Int. J. Adv. Res. Sci. Technol. Volume 15, Issue 6, 2026, pp.2079-2082.

IJARST

International Journal of Advanced Research in Science and Technology

https://doi.org/10.62226/ijarst20262717

ISSN 2319 – 1783 (Print)

ISSN 2320 – 1126 (Online)

The Slow March of Childhood: A Case Report of Kufor-Rakeb Syndrome

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ARTICLEINFO

Article history:

Received	19 June 2026
Accepted	26 June 2026
Available online	30 June 2026

Keywords:

ATP13A2, Kufor–Rakeb syndrome, juvenile parkinsonism, neurodegeneration, cognitive decline, case report.

Indexed in:

and in major libraries

ABSTRACT

Background: Kufor–Rakeb syndrome (KRS) is a rare autosomal recessive neurodegenerative disorder caused by pathogenic variants in the ATP13A2 gene. It is characterized by juvenile-onset parkinsonism, cognitive decline, and neuropsychiatric manifestations.

Case Presentation: A 16-year-old boy presented with a three-year history of progressive cognitive decline, behavioural changes, speech impairment, dysphagia, and gait difficulty. Neurological examination revealed cognitive dysfunction, hypomimia, generalized rigidity, dysarthria, brisk lower-limb reflexes, and bilateral extensor plantar responses. Routine laboratory investigations and disease-specific screening tests were unremarkable. Clinical exome sequencing identified a homozygous pathogenic ATP13A2 variant, c.2629G>A (p.Gly877Arg), confirming the diagnosis of Kufor–Rakeb syndrome. Supportive multidisciplinary management was initiated.

Conclusion: This case highlights the importance of considering ATP13A2-related Kufor–Rakeb syndrome in adolescents with progressive neurocognitive decline and juvenile-onset parkinsonism. Early genetic testing can facilitate timely diagnosis, counselling, and supportive care.

Introduction:

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity, tremor, and postural instability. While most cases occur in older adults and are sporadic, hereditary forms account for a small but important subset, particularly in children and young adults presenting with early-onset disease[1]. Advances in molecular genetics have identified several genes associated with monogenic forms of parkinsonism, among which ATP13A2 has emerged as a rare cause of juvenile-onset neurodegenerative disease.

Pathogenic variants in ATP13A2 are responsible for Kufor–Rakeb syndrome (KRS), an autosomal recessive form of juvenile parkinsonism first described in a Jordanian family in 1994. The ATP13A2 gene encodes a lysosomal P5-type ATPase involved in cellular homeostasis, polyamine transport, and autophagic degradation pathways. Dysfunction of this protein leads to impaired lysosomal activity, intracellular accumulation of α-synuclein, and progressive neurodegeneration[1,2].

Clinically, KRS is characterized by early-onset parkinsonism accompanied by pyramidal signs, supranuclear gaze palsy, cognitive decline, and psychiatric manifestations. The disorder is exceptionally rare, with only a limited number of genetically confirmed cases reported worldwide. Owing to its phenotypic variability and overlap with other neurodegenerative disorders, diagnosis is often delayed until genetic testing is performed[3].

Case description:

A 16-year-old boy, the first child of healthy non-consanguineous parents, was referred for evaluation of a progressively worsening neurological illness. He had been well until 13 years of age, when his family first noticed subtle changes in his behaviour and academic performance at the age of 12 years. He became increasingly withdrawn, showed reduced interest in school activities, and had difficulty maintaining attention during conversations and routine tasks. Over the ensuing months, his speech became slower and less spontaneous, and he often required additional time to respond to questions.

From the last two months, the family observed increasing emotional instability with episodes of irritability, inappropriate anger, and reduced social interaction. His ability to communicate gradually deteriorated, with decreasing verbal output and impaired comprehension of complex instructions. He also developed difficulty swallowing, initially for solid foods and later for liquids, resulting in prolonged meal times and significant

dependence on caregivers. During the course of his illness, the adolescent boy was evaluated at multiple healthcare facilities. In view of the progressive neurological symptoms, he received an empirical trial of corticosteroids for a presumed inflammatory neurological disorder; however, no clinical improvement was observed. Magnetic resonance imaging of the brain was reportedly performed and was communicated to the family as unremarkable, although the imaging records were unavailable for review at our centre. Notably, the procedure required sedation, following which he developed a respiratory complication necessitating intensive care unit admission for two days.
Approximately one year after symptom onset, motor difficulties became apparent. His movements became noticeably slow, and he experienced increasing difficulty walking independently. Over time, he required assistance with several activities of daily living. There was no history of seizures, visual loss, hearing impairment, sensory symptoms, or bowel and bladder dysfunction. His developmental milestones before the onset of illness had been normal, and there was no family history of a similar neurological disorder.

