Adult-Onset Dystonia with Late-Onset Epilepsy in *TUBB4A*-Related Hypomyelinating Leukodystrophy—A New Intermediate Phenotype

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).

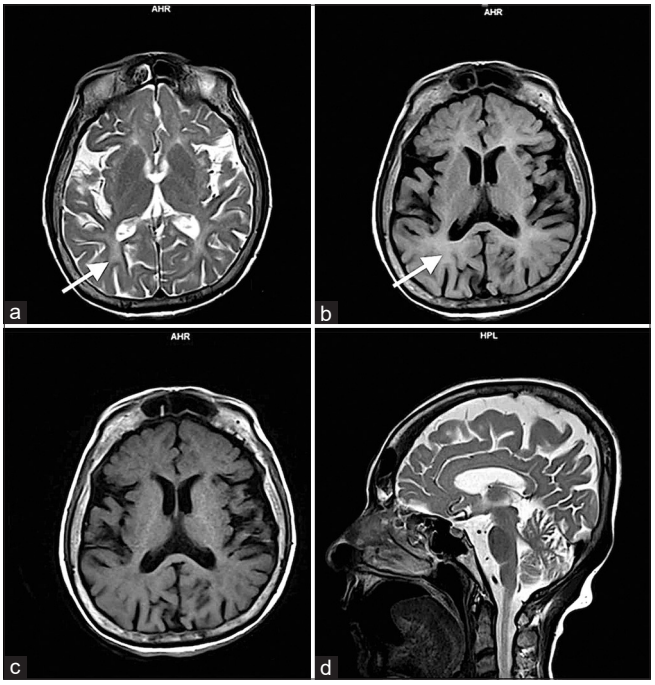

Figure 1: Hypomyelination with cerebellar and cortical atrophy. Magnetic resonance imaging of brain—axial T2-weighted (a), T2 fluid-attenuated inversion recovery (b), T1-weighted (c), and sagittal T2-weighted (d) images: showing symmetrical white matter signal intensity changes—hyperintense on T2/FLAIR (arrows) and isointense on T1, with cerebellar and cortical atrophy

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

Table 1: Studies elaborating prominent clinical radiological and genetic features of TUBB4A disease spectrum

Name of study	Total number of patients	Clinico-radiological profile				Mutation
		Movement disorder	Other neurological findings	Other system findings	Radiology	
1) Erro R, *et al*. H-ABC syndrome and DYT4: Variable expressivity or pleiotropy of TUBB4 mutations (2015)[6]	04 (age of onset first decade of life)	Generalized dystonia, ataxia. Bulbar involvement leading to aphonia and swallowing difficulty. Whispering dysphonia in one patient. Oculogyric crises	Spasticity, non-development of communication skills with preserved comprehension.		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.	One previously described and two novel mutations (c.941C >T; p.Ala314Val and c.900G >T; p.Met300Ile) in the exon 4 of the gene.
2) Hamilton EM, *et al*. Hypomyelination with atrophy of the basal ganglia and cerebellum: Further delineation of the phenotype and genotype-phenotype correlation. (2014)[7]	42 (median age of onset was 6 months, (range birth–3 years))	Dystonia, choreoathetosis (rarely)	Developmental delay, nystagmus, loss of speech from median age 7 years. Most patients unable to ambulate by the second decade. Ryles tube feeding required in 58% of patients.		Absent or disappearing putamen, variable cerebellar atrophy, and highly variable cerebral atrophy. Hypomyelination, agenesis of corpus callosum.	25 patients, a heterozygous c.745G >A *TUBB4A* mutation was identified. Thirteen other *TUBB4A* mutations were identified in 17 patients always in the heterozygous state.
3) Blumkin L, *et al*. Expansion of the spectrum of TUBB4A-related disorders: A new phenotype associated with a novel mutation in the TUBB4A gene. (2014)[8]	01	Segmental dystonia. Whispering dystonia: Present.	Slowly progressive spastic paraparesis. Intellectual disability		Permanent, incomplete myelination associated with progressive cerebellar atrophy	Novel E410K de novo heterozygous mutation in the *TUBB4A* gene
4) Lohmann K, *et al*. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. (2013)[3]		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 Missense variant in the TUBB4 (tubulin beta-4; Arg2Gly).
5) Simons C, *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. (2013)[9]	11 (9 months to 4.5 years: age of onset)	Hemidystonia. Ataxia with gait progressively deteriorating in all cases	Motor delayed developmental milestones. Dysarthria causing communication difficulty with preserved language and cognitive domains		MRI suggestive of hypomyelination with basal ganglia atrophy.	Heterozygous de novo mutation in *TUBB4A* was identified in all affected individuals: 745G >A (g. 6495765C >T)

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6) Wilcox RA, *et al.* Whispering dysphonia in an Australian family (DYT4): A clinical and genetic reappraisal. (2011)[10]	One family with nine affected members.	Isolated spasmodic dysphonia (whispering dysphonia) often with mild craniocervical dystonia to severe generalized dystonia. Extrusional tongue dystonia and a unique "hobby horse gait."				Missense (c.2297C >G; p.T766R) and a splice-site mutation (IVS5 + 1G >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)[5]	01 (onset after age of 17)	Ataxia, dystonia without dysphonia			MRI findings suggestive of hypomyelination of cerebellum, without significant basal ganglia atrophy.	TUBB4A: c. 86G >A [p.Gly (G) 96Arg (R)] was detected in the conserved region (*de novo* mutation).
8) Tonduti D, TUBB4A-related hypomyelinating leukodystrophy: New insights from a series of 12 patients. (2016).[2]	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.	White matter hypomyelination, while cerebellar atrophy. 1 image showed "globular" appearance of the basal ganglia because the anterior limb of internal capsule was not recognizable on FLAIR	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.

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