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Kufor-Rakeb Syndrome: Recognising a Rare Genetic Cause of Early-Onset Parkinsonism

Pulendhar Reddy[1], Shivangi Sinha[2], Sabavath Arun[2], Naveen Kulkarni[2], Rudra Narayan Behera[2]

[1]Andhra Medical College, Visakhapatnam, Andhra Pradesh, India

[2]All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Corresponding author:

Shivangi Sinha

MBBS, MD Pediatrics

All India Institute of Medical Sciences, Bhopal

sinha.shivangi54820@gmail.com

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ABSTRACT

Background: Kufor–Rakeb syndrome (KRS) is a rare inherited neurodegenerative disorder caused by pathogenic variants in the ATP13A2 gene. It is characterised by juvenile-onset parkinsonism with progressive cognitive, neuropsychiatric, pyramidal, and bulbar manifestations.

Case Presentation: A 22-year-old boy presented with approximately 2.5 years of progressive cognitive and behavioural decline, followed by bulbar dysfunction and motor impairment. Symptoms began at 19.5 years of age with cognitive and behavioural changes; speech impairment and dysphagia developed during the subsequent months, and motor difficulties became prominent approximately one year after symptom onset. Neurological examination demonstrated cognitive impairment, hypomimia, generalised rigidity, dysarthria, brisk lower-limb deep tendon reflexes, and bilateral extensor plantar responses. Routine laboratory investigations and targeted metabolic and disease-specific evaluations were unrevealing. Clinical exome sequencing identified a homozygous pathogenic variant in the ATP13A2 gene, c.2629G>A (p.Gly877Arg), confirming KRS.

Conclusion: KRS should be considered in adolescents with progressive cognitive decline and juvenile-onset parkinsonism, particularly when routine investigations are non-diagnostic. Genetic testing is central to diagnosis and enables genetic counselling and multidisciplinary supportive care.

Introduction:

Parkinsonism is a clinical syndrome characterised by bradykinesia, rigidity, resting tremor, and postural instability. Although it predominantly affects older adults, hereditary forms account for a small proportion of cases and should be considered in children and adolescents presenting with early-onset neurological deterioration. Advances in molecular genetics have enabled the identification of several monogenic causes of juvenile-onset parkinsonism, among which pathogenic variants in ATP13A2 represent a rare but important aetiology.

Kufor–Rakeb syndrome (KRS) is an uncommon autosomal recessive neurodegenerative disorder resulting from pathogenic variants in the ATP13A2 gene. The gene encodes a lysosomal P5-type ATPase that plays an essential role in lysosomal homeostasis, intracellular polyamine transport, and autophagic degradation. Loss of ATP13A2 function leads to lysosomal dysfunction, impaired cellular protein clearance, accumulation of α-synuclein, and progressive neuronal degeneration (1,2).

Clinically, KRS is characterised by juvenile-onset parkinsonism associated with pyramidal signs, cognitive impairment, psychiatric manifestations, bulbar dysfunction, and, in some patients, supranuclear gaze palsy. The clinical phenotype is heterogeneous, often resembling other inherited neurodegenerative disorders, which may delay recognition.

Consequently, molecular genetic testing has become the cornerstone for establishing a definitive diagnosis (3).

We report the case of a 22-year-old boy with progressive cognitive decline, behavioural disturbances, dysarthria, dysphagia, and juvenile-onset parkinsonism in whom clinical exome sequencing identified a homozygous pathogenic variant in the ATP13A2 gene, confirming the diagnosis of Kufor–Rakeb syndrome.

Case description:

A 22-year-old boy, the first child of healthy non-consanguineous parents, presented with a progressively worsening neurological disorder of approximately 2.5 years' duration. He had achieved normal developmental milestones and had no significant past medical history or family history of neurological disease.

The illness began at 19.5 years of age with subtle behavioral and cognitive decline evidenced by forgetfulness. His parents noticed progressive social withdrawal, declining academic performance, reduced attention span, and loss of interest in routine activities. Over the following months, his speech became slow and less spontaneous, with delayed responses during conversation.

Over the subsequent two months, his condition worsened noticeably. He became increasingly irritable, with frequent episodes of inappropriate anger and progressive social withdrawal. His speech output gradually diminished, and he had increasing difficulty understanding complex instructions. During the same period, he developed progressive swallowing difficulties, initially with solid foods and later with liquids, leading to prolonged meal times and greater dependence on his caregivers.

The patient had undergone evaluation at several healthcare facilities before referral to our centre. In view of the progressive neurological deterioration, he received an empirical course of corticosteroids for suspected autoimmune encephalitis; however, no clinical improvement was observed. Magnetic resonance imaging of the brain performed elsewhere was reported as normal, although the images were unavailable for review. The imaging procedure required sedation, after which he developed respiratory complications necessitating intensive care unit admission for two days.