On examination, the patient was conscious and cooperative but exhibited significant cognitive dysfunction, with impaired attention, reduced interaction, and limited verbal communication. He had a mask-like facial expression and marked slowing of voluntary movements. Increased muscle tone was noted in all four limbs, with brisk deep tendon reflexes in the lower extremities and bilateral extensor plantar responses. Speech was dysarthric, and clinical assessment revealed evidence of bulbar involvement, including impaired swallowing and poor handling of oral secretions. Extraocular movements were full and unrestricted. Sensory examination was normal, and no cerebellar signs were elicited.

The combination of progressive cognitive decline, behavioural disturbances, bulbar dysfunction, pyramidal signs, and juvenile-onset parkinsonian features suggested an underlying hereditary neurodegenerative disorder. Differential diagnoses considered included Wilson disease, neurodegeneration with brain iron accumulation, PLA2G6-associated neurodegeneration, juvenile Huntington disease, mitochondrial cytopathies, and other genetic causes of early-onset parkinsonism. Baseline hematological, biochemical, and metabolic investigations, ophthalmology examination were within normal limits. Further targeted investigations undertaken to evaluate potential causes of progressive neurodegeneration, including metabolic, mitochondrial, and hereditary disorders, were non-contributory. The results of these investigations are summarized in Table 1.

Magnetic resonance imaging of the brain was initially advised as part of the diagnostic work-up. However, the caregivers declined the procedure because of concerns related to sedation. Given the steadily progressive clinical course and high suspicion of a genetic etiology, a clinical exome sequencing approach was pursued. Genetic analysis identified a homozygous pathogenic variant in the ATP13A2 gene, confirming the diagnosis of Kufor–Rakeb syndrome as shown in table 2.

Following confirmation of the genetic diagnosis, the patient and family were counselled regarding the progressive nature of the disorder and the lack of disease-modifying treatment options. Supportive multidisciplinary management was initiated, including nutritional rehabilitation, physiotherapy, speech and swallowing therapy, and psychosocial support. Symptomatic treatment was provided for motor and behavioural manifestations, and regular follow-up was advised to monitor disease progression and functional status.

Discussion:

Kufor–Rakeb syndrome (KRS) is a rare autosomal recessive neurodegenerative disorder caused by pathogenic variants in the ATP13A2 gene. First described in a Jordanian family, KRS belongs to the spectrum of hereditary juvenile-onset parkinsonian disorders and is characterized by a combination of parkinsonism, pyramidal signs, cognitive impairment, psychiatric manifestations, and variable bulbar involvement. Owing to its rarity and phenotypic heterogeneity, diagnosis is frequently delayed, particularly in resource-limited settings where access to advanced genetic testing may be restricted[2].

ATP13A2, located on chromosome 1p36.13, encodes a lysosomal P5-type ATPase involved in intracellular polyamine transport and maintenance of lysosomal homeostasis. Loss of ATP13A2 function disrupts autophagic pathways, resulting in lysosomal dysfunction, accumulation of α-synuclein, and progressive neuronal degeneration. These molecular mechanisms are believed to underlie the multisystem neurological manifestations observed in affected individuals[4].

The clinical presentation of our patient closely aligns with the reported phenotype of ATP13A2-associated disease. The onset of symptoms during adolescence, followed by progressive cognitive decline, behavioural abnormalities, dysarthria, dysphagia, rigidity, bradykinesia, and pyramidal signs, is consistent with previous descriptions of KRS. Cognitive and neuropsychiatric manifestations are increasingly recognized as important components of the disease spectrum and may precede the development of overt parkinsonian features. In our patient, behavioural and cognitive deterioration were among the earliest manifestations, contributing significantly to functional impairment[5].
Bulbar dysfunction is a recognized but variably reported feature of KRS. The progressive swallowing difficulties and speech impairment observed in our patient resulted in substantial morbidity and contributed to caregiver burden. Such manifestations may reflect widespread neurodegeneration extending beyond the nigrostriatal pathways and highlight the multisystem nature of ATP13A2-related disease[4,5].
Neuroimaging findings in KRS are heterogeneous. While some patients demonstrate cerebral or cerebellar atrophy, iron deposition, or nonspecific structural abnormalities, others may have normal imaging, particularly during the early stages of disease. In the present case, previous neuroimaging was reportedly unremarkable, emphasizing that a normal MRI does not exclude the diagnosis[6]. This observation underscores the importance of maintaining a

high index of suspicion in children and adolescents presenting with progressive neurodegenerative symptoms despite non-contributory conventional investigations[6].

