ECRONICON OPEN ACCESS

EC NEUROLOGY
Case Series

Familial Early-Onset Atypical Parkinsonism with Supranuclear Gaze Palsy and Autonomic Failure: A Case Series

Tayyeb Ali[1]*, Muhammad Hassaan Javaid[2], Sibgha Fawad Memon[3], Zauha Fawad Memon[3], Muhammad Taimour Sultan[2], Maaz Ullah[4], Zeeshan Ahmad[5], Ejaz Ali[6], Munazza Iqbal[7] and Zuhaib Ali[8]

[1]*Gomal Medical College, Dera Ismail Khan, Pakistan*

[2]*Shifa College of Medicine, Islamabad, Pakistan*

[3]*People's University of Medical and Health Sciences for Women, Shaheed Benazirabad, Pakistan*

[4]*Bannu Medical College, Bannu, Pakistan*

[5]*Khyber Medical University Institute of Medical Sciences, Kohat, Pakistan*

[6]*Chengde Medical University, Chengde, China*

[7]*Khyber Girls Medical College, Peshawar, Pakistan*

[8]*Dentist, Liaqat University of Medical and Health Sciences (LUMHS), Pakistan*

***Corresponding Author:** Tayyeb Ali, Gomal Medical College, Dera Ismail Khan, Pakistan.

Received: April 10, 2026; **Published:** April 24, 2026

Abstract

Introduction and Importance: Early-onset parkinsonism is rare and is typically characterized by atypical presentations and genetic causes. The case presented here is a rare instance of familial early-onset atypical parkinsonism in a set of biological siblings belonging to a South Asian family.

Case Presentation: One sibling presented with juvenile-onset disease at 18 years and one with young-onset disease at 32 years. These two individuals developed typical motor symptoms of parkinsonism, characterized by early autonomic dysfunction, psychosis, dysphagia, rapid disease progression, levodopa refractoriness, and supranuclear gaze palsy. Exhaustive investigations ruled out other causes such as Wilson's disease, while non-contrast structural neuroimaging studies lacked specificity.

Conclusion: Although genetic analysis and functional dopaminergic studies could not be carried out, the development of early-onset parkinsonism, multiple system affection, partial and brief levodopa responses, as well as familial affection, clearly points towards a diagnosis of hereditary atypical parkinsonism, with Kufor-Rakeb syndrome related to ATP13A2 mutations as a case for consideration.

Keywords: *Young Onset Parkinson's Disease Juvenile Parkinsonism; Hereditary Parkinson's Disease*

Introduction

Parkinson's disease is a neurodegenerative condition attributed to the degeneration of the midbrain dopaminergic neurons, particularly those in the substantia nigra. Clinical manifestations generally include rest tremors, bradykinesia, rigidity, and unstable posture. These are most prevalent among the adult elderly and secondarily in the younger population.

PD is classified on the basis of age of onset. Juvenile onset PD (JOPD) happens under 21 years, and young onset PD (YOPD) affects people in 21 to 40 years. Both are rare forms and are subtypes of Early Onset PD (EOPD). Both are often associated with diagnostic delay, refractoriness to standard dopaminergic treatment as well as typical management complexity. According to epidemiological data, there is a total incidence of 13.4 per 100,000 population with much lower rates in the lower age groups (0.5 per 100,000 30 - 39 years) compared to the elderly [1].

We report a rare presentation in two biological siblings, one with juvenile onset at 18 years and the other with young onset at 32 years who demonstrated multiple atypical features, including early autonomic dysfunction, psychosis, rapid progression, and supranuclear gaze impairment. These features are red flags against idiopathic PD and suggest a phenotype more consistent with hereditary atypical parkinsonism, potentially within the ATP13A2/PLA2G6 spectrum. This case highlights the heterogeneity of early-onset parkinsonism and underscores the importance of comprehensive evaluation and longitudinal reassessment in young patients presenting with parkinsonian features.

This case report is written according to CARE guidelines [27].

