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Case Report

Internal Medicine Section

A Classical Sign with Uncommon Symptoms: Joubert Syndrome Presenting with Retinal Dystrophy and Keratoconus

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ABSTRACT

Joubert Syndrome and Related Disorders (JSRD) are a rare group of autosomal recessive ciliopathies characterised by the pathognomonic molar-tooth sign on Magnetic Resonance Imaging (MRI) of the brain. The clinical manifestations are usually multisystemic and may involve multiple organs. Early diagnosis is warranted, as neurological, renal, and ocular symptoms may remain latent that require multidisciplinary management. A 20-year-old male born to third-degree consanguineous parents, with a known history of global developmental delay and stage V chronic kidney disease on regular maintenance haemodialysis, presented with acute-onset high-grade fever and cough, along with a recent history of severe lower respiratory tract infection requiring mechanical ventilation. On examination, cerebellar signs including broad-based gait, dysmetria, dysdiadochokinesia, and intention tremors were noted, along with bilateral retinal dystrophy and keratoconus of the left eye. Laboratory investigations revealed anaemia and deranged renal function tests. MRI of the brain demonstrated the characteristic molar-tooth sign, with elongated superior cerebellar peduncles, agenesis of the cerebellar vermis, and a characteristic bat-wing appearance of the fourth ventricle. Ultrasonography of the kidneys showed bilaterally atrophied kidneys. A diagnosis of Joubert Syndrome with oculorenal involvement was made based on the neurological, renal, and ocular manifestations. This case highlights the typical clinical and neuroimaging features of JSRD, along with the additional finding of keratoconus, an uncommon ocular manifestation. Early diagnosis is essential for appropriate prognostication, genetic counselling, and timely intervention of organ-specific screening and surveillance, particularly in consanguineous families since the pattern of inheritance is recessive.

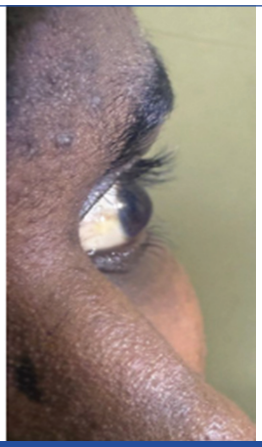
Keywords: Ciliopathies, Cerebellar diseases, Eye abnormalities, Neurodevelopmental disorders

CASE REPORT

A 20-year-old male, born to third-degree consanguineous parents presented with complaints of high-grade continuous fever not associated with chills and rigors with continuous non-productive cough of one-day duration. No history of breathlessness, or wheeze was present. One month prior to the current admission, he had been hospitalised at an outside facility for severe lower respiratory tract infection diagnosed to have community acquired pneumonia complicated by septic shock, requiring invasive mechanical ventilation for more than 12 days followed by supplemental oxygen. He was a known case of global developmental delay and intellectual disability with stage V chronic kidney disease on maintenance haemodialysis. Birth history was uneventful, with a full-term normal vaginal delivery following an uncomplicated pregnancy. There was no history of substance use or other significant habits. Family history was significant for consanguinity in the third degree with no other siblings affected with similar disorder and also in the preceding two generations.

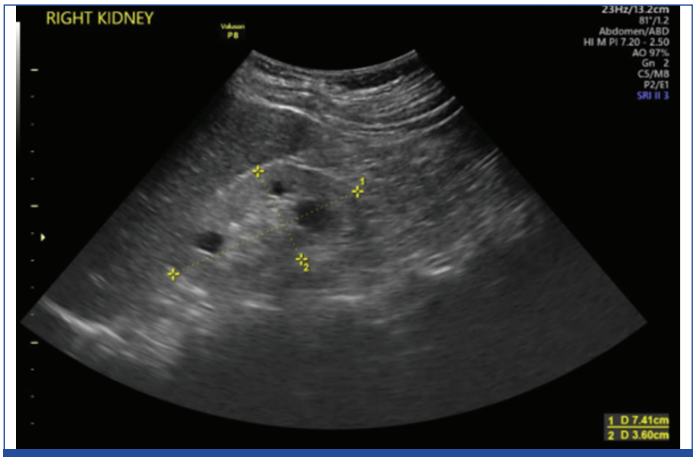
On examination, the patient was conscious and haemodynamically stable. Pallor was present, along with blackish pigmentation over the cheeks and multiple scratch marks over the forehead, cheeks, neck, abdomen, cubital fossae, and knees. Eye examination revealed keratoconus of the left eye [Table/Fig-1]. Cardiovascular examination showed normal heart sounds without murmurs. Respiratory system examination revealed bilateral normal vesicular breath sounds with weak basal crackles. Examination of the abdomen revealed a soft, non-tender abdomen without organomegaly, distension, or abnormal bowel sounds. Neurological examination showed intact cranial nerves, normal muscle tone and bulk, preserved motor power (5/5) in all limbs, normal deep tendon reflexes, and bilateral flexor plantar responses. Cerebellar signs including broad-based gait, dysmetria, dysdiadochokinesia, intention tremors, and ataxia were present, while sensory examination was normal. Based on the developmental delay, cerebellar signs, renal dysfunction, and ocular abnormalities, a provisional diagnosis of a syndromic ciliopathy was considered. Differential diagnoses included cerebellar ataxia syndromes, Senior-Løken syndrome, and other hereditary ciliopathies with oculorenal involvement.