Approximately one year after symptom onset, motor difficulties became more apparent. His movements gradually became slow, and he developed increasing difficulty walking independently. As the disease progressed, he required assistance with several activities of daily living, including routine self-care. There was no history of seizures, visual or hearing impairment, sensory symptoms, bowel or bladder disturbances, or any preceding febrile illness.

On neurological examination, the patient was conscious and cooperative but had significant cognitive impairment, with poor attention, reduced interaction, and limited spontaneous speech. He had a mask-like facial expression (hypomimia), generalised bradykinesia, and increased muscle tone in all four limbs. Deep tendon reflexes were brisk in the lower limbs, with bilateral extensor plantar responses. His speech was dysarthric, and clinical evaluation revealed bulbar involvement, manifested by impaired swallowing and poor control of oral secretions. Extraocular movements were full, with no evidence of supranuclear gaze palsy. Sensory examination and cerebellar function were normal.

The patient's progressive cognitive decline, behavioural changes, bulbar symptoms, pyramidal signs, and juvenile-onset parkinsonian features suggested an underlying hereditary neurodegenerative disorder. Based on the clinical presentation, differential diagnoses included Wilson disease, neurodegeneration with brain iron accumulation, PLA2G6-associated neurodegeneration, juvenile Huntington disease, mitochondrial disorders, and other inherited causes of early-onset parkinsonism.

Routine laboratory investigations, including complete blood count, liver and renal function tests, serum electrolytes, metabolic screening, and ophthalmological evaluation, were within normal limits. Further disease-specific investigations performed to identify metabolic and hereditary neurodegenerative disorders were also unrevealing (Table 1).

Although repeat magnetic resonance imaging of the brain was recommended as part of the diagnostic evaluation, the family declined because of concerns about the sedation-related respiratory complication that had occurred during the previous MRI. In view of the characteristic clinical features, progressive disease course, and non-diagnostic conventional investigations, clinical exome sequencing was pursued. Genetic analysis identified a homozygous pathogenic variant in the ATP13A2 gene (c.2629G>A; p.Gly877Arg), confirming the diagnosis of Kufor–Rakeb syndrome (Table 2).

The patient and his family were counselled regarding the genetic basis, expected clinical course, and prognosis of the disorder. A multidisciplinary treatment plan was initiated, including nutritional support, physiotherapy, speech and swallowing therapy, psychological counselling, and symptomatic medical management. Regular follow-up was advised to assess disease progression, nutritional status, functional abilities, and overall quality of life. During follow-up, the patient's neurological condition continued to deteriorate despite supportive multidisciplinary management, and he succumbed to death at 24 years of age, almost after 4.5 years of disease onset due to disease related comorbidities (aspiration pneumonia and septic shock).

Discussion:

Kufor–Rakeb syndrome (KRS) is an uncommon inherited neurodegenerative disorder caused by biallelic pathogenic variants in the ATP13A2 gene. It represents a rare cause of juvenile-onset parkinsonism and has been described in only a small number of genetically confirmed patients worldwide since it was first reported in 1994. Because of its rarity and variable clinical manifestations, affected individuals often

experience a prolonged diagnostic journey before the underlying genetic cause is identified (2,3).

The ATP13A2 gene encodes a lysosomal P5-type ATPase that is essential for normal lysosomal function and intracellular protein homeostasis. Impaired ATP13A2 activity disrupts autophagy and lysosomal degradation pathways, leading to the accumulation of toxic proteins, including α-synuclein, and progressive neuronal injury. These pathological changes predominantly affect the basal ganglia and are believed to account for the characteristic motor and non-motor manifestations of the disease (4).

The clinical course in our patient was consistent with the expanding phenotype of ATP13A2-associated disease. Behavioural changes and cognitive decline were the earliest manifestations and preceded the development of motor symptoms. As the illness progressed, he developed bradykinesia, generalised rigidity, dysarthria, dysphagia, and pyramidal signs, resulting in significant functional impairment. This sequence of events supports previous observations that cognitive and neuropsychiatric symptoms may appear before classical parkinsonian features become evident (3,5).

Bulbar involvement was an important component of the disease in our patient. Progressive swallowing difficulty and dysarthria substantially affected nutrition, communication, and independence in daily activities. Although not present in every individual with KRS, bulbar dysfunction is increasingly recognised as a clinically significant manifestation that contributes to disease burden and highlights the multisystem nature of ATP13A2-related neurodegeneration (5).

Brain MRI findings in KRS are inconsistent. While some affected individuals demonstrate cerebral or cerebellar atrophy, basal ganglia abnormalities, or evidence of iron deposition, others have normal neuroimaging, particularly during the earlier stages of the disease. In our patient, the previously performed MRI was reported as normal, illustrating that normal structural imaging does not exclude the diagnosis when the clinical picture strongly suggests an inherited neurodegenerative disorder (6). The unavailability of the MRI images for independent review is a limitation of this report.