Case Presentation

Case 1

A 32-yr-old South Asian male presented to the OPD with complaints of bradykinesia, rigidity, and sleeplessness for 8 months. On admission, his vitals were normal: Blood pressure, 110/70 mmHg; Heart rate, 78 beats/min; Respiratory rate, 17 breaths/min; and temperature, 36.5°C. There was no evidence of jaundice, anemia, cyanosis, and edema. Thorough examination revealed pill-rolling tremors, masked facies, shuffling gait, rigidity in all limbs. He further showed hyposmia (reduced sense of smell) with no impairment of other sensory modalities, consistent with early nonmotor features of parkinsonism. His parents had a consanguineous marriage. He was the oldest of 6 siblings, and his brother had the same problem. He was also married with 3 children, one of whom had cerebral palsy. Apart from this, other alarming symptoms such as autonomic dysfunction like urinary incontinence, altered bowel habits, and difficulty swallowing were also noticed.

Investigations

Initial laboratory workup was done which is summarized in table 1. The elevated WBC count and neutrophilia (11.13 × 10^9/L, neutrophils 78%) likely reflect secondary infection related to his prolonged immobilization, bedsores, and post-fracture inflammatory response, rather than a primary hematologic abnormality. Ophthalmologic examination was done to exclude Wilson's disease, in which no trace of Kayser-Fleischer ring was shown. Oculomotor examination revealed slowing of vertical saccades with mild limitation of upward gaze, consistent with early supranuclear gaze impairment. Genetic Testing was not possible due to resource constraints and religious and ethnic concerns.

Parameters	Reference Range	Value
Hemoglobin (g/dL)	13 - 17.2	13.9
WBC Count (×10^9/L)	3.7 - 11	11.13
Neutrophils (%)	45 - 65	78.1
Lymphocytes (%)	20 - 40	9.7
Platelets (×10^3/µL)	145 - 450	401
ESR (mm/hr)	0 - 25	32
Creatine Phosphokinase - CPK (U/L)	25 - 196	285
HBsAg	—	Negative
Anti-HCV	—	Negative
HIV (ICT)	—	Negative

Table 1: *Laboratory investigations of patient 1.*

Management

He was started on Parkinson's medicines but was non-compliant and presented after a few months with worsening symptoms, which included psychosis that started as mood changes, ranging from sitting quiet for hours to crying out loud and gradually turning to delusions and hallucinations. He had a fall and had a femoral fracture, after which he underwent surgery. He has been bedridden since the incident; he developed bedsores and continues to deteriorate with increasing frequency of psychosis and dysphagia.

Diagnostic assessment

Although initially treated as Parkinson's disease, the presence of early autonomic failure, psychosis, levodopa refractoriness, rapid progression, and emerging supranuclear gaze impairment are incompatible with idiopathic PD under MDS diagnostic criteria. These features raise suspicion for hereditary atypical parkinsonism, particularly ATP13A2-related Kufor-Rakeb Syndrome or other autosomal-recessive neurodegenerative disorders. To evaluate Wilson's disease, an ophthalmologic slit-lamp examination was performed, revealing no Kayser-Fleischer rings. Serum ceruloplasmin was normal. These findings did not support Wilson's disease.

Case 2

The case presented an 18-year-old male from South Asia to the OPD with complaints of weight loss and reduced appetite for 5 months and difficulty walking and swallowing since the last 2 months. On arrival his temperature, Heart rate, respiratory rate, Blood Pressure was measured at 98F, 82 beats/min, 18 br/min and 110/70 mm of Hg, respectively.

Examination revealed classical signs of Parkinsonism with pill rolling tremors, cogwheel rigidity, forward stooped posture, shuffling gait, and masked facies. On further enquiry, he gave a history of aggravation of symptoms with homeopathic medicines started for erectile dysfunction.

Investigations

Multiple investigations were done to rule out the cause and reach a definitive diagnosis which are summarized in table 2. The raised urea and creatinine levels (Urea 77.9 mg/dL, Cr 1.36 mg/dL) were interpreted as pre-renal azotemia, most likely due to dehydration and reduced oral intake secondary to dysphagia during his rapid clinical decline. Fundoscopy was done to exclude Wilson's disease and other rheumatologic diseases, which did not show any Kayser-Fleischer ring. The normal Creatinine kinase level was helpful to rule out musculoskeletal disorders. CT and MRI brain scans revealed no focal structural lesions.