Laboratory investigations revealed severe anaemia (haemoglobin 5.9 g/dL), deranged renal parameters (blood urea 45 mg/dL and serum creatinine 2 mg/dL). Serum creatinine was 2 mg/dL because the patient was vegetarian, with low muscle mass (he was lean and poorly nourished), the value was taken post dialysis as well, whereas there were other values ranging from 2.6-3.4 mg/dL throughout his hospital stay. Alkaline Phosphatase (ALP) 978 U/L was markedly elevated,whereas other liver function parameters like Alanine Transaminase (ALT) was 96 U/L, suggesting the cause of elevated ALP to be intrahepatic cholestasis leading on to fibrosis in future which is a known manifestation in JS. Further patient's parathyroid level and Vitamin D level was normal, hence raise in ALP could not be attributed to source from bone as secondary hyperparathyroidism and vitamin D deficiency was ruled out.

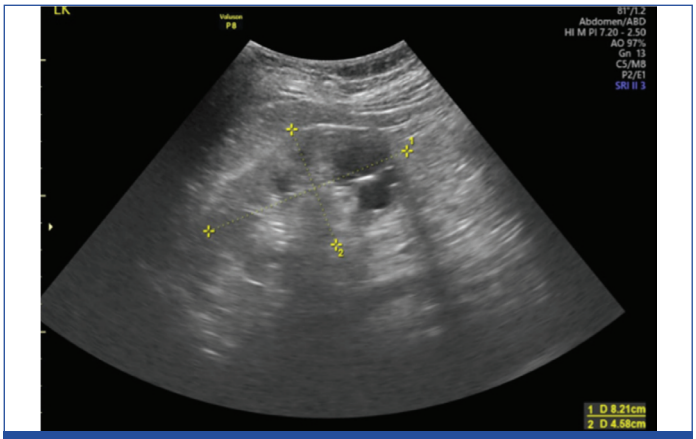


[Table/Fig-1]: External examination of the left eye showing keratoconus.

Ultrasonography of the abdomen and pelvis demonstrated bilaterally atrophic kidneys, with the right kidney measuring 7.4×3.6 cm and the left kidney measuring 8.2×4.5 cm [Table/Fig-2a,b] with altered echotexture of the liver. High-Resolution Computed Tomography (HRCT) of the chest showed paraseptal emphysematous changes in the medial segment of the right middle lobe and centrilobular soft-tissue nodules in the anterior basal and apicoposterior segments [Table/Fig-3]. Neurology consultation was sought, and MRI of the brain demonstrated the classical molar-tooth sign [Table/Fig-4], characterised by thickened and elongated superior cerebellar peduncles, agenesis of the cerebellar vermis and a bat-wing appearance of the fourth ventricle. Ophthalmological fundus evaluation was done which revealed bilateral retinal dystrophy [Table/Fig-5] along with left-eye keratoconus. The combination of global developmental delay, truncal ataxia, ocular defects, and Stage V chronic kidney disease in our patient was consistent with the spectrum of clinical manifestations of the classical neurological triad and the variability of the multisystems in the JSRD.