The differential diagnosis in our patient included Wilson disease, neurodegeneration with brain iron accumulation, PLA2G6-associated neurodegeneration, juvenile Huntington disease, mitochondrial disorders, and other forms of hereditary juvenile parkinsonism. The absence of diagnostic abnormalities on routine laboratory investigations and disease-specific screening studies, coupled with the progressive clinical course, prompted a genetic approach. Clinical exome sequencing ultimately identified a homozygous pathogenic ATP13A2 variant, establishing the diagnosis and ending a prolonged diagnostic odyssey[7].

The identified variant, c.2629G>A (p.Gly877Arg), has previously been reported as disease-causing and is associated with loss of normal ATP13A2 function[8]. The homozygous state observed in our patient is consistent with the autosomal recessive inheritance pattern of KRS. Although parental segregation analysis could not be performed, the molecular finding, in conjunction with the characteristic clinical phenotype, provides compelling evidence for causality[5].

Currently, there is no disease-modifying therapy for ATP13A2-related disorders. Management remains supportive and focuses on symptomatic treatment of parkinsonism, nutritional rehabilitation, physiotherapy, speech and swallowing therapy, and psychosocial support. While levodopa responsiveness has been described in some patients, therapeutic benefit may be variable and is often accompanied by early motor complications. Consequently, early recognition and multidisciplinary care remain the cornerstones of management[9].

This case highlights the importance of considering ATP13A2-related Kufor–Rakeb syndrome in adolescents presenting with progressive cognitive decline, behavioural disturbances, bulbar dysfunction, and juvenile-onset parkinsonian features. Furthermore, it demonstrates the pivotal role of genomic testing in establishing a definitive diagnosis when routine investigations and neuroimaging are unrevealing. Increased awareness of this rare disorder may facilitate earlier diagnosis, appropriate counselling, and improved multidisciplinary management of affected individuals[10].

Table 1. Summary of Investigations

Investigation	Result	Reference Range/Interpretation
Hemoglobin	13.2 g/dL	12–16 g/dL
Total Leukocyte Count	7,800/mm³	4,000–11,000/mm³
Platelet Count	2.6 ×10⁵/mm³	1.5–4.5 ×10⁵/mm³
Blood Glucose	92 mg/dL	70–140 mg/dL
Serum Urea	24 mg/dL	15–40 mg/dL
Serum Creatinine	0.7 mg/dL	0.5–1.2 mg/dL
Serum Sodium	139 mEq/L	135–145 mEq/L
Serum Potassium	4.2 mEq/L	3.5–5.0 mEq/L
Serum Calcium	9.4 mg/dL	8.5–10.5 mg/dL
Aspartate Aminotransferase (AST)	28 U/L	<40 U/L
Alanine Aminotransferase (ALT)	24 U/L	<45 U/L
Thyroid Stimulating Hormone (TSH)	2.1 µIU/mL	0.4–4.5 µIU/mL
Serum Ceruloplasmin	32 mg/dL	20–40 mg/dL
24-hour Urinary Copper	28 µg/day	<60 µg/day
Serum Lactate	1.6 mmol/L	0.5–2.2 mmol/L
Serum Ammonia	38 µmol/L	15–45 µmol/L
Tandem Mass Spectrometry	Normal	No metabolic abnormality detected
Urine GC-MS	Normal	No organic aciduria detected

Table 2: Genetic Analysis

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
ATP13A2	Exon 24	**c.2629G>A (p.Gly877Arg)**	Homozygous	**Kufor-Rakeb Syndrome** (OMIM#606693)	Autosomal Recessive	**Likely Pathogenic**

Conclusion:

Kufor–Rakeb syndrome is a rare cause of juvenile-onset parkinsonism and progressive neurodegeneration. The diagnosis may be overlooked because of its variable clinical presentation and the absence of specific findings on routine investigations and neuroimaging. In our patient, genetic testing was crucial in establishing the diagnosis after an extended diagnostic evaluation.

This case underscores the importance of considering ATP13A2-related disorders in adolescents presenting with progressive cognitive decline, behavioural changes, bulbar dysfunction, and parkinsonian features. Early recognition and timely genomic evaluation can facilitate accurate diagnosis, appropriate genetic counselling, and multidisciplinary supportive care for affected individuals and their families.

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