Sir,

Leukodystrophies usually manifest as childhood-onset disorders; however, adult-onset presentations are not rare. Intriguingly, mutations of the TUBB4A gene are associated with two apparently distinct syndromes—one presenting as an adult-onset genetic dystonia, while the other as a childhood-onset hypomyelinating disorder.\(^1\)\(^2\) Herein, we present a case of TUBB4A mutation demonstrating an atypical phenotype, which indicates a clinico-radiological intermediate between the two syndromes. It also illustrates the importance of regular follow-up in such patients as they may accrue new symptoms requiring adequate management.

A 61-year-old unmarried lady, without any known comorbidities or any family history of seizures or movement disorders, presented with gradually progressive dystonia, gait impairment, dysarthria, and cognitive decline, along with new onset seizure. Symptoms started about 20 years ago, in the form of cervical dystonia (right torticollis) along with tremulousness of the head, which was more pronounced during any activity like nodding her head or looking to a particular side. Later, it persisted even at rest and gradually progressed over years to involve the limbs (which was noticed by her as difficulty in cooking and holding utensils with posturing of limbs); however, she did not notice any sensory tricks. She developed progressive gait unsteadiness and stiffness for the last 10 years and ultimately required aid for ambulation. This was followed by dysarthria without any spasmodic dysphonia. For the last 5 years, there has been progressive impairment of attention, executive function, and memory reported as difficulty in keeping track of conversation, frequent difficulty in recalling recent events, and tendency to skip steps in performing an activity, leading to errors. She developed two episodes of new onset seizure (generalized tonic clonic convulsions) a few days before her admission. On admission, her MoCA score was 22; there was predominantly cervical dystonia with dystonic head tremor, and spasticity and hyperreflexia in all four limbs [Video 1]. Ophthalmological evaluation and other cranial nerves were essentially normal. Investigations revealed normal blood parameters (including complete blood count, erythrocyte sedimentation rate, urea, creatinine, sodium, potassium, calcium, glucose, and liver and thyroid function tests), parathormone, ceruloplasmin, and ferritin values. Nerve conduction study and electroencephalography were normal. Magnetic resonance imaging of the brain revealed T2/fluid-attenuated inversion recovery sequence and hyperintensity of subcortical white matter with diffuse cortical atrophy [Figure 1]. Considering genetic disorders such as adult-onset leukodystrophy, clinical exome sequencing was performed, which revealed a heterozygous pathogenic variant in exon 4 of the TUBB4A gene, c.286G>A(p.Gly96Arg).

She was treated symptomatically with levetiracetam (1500 mg), trihexyphenidyl (8 mg), and baclofen (30 mg) and had no further episodes of seizures with some reduction in dystonia (especially in the limbs) and spasticity. The patient is being followed up at the institute for the last 1 year, and botulinum toxin therapy has not been tried as she had responded to medications and was reluctant for botox therapy. TUBB4A (cytogenetic location: 19p13.3) (tubulin beta-4A gene) encodes a brain-specific member of beta-tubulin family, highly expressed in the cerebellum, putamen, and white matter.\(^1\) Mutations of the TUBB4A, on the one end of the spectrum, are associated with adult-onset genetic dystonia without significant MRI changes (DYT 4, MIM #128101).\(^1\)\(^3\) At the other end, it is associated with hypomyelinating leukodystrophy-6 (MIM #612438) or hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) with clinical and radiological traits of hypomyelination, cerebellar atrophy, and progressive atrophy of the neostriatum (caudate and putamen), which