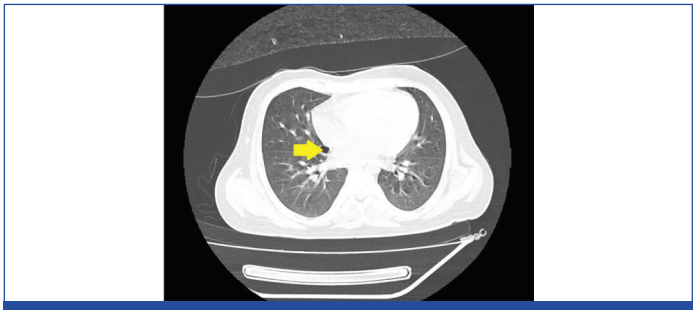


[Table/Fig-2a]: Ultrasonography of the abdomen and pelvis demonstrated bilaterally atrophic kidneys, with the right kidney measuring 7.4×3.6 cm.

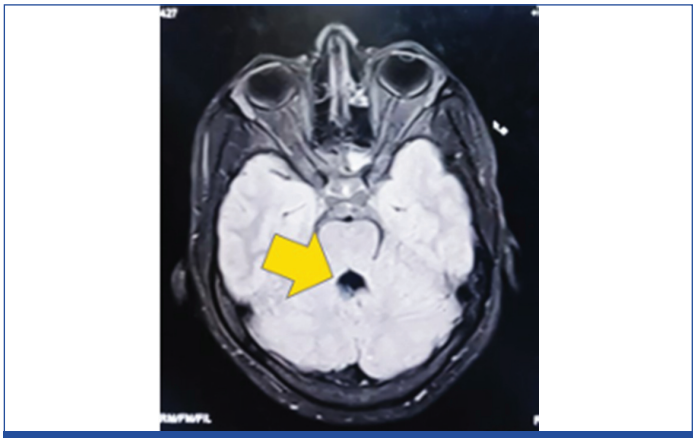


[Table/Fig-2b]: Ultrasonography of the abdomen and pelvis demonstrated bilaterally atrophic kidneys, with the left kidney measuring 8.2×4.5 cm.

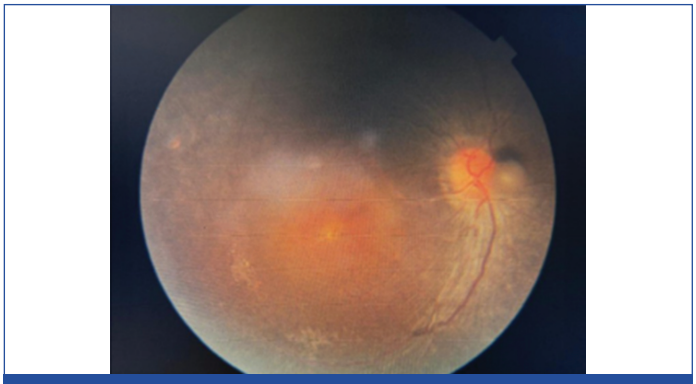
A multidisciplinary approach with neuro rehabilitative care included physical therapy, along with occupational and speech therapy as well as cognitive and behavioural support for improving intellectual disability. The necessity for requirement of visual aids was emphasised. Prevention of recurrent respiratory tract infections and appropriate vaccinations were addressed like flu and pneumococcal vaccines. The patient was managed symptomatically and restarted on maintenance haemodialysis, following which his respiratory symptoms improved during hospitalisation along with chest physiotherapy and breathing exercises. He was discharged in a stable clinical condition with advice for regular follow-up with nephrology, neurology, and ophthalmology services, and he was advised for continuation of haemodialysis, and long-term multidisciplinary surveillance. Patient consent was taken for the publication of this case.



[Table/Fig-3]: High-Resolution Computed Tomography (HRCT) of the chest showed paraseptal emphysematous changes in the medial segment of the right middle lobe and centrilobular soft-tissue nodules in the anterior basal and apico-posterior segments.



[Table/Fig-4]: MRI brain showing Molar Tooth Sign (MTS).



[Table/Fig-5]: Retinal dystrophy.