Parameters	Reference range	Value
Hemoglobin (g/dL)	11 - 17	15
WBC Count ($\times 10^9$/L)	4 - 11	13.2
Neutrophils ($\times 10^9$/L)	1.5 - 7.5	8.6
Lymphocytes ($\times 10^9$/L)	1.3 - 4	3.9
Platelets ($\times 10^3$/µL)	150 - 450	352
Random Blood Glucose (mg/dL)	65 - 170	126
ALT (U/L)	5 - 50	61.6
Creatinine (mg/dL)	0.3 - 1.3	1.36
Urea (mg/dL)	10 - 50	77.9
Calcium (mg/dL)	8.5 - 10.5	10.4
Serum Copper (µg/dL)	70 - 140	127
Total Bilirubin (mg/dL)	0.1 - 1.1	1.27
TSH (mIU/mL)	0.38 - 4.31	0.38
Total T4 (nmol/L)	71.2 - 141	118

Table 2: *Lab investigations for patient 2.*

Management

He was diagnosed with JOPD and was started with levodopa in combination with carbidopa; his symptoms started to improve but after a few months the disease became refractory and symptoms relapsed. He continued on and off medicines for two years, but his symptoms persisted throughout the whole episode.

His family also reported the incidents of psychosis, wherein he used to shout and cry. Because of his forward posture, he met with a fatal fall resulting in fractures and thus bedridden for a few months, due to which he developed bedsores. During this time, his dysphagia worsened and a Nasogastric tube was passed. However, despite all efforts from the doctors, he could not be saved and died unfortunately.

Diagnostic assessment

The early onset of symptoms, levodopa refractoriness, early dysphagia, autonomic dysfunction, and psychosis point away from juvenile idiopathic PD and toward hereditary atypical parkinsonism, again raising suspicion for ATP13A2-associated Kufor-Rakeb Syndrome or similar recessive neurodegenerative syndromes.

Patient also had a history of ingesting homeopathic preparations for erectile dysfunction. This raises the possibility of drug-induced or toxin-triggered parkinsonism, which must be considered in the differential diagnosis. However, the progressive course, early dysphagia, oculomotor findings, and partial levodopa response favor an underlying degenerative or hereditary parkinsonian syndrome.

Discussion

In light of the exclusionary features for idiopathic PD particularly early autonomic dysfunction and supranuclear gaze impairment the diagnosis in both siblings is best framed as hereditary atypical parkinsonism, rather than definitive Parkinson's disease. While ATP13A2-related Kufor-Rakeb syndrome is a plausible unifying diagnosis, this remains hypothesis-based due to the absence of genetic confirmation or functional dopaminergic imaging. As mentioned earlier that due to financial constraints and religious and ethical issues genetic testing was not possible.

The most common autosomal recessive genes, PRKN/PARK2, PINK1, DJ-1, are highly associated with EOPD and an onset <40 years, whereas ATP13A2, PLA2G6, VPS13C, and others may present with earlier, sometimes juvenile, phenotypes involving multiple systems [5-7]. On the contrary, LRRK2 and SNCA dominant mutations are more characteristic of a later onset but may overlap. A lack of genetic testing is one of the shortcomings of our cases; however, this sib-pair fits into the biology of recessive EOPD with early onset and partial levodopa response, specifically dysfunctional mitophagy in PRKN/PINK1, and variable expressivity that can bifurcate onset ages in a single family model. Genetic counseling and panel testing are thus indicated in probands and at-risk relatives [8].

The presence of early autonomic dysfunction and supranuclear gaze limitation are red-flag features that formally exclude idiopathic PD under the MDS Clinical Diagnostic Criteria [9,10]. The PSP diagnostic schemes emphasize vertical gaze palsy or slow vertical saccades with initial postural instability while MSA is typified by more marked diffuse autonomic pattern. The insidious onset and at least temporary responsiveness to levodopa in both siblings continues to favor PD, in an EOPD spectrum; however, the salience of dysautonomia and gaze features mandates longitudinal re-evalution against MDS PSP criteria and MSA-PD differentiation studies Due to the siblings' early age of onset, rapid progression, psychosis, dysautonomia, and partial/unsustained levodopa response, their phenotype aligns more closely with hereditary atypical parkinsonism, especially ATP13A2-related Kufor-Rakeb Syndrome, rather than idiopathic PD [12,13].