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**Figure 1:** Hypomyelination with cerebellar and cortical atrophy. Magnetic resonance imaging of brain—axial T2-weighted (a), T2 fluid-attenuated inversion recovery (b), T1-weighted (c), and sagittal T2-weighted (d) images: showing symmetrical white matter signal intensity changes—hyperintense on T2/FLAIR (arrows) and isointense on T1, with cerebellar and cortical atrophy.
| Name of study | Total number of patients | Clinico-radiological profile | Mutation |
|---------------|--------------------------|-----------------------------|----------|
| 1) Erro R, et al. | 04 (age of onset first decade of life) | Generalized dystonia, ataxia. Bulbar involvement leading to aphonia and swallowing difficulty. | Hypomyelination of cerebellum with atrophy of basal ganglia except two cases: One did not show hypomyelination and the other did not show basal ganglia atrophy. |
| 2) Hamilton EM, et al. | 42 (median age of onset was 6 months, (range birth-3 years)) | Dystonia, choreothetosis (rarely) | Absent or disappearing putamen, variable cerebellar atrophy, and highly variable cerebral atrophy. Hypomyelination, agenesis of corpus callosum. |
| 3) Blumkin L, et al. | 01 | Segmental dystonia. | Permanent, incomplete myelination associated with progressive cerebellar atrophy |
| 4) Lohmann K, et al. | Whispering dystonia: Present. Whispering dysphonia: Present. Focal or generalized dystonia. | Distinctive facies and body habitus. | Disease-causing gene was mapped to a 23cM region on chromosome 19p13.3-p13.2 |
| 5) Simons C, et al. | 11 (9 months to 4.5 years: age of onset) | Hemidystonia. Ataxia with gait progressively deteriorating in all cases | MRI suggestive of hypomyelination with basal ganglia atrophy. |

Contd...
| Name of study                                                                 | Total number of patients | Clinico-radiological profile                                                                 | Mutation                                                                 |
|------------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 6) Wilcox RA, et al. Whispering dysphonia in an Australian family (DYT4): A clinical and genetic reappraisal. (2011) | One family with nine affected members.                                             | Isolated spasmodic dysphonia (whispering dysphonia) often with mild craniocervical dystonia to severe generalized dystonia. Extrinsic tongue dystonia and a unique “hobby horse gait.” | Missense c.2297C >G; p.T766R and a splice-site mutation (IVS5 + 1 G >T) were identified. |
| 7) Lu Y, Ondo Y, Shimojima K, Osaka H, Yamamoto T. A novel TUBB4A mutation G96R identified in a patient with hypomyelinating leukodystrophy onset beyond adolescence. (2017) | 01 (onset after age of 17)                                           | Ataxia, dystonia without dysphonia                                                                                           | MRI findings suggestive of hypomyelination of cerebellum, without significant basal ganglia atrophy. |
| 8) Tonduti D, TUBB4A-related hypomyelinating leukodystrophy: New insights from a series of 12 patients. (2016). | 12 patients (disease onset at a mean age of 19 months (range 3 months–5 years).) | Dystonia, 2 had a severe hypokinetic-rigid syndrome, 1 manifested only postural tremor. Motor delayed developmental milestones. Dysarthria/anarthria, spastic diplegia with cerebellar signs, spastic paraplegia, ataxia, spastic tetraparesis. 1 had hypodontia and 1 manifested type 1 diabetes mellitus. | TUBB4A: c. 86G >A [p.Gly (G) 96Arg (R)] was detected in the conserved region (de novo mutation). |

1) 6 carried the mutation c.731G >T (p.Gly244Val)  
2) 1 showed the nucleotide change c.1163T >C leading to the amino acid change Met388Thr.  
3) Novel mutations—c. 544C >A (p.Pro182Thr), c. 533C >T (p.Thr178Met), c. 731G >A (p.Gly244Asp) missense mutation
usually presents in children.[2,4] Our patient was unique in terms of age of disease onset and temporal profile of symptomatology. Her onset of symptoms was in the fifth decade, when she initially had dystonia and was in the DYT4 range of the spectrum, although without typical “whispering dysphonia.” After she developed ataxia, spasticity, cognitive impairment, and eventually, seizures, and her MRI being suggestive of hypomyelination, she manifested features in the H-ABC range of the spectrum. Previously, the same mutation [c.286G>A(p.Gly96Arg)] was demonstrated in a Japanese patient with hypomyelinating leukodystrophy, whose symptoms started in the second decade with spasticity and dystonia.[5] An overview of the various studies on TUBB4A mutation disease spectrum with their prominent clinical findings is given in Table 1. Notably, our patient had a much later onset and, additionally, developed seizures. One patient of spasmodic dysphonia and oromandibular dystonia and dyskinesia with p.Ala271Thr variant of TUBB4A had onset at 60 years.[3] However, there was no history of ataxia or seizures.