DISCUSSION

The JS and JSRD are a heterogeneous collection of uncommon neurodevelopmental disorders whose chief pathological feature is the pathognomonic MTS on MRI. The syndrome was initially characterised by Marie Joubert in 1969 and has since been recognised as a spectrum of ciliopathies, due to the defect in genes involving primary cilium organisation and functioning [1]. This genetic deviation interferes with essential developmental processes, especially those that control neuronal migration, axonal guidance and cerebellar vermis formation, the source of the hallmark clinical triad of hypotonia, ataxia, and abnormal respiratory patterns experienced in early infancy [2].

The last 20 years have witnessed an increase in the number of causative genes of both JS and JSRD, with over 35 genes identified due to advances in molecular diagnostic techniques, such as next-generation sequencing and whole-exome analysis, which indicates the important diversity in phenotypes and genotypes of the disorder [3]. Affected individuals have a broad range of phenotypes, which vary between global developmental delay, intellectual disability, and oculomotor apraxia, and multisystem involvement, including retinal dystrophy, nephronophthisis, hepatic fibrosis, and skeletal abnormalities. Thus, a multidisciplinary method to diagnosis and treatment is significant [4]. Not only does the existence of systemic

involvement complicate the clinical course, it also leads to significant long-term morbidity, especially in progressive renal or hepatic failure in some subtypes. Epidemiologically, the disease is thought to be rare, and its incidence is 1 in 80,000 to 1 in 100,000 live births, but it could be undervalued in resource-poor countries because of the absence of awareness and imaging facilities [5]. Neuroimaging improvement has also significantly increased diagnostic accuracy in Joubert Syndrome; high resolution MRI continues to play a crucial role in identifying the typical MTS, characterised by cerebellar vermis hypoplasia, thickened and elongated superior cerebellar peduncles, and deepened interpeduncular fossa, which combined give an effective radiological signature of the disorder [6].

The diagnostic relevance of the hallmark MRI observation of thickened, elongated superior cerebellar peduncles with vermian hypoplasia- all of which lead to the molar-tooth sign- has been well illustrated by Maria BL et al., (1999) as they possess diagnostic relevance across phenotypic subgroups [7]. The retinal dystrophy of the patient falls under the category of the oculo-renal form of JSRD, which is in line with the comprehensive ophthalmic characterisations by Brooks BP et al., (2018) that showed up to two-thirds of the patients have retinal degeneration that is often related to the mutations of CEP290, TMEM67, or AHI1 [8]. JSRD renal involvement is also well-known; Fleming LR et al. (2017) found in a prospective study of 97 patients that almost 30% developed chronic kidney disease or end stage renal disease- our patient with CKD-V is on haemodialysis [9]. Essentially, the same is supported by genotype-phenotype correlations. Genetic testing, as proposed by Brancati F et al., (2007), indicated that CEP290 mutations are firmly associated with the oculo-renal phenotype, which crystallises the notion of genetic testing, especially the use of genetic testing in consanguinity [10]. Parisi MA (2009), in his expanded clinical and molecular understanding, acknowledges the heterogeneity of JSRD and pushes in favour of early multidisciplinary surveillance since renal and ocular complications can remain silent in the long run [11]. The other characteristic of interest in our case is the presence of keratoconus, which is not traditionally associated with JS. However, cases of isolated occurrence of keratoconus in concomitant inpatients with complex genotypes with JS suggests either a phenomenological expansion or dual pathology [12]. Better still, ocular findings reviews by Salehi O et al., in ciliopathies underscore that in spite of the knowledge that retinal degeneration is widespread, corneal abnormalities are occasional, particularly in individuals having prior renal ciliopathies [13]. Premature genetic diagnosis can provide prognostic visibility, predictive organ surveillance, and reproductive counselling that is vital in consanguineous patients.

CONCLUSION(S)

This case highlights JSRD as a complex, evolving multisystemic ciliopathy. The patient's ataxia, retinal dystrophy, and renal dysfunction confirm the oculo-renal phenotype. This multisystemic presentation requires high suspicion, especially in consanguineous families. Identifying the MRI "molar-tooth sign" remains crucial for accurate diagnosis. Since JSRD therapy is purely supportive, early intervention is essential. Immediate, comprehensive evaluation across neurological, renal, and ocular systems is required. A multidisciplinary approach is vital to optimise long-term patient outcomes. Continuous monitoring maximises clinical results through personalised, targeted medical care. Accurate diagnosis facilitates the importance of genetic counselling, enabling families for future planning.

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