Structural neuroimaging was non-specific, as mild cerebral atrophy can be seen in certain metabolic or genetic parkinsonian syndromes [11]. When available, DAT SPECT or [18] FDOPA PET can confirm presynaptic dopaminergic deficiency with high sensitivity and distinguish degenerative parkinsonism from its mimics, thus increasing diagnostic confidence in young patients presenting atypically

[16,23]. In resource-poor settings, selective use of DAT SPECT where it would change management is an effective strategy [12,17]. Without genetic testing or DAT-SPECT/FDOPA PET imaging, the etiological interpretation remains probabilistic rather than conclusive.

Levodopa remains the best symptomatic treatment, but younger age at onset predicts earlier motor complications and fluctuating responses [14]. The two brothers initially improved on levodopa carbidopa then became resistant with debilitating nonmotor symptoms such as psychosis and dysphagia. The course is consistent with the observation that motor complications tend to cluster with young age at onset, greater cumulative levodopa exposure, and disease duration [15,16,18]. Optimal function can be preserved under ideal circumstances through early use of dopamine agonists or MAO B inhibitors and timely consideration for DBS, but social and access issues typically limit such strategies [20,21].

Global PD incidence in 2019 was ≈13.4/100,000, with the incidence rising continuously since 1990 [22]. Incidence is age related, with rates of ~0.5/100,000 aged 30-39 and 9.8/100,000 aged 50-59 [2,18,19]. Contemporary estimates for YOPD are for age-standardized incidence of ~1.3/100,000 person years, orders of magnitude lower than that of older groups, reinforcing the rarity of EOPD/JOPD [20,23].

These sibling cases represent heterogeneity of early-onset parkinsonism, where juvenile and young-onset disease may exist within the same family. Overlap among central parkinsonian features with autonomic dysfunction and gaze defects made diagnosis challenging as it showed spectrum between PD and atypical parkinsonian syndromes. Lack of genetic investigation and functional imaging constrains diagnostic accuracy but in no way lessens the value of reporting such patients, which widens the clinical spectrum of familial EOPD/ JOPD and emphasizes the need for multidisciplinary treatment and genetic counseling [24,25].

Conclusion

This case report of two children with different early onset parkinsonism, one juvenile and one young onset, represents the broad phenotypic variability of genetic Parkinson's disease and the diagnostic challenge it presents. The atypical features mentioned, i.e., early autonomic failure, psychosis, and supranuclear gaze palsy, point to the partial overlap between PD and atypical parkinsonian disorders, again reminding us about the importance of close longitudinal follow-up. Even in the absence of restricted access to genetic analysis and high-powered imaging, reports illustrate that comprehensive clinical evaluation, symptomatic treatment, and supportive care remain of primary importance in optimizing the prognosis of patients. Consideration and counseling for genetic panel testing could be offered to such families with early onset parkinsonism in order to better guide prognosis, identify at-risk relatives, and allow subsequent therapeutic planning.

We confirm that no AI tools were utilized in the conduct or writing of this manuscript, in accordance with the TITAN checklist [26].

Ethical Approval and Informed Consent

Written informed consent was obtained from the patient's guardian for publication.

Funding Statement and Affiliation

All authors certify that they have no affiliation with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Acknowledgments

Not applicable.

Peer and Provenance Statement

Not commissioned, externally peer-reviewed.

Conflict of Interest

Authors don't have any conflicts of Interest

Contribution and Acknowledgment

Tayyeb Ali: Case selection. Muhammad Hassaan Javaid, Sibgha Fawad Memon: Writing 1st draft. Zauha Fawad Memon: Reviewing manuscript, Muhammad Taimour Sultan, Maaz Ullah, Zeeshan Ahmad, Ejaz Ali and Munazza Iqbal: References. The author(s) read and approved the final manuscript.

Research Registration Unique Identification Number (UIN)

Not applicable.