Therefore, this patient represents a new phenotype associated with TUBB4A mutation, as a hypomyelinating leukodystrophy with very late age of onset, starting as dystonia, progressing over decades, and finally manifesting seizures, thus highlighting the role of thorough investigation and long-term follow-up in such patients.

Declaration of patient consent
Written informed consent was duly obtained.

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Conflicts of interest
There are no conflicts of interest.

Peyalee Sarkar, Adreesh Mukherjee, Sumanta Sarkar, Raju Agrawal, Souvik Dubey, Alak Pandit

Bangur Institute of Neurosciences, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India

Address for correspondence: Dr. Adreesh Mukherjee, 2-B, Surja Kumar Chatterjee Street, Kolkata, West Bengal, India. E-mail: adreesh03@yahoo.co.in

REFERENCES

1. Hersheson J, Mencacci NE, Davis M, MacDonald N, Trabzuni D, Ryten M, et al. Mutations in the autoregulatory domain of β-tubulin 4a cause hereditary dystonia. Ann Neurol 2013;73:546-53.

2. Tonduti D, Aiello C, Renaldo F, Dorboz I, Saaman S, Rodriguez D, et al. TUBB4A-related hypomyelinating leukodystrophy: New insights from a series of 12 patients. Eur J Paediatr Neurol 2016;20:323-30.

3. Lohmann K, Wilcox RA, Winkler S, Ramirez A, Rakovic A, Park J-S, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. Ann Neurol 2013;73:537-45.

4. Ferreira C, Poretti A, Cohen J, Hamosh A, Naidu S. Novel TUBB4A mutations and expansion of the neuroimaging phenotype of hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). Am J Med Genet A 2014;164:1802-7.

5. Lu Y, Ondo Y, Shimojima K, Osaka H, Yamamoto T. A novel TUBB4A mutation G96R identified in a patient with hypomyelinating leukodystrophy onset beyond adolescence. Hum Genome Var 2017;4:17035.

6. Erro R, Hersheson J, Ganos C, Mencacci NE, Stamelou M, Batla A, et al. H-ABC syndrome and DYT4: Variable expressivity or pleiotropy of TUBB4 mutations? Mov Disord 2015;30:828-33.

7. Hamilton EM, Polder E, Vanderver A, Naidu S, Schiffmann R, Fisher K, et al. Hypomyelination with atrophy of the basal ganglia and cerebellum: Further delineation of the phenotype and genotype-phenotype correlation. Brain 2014;137:1921-30.

8. Blumkin I, Halevy A, Ben-Ami-Raichman D, Dahari D, Haviv A, Sarit C, et al. Expansion of the spectrum of TUBB4A-related disorders: a new phenotype associated with a novel mutation in the TUBB4A gene. Neurogenetics 2014;15:107-13. doi: 10.1007/s10048-014-0392-2. Erratum in: Neurogenetics 2014;15:115.

9. Simons C, Wolf NI, McNeil N, Caldovic L, Devaney JM, Takanohashi A, et al. A de novo mutation in the β-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. Am J Hum Genet 2013;92:767-73.

10. Wilcox RA, Winkler S, Lohmann K, Klein C. Whispering dysphonia in an Australian family (DYT4): A clinical and genetic reappraisal. Mov Disord 2011;26:2404-8.

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