head revealed several significant findings. The presence of the "molar tooth sign" indicates enlargement of the interpeduncular fossa and the superior cerebellar peduncle. This

observation is commonly seen in individuals with JS, a rare genetic condition that primarily affects brain development, particularly in the brain stem. Additionally, the MRI shows features associated with Dandy-Walker Malformation (DWM), a congenital anomaly characterized by underdevelopment or abnormal formation of the posterior area of the brain (vermis cerebelli) and enlargement of the brain ventricles in the posterior region. The findings include vermian hypoplasia with cephalad rotation, meaning the cerebral vermis develops atypically and rotates towards the head.[8] Cystic lesions were identified in the posterior fossa, connected to the fourth ventricle, which could also indicate the presence of Dandy-Walker Malformation. Furthermore, an atretic encephalocele was discovered in the occipital region. This condition results from anomalies in brain development that create gaps or irregularities in the skull bones. It is important to note that the MRI findings align with the typical characteristics of Joubert Syndrome, particularly the presence of the molar tooth sign. However, Dandy-Walker Malformation and atretic encephalocele can also occur in other neurological conditions and may produce symptoms similar to those of JS. In summary, the MRI results provide general support for a potential diagnosis of Joubert Syndrome. Nevertheless, it is crucial to evaluate these findings comprehensively and consult with specialists in neurology and genetics to confirm the diagnosis accurately and develop an appropriate treatment plan for the patient.[8]

The patient was diagnosed with bilateral diffuse parenchymal kidney disease based on the abdominal ultrasound findings, which revealed numerous tiny cystic lesions. This discovery suggests multiple disorders, including multicystic dysplastic kidney (MCDK) and cystic kidney disease. Both of these conditions are inherent abnormalities of the kidneys characterized by the formation of cysts within the kidney tissue. It's important to note that cystic kidney disorders can be associated with JS, a rare genetic condition affecting brain development. Many cases of JS have been reported to exhibit renal abnormalities, such as cystic kidney disease. However, these findings alone are insufficient for confirming a diagnosis of JS, as numerous other symptoms and indicators need to be considered.[9] The absence of hydroureteronephrosis or nephrocalcinosis suggests there is no urinary tract obstruction or calcium buildup in the kidneys. Additionally, there were no abnormalities detected in the liver, gallbladder, spleen, pancreas, or intestines. The patient's medical history indicates that he was born via cesarean section (C-section) and later admitted to the Neonatal Intensive Care Unit (NICU)

due to respiratory distress. The treatment involved the use of Continuous Positive Airway Pressure (CPAP) and antibiotics. On the second day of treatment, the patient exhibited symptoms of dyspnea, rapid breathing, and convulsions, necessitating further medical intervention in the hospital. A chest X-ray revealed interstitial infiltrates in the lungs, suggesting pneumonia; however, no irregularities were observed in the abdominal region. The patient was diagnosed with several issues, including being aterm for appropriate gestational age, possible posterior meningoceles, pneumonia, and newborn seizures. He received antibacterial and anticonvulsant treatments. An echocardiogram indicated normal atrial positioning (atrial situs solitus), proper alignment of the atrioventricular valves (AV VA concordance), and the presence of a patent foramen ovale with a left-to-right shunt. While the heart appeared normal, the existence of an open foramen ovale poses a potential risk for future cardiac complications. Following this, a head MRI revealed features indicative of Joubert Syndrome, such as posterior meningoceles, ventriculomegaly, white matter atrophy, and corpus callosum hypotrophy. Despite the absence of other anomalies like cortical deformities or cerebral edema, the findings supported the diagnosis of JS. Furthermore, the ultrasound examination of the abdomen and urinary tract suggested possible bilateral parenchymal kidney disease, particularly in the left kidney, without distinct cystic characteristics or hydroureteronephrosis. Nevertheless, neither imaging technique is sufficient to definitively rule out cystic kidney disease, which may be associated with JS.

Conclusion

The diagnosis of Joubert Syndrome (JS) is supported by clinical signs and examination results, indicating potential complications such as posterior meningocele, pneumonia, and possible heart and renal abnormalities. However, confirmation requires further tests and careful monitoring of the patient's progress. Treatment and monitoring should be individualized based on the patient’s condition and the specific consequences of JS. In both cases, the male patients presented with a head lump, which aligns with Van Dorp et al. (1991), who described a case of a severely intellectually disabled boy with neurological issues, including Dandy-Walker malformation, corpus callosum hypoplasia, occipital meningoencephalocele, and bilateral coloboma of the optic nerve, along with a cystic mass behind the eyeball. Rare genetic disorders can manifest during the neonatal stage, often presenting with nonspecific symptoms that may be mistaken for common neonatal illnesses.

Tachypnea, a frequent symptom in neonates, can signal various underlying conditions, including respiratory, hemodynamic, viral, hematological, and neurological disorders. This case highlights the importance of physical examination and clinical evaluation in ensuring an accurate diagnosis and an effective treatment plan.

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