Bibliography

1. Bhattarai HB., *et al*. "Diagnostic pitfalls in young onset parkinsonism and its unique challenges: A case report from rural Nepal". *SAGE Open Medical Case Reports* 11 (2023): 2050313X231197062.
2. Schrag A and Schott JM. "Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism". *Lancet Neurology* 5.4 (2006): 355-363.
3. Wickremaratchi MM., *et al*. "Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study". *Journal of Neurology, Neurosurgery and Psychiatry* 80.7 (2009): 805-807.
4. Postuma RB., *et al*. "MDS clinical diagnostic criteria for Parkinson's disease". *Movement Disorders* 30.12 (2015): 1591-1601.
5. Lücking CB., *et al*. "Association between early-onset Parkinson's disease and mutations in the parkin gene". *New England Journal of Medicine* 342.21 (2000): 1560-1567.
6. Bonifati V., *et al*. "Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism". *Science* 299.5604 (2003): 256-259.
7. Kitada T., *et al*. "Mutations in the PINK1 gene cause autosomal recessive early-onset parkinsonism". *Nature* 430.6995 (2004): 320-323.
8. Klein C and Westenberger A. "Genetics of Parkinson's disease". *Cold Spring Harbor Perspectives in Medicine* 2.1 (2012): a008888.
9. Höglinger GU., *et al*. "Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society criteria". *Movement Disorders* 32.6 (2017): 853-864.
10. Wenning GK., *et al*. "Multiple system atrophy: a primary oligodendrogliopathy". *Annals of Neurology* 64.3 (2008): 239-246.
11. Brooks DJ and Pavese N. "Imaging biomarkers in Parkinson's disease". *Progress in Neurobiology* 95.4 (2011): 614-628.
12. Morbelli S., *et al*. "EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 2020". *European Journal of Nuclear Medicine and Molecular Imaging* 47.8 (2020): 1885-1912.
13. Olszewska DA., *et al*. "PARK2/PINK1/DJ-1 mutation screening in young-onset Parkinson's disease: frequency, phenotype, and outcome". *Journal of Neurology* 268.5 (2021): 1702-1714.

14. Schapira AH., *et al*. "Levodopa in the treatment of Parkinson's disease: current status and new developments". *Lancet Neurology* 8.8 (2009): 813-822.

15. Ahlskog JE and Muenter MD. "Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature". *Movement Disorders* 16.3 (2001): 448-458.

16. Thanvi B., *et al*. "Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment". *Postgraduate Medical Journal* 83.980 (2007): 384-388.

17. Dorsey ER., *et al*. "Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016". *Lancet Neurology* 17.11 (2018): 939-953.

18. Pringsheim T., *et al*. "The prevalence of Parkinson's disease: a systematic review and meta-analysis". *Movement Disorders* 29.13 (2014): 1583-1590.

19. Hirsch L., *et al*. "The incidence of Parkinson's disease: a systematic review and meta-analysis". *Neuroepidemiology* 46.4 (2016): 292-300.

20. Ou R., *et al*. "Incidence of young-onset Parkinson's disease: a systematic review and meta-analysis". *Parkinsonism and Related Disorders* 87 (2021): 31-36.

21. Lipp A., *et al*. "Autonomic dysfunction in Parkinson's disease and other synucleinopathies: differences and similarities". *Journal of the Neurological Sciences* 276.1-2 (2009): 9-12.

22. Post B., *et al*. "Young-onset Parkinson's disease: a modern perspective". *Journal of Neural Transmission* 127.12 (2020): 1487-1500.

23. Akdemir ÜÖ., *et al*. "Dopamine transporter SPECT imaging in Parkinson's disease and parkinsonian disorders a meta-analysis". *Clinical Nuclear Medicine* 46.7 (2021): e338-e345.

24. Kolicheski A., *et al*. "Clinical spectrum and genetic basis of early-onset Parkinson's disease". *npj Parkinson's Disease* 8.1 (2022): 1-14.

25. Nabizadeh F., *et al*. "Epidemiology and outcomes of young-onset Parkinson's disease: global evidence synthesis". *Journal of Parkinson's Disease* 14.3 (2024): 521-533.

26. Agha RA., *et al*. "Transparency in the reporting of artificial intelligence - the TITAN guideline". *Premier Journal of Science* 10 (2025): 100082.

27. Riley DS., *et al*. "CARE guidelines for case reports: explanation and elaboration document". *Journal of Clinical Epidemiology* 89 (2017): 218-235.

Volume 18 Issue 5 May 2026