The differential diagnosis of juvenile-onset parkinsonism remains extensive and includes Wilson disease, neurodegeneration with brain iron accumulation (NBIA), PLA2G6-associated neurodegeneration, juvenile Huntington disease, mitochondrial disorders, and several other genetic conditions. In this patient, Wilson disease was considered less likely because serum ceruloplasmin, 24-hour urinary copper, liver function tests, and ophthalmological evaluation were unremarkable. NBIA and PLA2G6-associated neurodegeneration were considered, but the available investigations did not demonstrate an alternative metabolic or disease-specific abnormality, importantly, brain MRI images were unavailable for independent assessment, so radiological exclusion of NBIA cannot be confirmed. Juvenile Huntington disease and mitochondrial disorders were also considered clinically but were not supported by the available phenotype and metabolic investigations. These considerations, together with the progressive course and characteristic combination of parkinsonian, pyramidal, cognitive, and bulbar features, prompted genomic testing (1,7).

Despite comprehensive laboratory evaluation and targeted metabolic investigations, no alternative diagnosis was identified in our patient. The definitive diagnosis was established only after clinical exome sequencing demonstrated a homozygous pathogenic ATP13A2 variant (c.2629G>A; p.Gly877Arg) (3,8). This case illustrates the growing importance of genomic testing in adolescents with unexplained progressive neurological disease, particularly when conventional investigations fail to provide a diagnosis (9).

The identified c.2629G>A (p.Gly877Arg) variant has previously been classified as pathogenic. ClinVar records this variant as pathogenic for Kufor–Rakeb syndrome, based on an OMIM submission, and cites the original report by Santoro et al., who identified the homozygous variant in a family with KRS (10). At present, treatment for KRS is primarily supportive, as no therapy has been shown to halt or reverse disease progression (11,12).

Key Learning Points

The following points summarise the principal clinical and diagnostic lessons from this case.

• Kufor–Rakeb syndrome is a rare autosomal recessive cause of juvenile-onset parkinsonism caused by pathogenic variants in the ATP13A2 gene.

• Behavioural and cognitive changes may precede the onset of motor manifestations, contributing to delayed diagnosis.

• Normal routine laboratory investigations and a reported normal brain MRI do not exclude the diagnosis.

• Clinical exome sequencing is a valuable diagnostic tool in adolescents with unexplained progressive neurodegenerative disorders.

• Early diagnosis allows appropriate genetic counselling and timely multidisciplinary supportive management.

Conclusion:

Kufor–Rakeb syndrome should be considered in adolescents presenting with progressive cognitive decline, behavioural changes, bulbar dysfunction, and juvenile-onset parkinsonism. Genetic testing is central to establishing the diagnosis when routine investigations are non-diagnostic and enables appropriate genetic counselling. Multidisciplinary supportive care is essential for addressing the progressive functional, nutritional, communication, and swallowing complications of the disorder.

Consent for Publication

Written informed consent for publication of the patient's clinical information and accompanying images was obtained

from the patient's parents/legal guardians. A copy of the signed consent form is available for review by the Editor on request.

Availability of Data and Materials

All relevant data supporting the findings of this case are included within the manuscript. Additional information is available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

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Author Contributions

Pulendhar Reddy: Conceptualization, patient management, data collection, literature review, interpretation of clinical findings, manuscript preparation, and final approval of the manuscript.

Co-authors: Clinical supervision, data collection, interpretation of clinical findings, critical revision of the manuscript for important intellectual content, interpretation of findings, and approval of the final version.

All authors have read and approved the final manuscript.

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Guarantor Statement

Sabavath Arun and Pulendhar Reddy accept full responsibility for the integrity and accuracy of the clinical data presented in this manuscript and serve as the guarantors of the work.

Table 1. Summary of Investigations

Investigation	Result	Reference range / Interpretation
Haemoglobin	10.2 g/dL	12–16 g/dL
Total Leukocyte Count	8,560/mm³	4,000–11,000/mm³
Platelet Count	4.4 × 10⁵/mm³	1.5-4.5 lacs/mm³
Blood Glucose	112 mg/dL	70–140 mg/dL
Serum Urea	29 mg/dL	15–40 mg/dL
Serum Creatinine	0.9 mg/dL	0.5–1.2 mg/dL
Serum Sodium	133 mEq/L	135–145 mEq/L
Serum Potassium	4.9 mEq/L	3.5–5.0 mEq/L
Serum Calcium	9.1 mg/dL	8.5–10.5 mg/dL
Aspartate Aminotransferase (AST)	28 U/L	<40 U/L
Alanine Aminotransferase (ALT)	21 U/L	<45 U/L
Thyroid Stimulating Hormone (TSH)	2.3 µIU/mL	0.4–4.5 µIU/mL
Serum Ceruloplasmin	35 mg/dL	20–40 mg/dL
24-hour Urinary Copper	29 µg/day	<60 µg/day
Serum Lactate	1.1 mmol/L	0.5–2.2 mmol/L
Serum Ammonia	39 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	Pathogenic (10)

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