Adult-onset Leukodystrophy due to *TMEM63A* Variant Presenting with Rapidly Progressive Dementia with Parkinsonism

Dear Editor,

Disorders of cerebral white matter with onset in adults are a complex group of disorders, whose etiology may include infections, inflammatory, malignant causes, and extensive small vessel disease. Inherited disorders include genetic leukoencephalopathies and leukodystrophies.[1] Leukodystrophies usually occur in childhood. However, adult-onset leukodystrophies are rarely reported. Presence of certain clinical features may provide a clue to the specific disease entity. For example, parkinsonism may be observed in hereditary diffuse leukoencephalopathy with spheroids (HDLS); early prominent ataxia is seen in cerebrotendinous xanthomatosis, Gordon Holmes syndrome, and leukoencephalopathy with ataxia (LKPAT); and occasional rapid progression may be seen in adrenoleukodystrophy and Krabbe's disease.[2] We report an extremely rare cause of adult-onset leukodystrophy caused by *TMEM63A* mutation.

A 32-year-old female presented with cognitive impairment for 1 year. Her symptoms initially included dressing apraxia, which was followed by the development of right–left confusion and dyscalculia after 3 months of the initial symptom. Her symptoms showed progressive worsening. She had also been noted to develop slowness of activities and a blank facial expression. There was no history of tremor or postural instability. She had no history of seizures, myoclonus, or psychosis. Her family history was negative for similar complaints. She had no history of medical comorbidities or substance dependence. Birth and developmental history had been normal. Detailed lobar assessment revealed severe bilateral frontal, temporal, and parietal cognitive impairment. She had symmetrical bradykinesia, hypomimic facies, and slow saccades. Deep tendon reflexes were brisk. Routine blood investigations, including hemogram, liver, renal, thyroid functions, serum ammonia, antinuclear antigen, serum ceruloplasmin, and copper, were normal. Serum human immunodeficiency virus (HIV) and Venereal Disease Research Laboratory (VDRL) test were nonreactive. Autoimmune and paraneoplastic panel was negative. Brain magnetic resonance imaging (MRI) showed leukodystrophy with striking enlargement of bilateral sylvian fissures [Figure 1]. Whole exome sequencing showed the presence of a novel *de novo* heterozygous c.1613C>T (p.Ser538Leu) variant in exon 18 of the *TMEM63A* gene, which was confirmed on Sanger sequencing. Genetic testing of other family members was negative for this variant. The observed variant has minor allele frequency of 0.00003 in gnomAD exomes and is novel in genomes. *In silico* parameters revealed the mutation to be pathogenic by Mutation Taster and a Combined annotation dependent depletion (CADD) score of 17.54. The severity of the impact of this variant on the protein is medium, based on the effect of the protein and the Rare exome variant ensemble learner (REVEL) score. Hence, a diagnosis of *de novo* *TMEM63A*-related leukodystrophy was established, although we were unable to perform cell line functional studies. The patient's parents and brother were clinically examined and were found to have no neurological deficits. Their MRI brain was not suggestive of leukodystrophy.

Differential diagnosis of white matter abnormalities in adults includes inflammatory, toxin/drug-induced, infective, or neurodegenerative disorders including leukodystrophies and genetic leukoencephalopathies. Treatable disorders include autoimmune, tumors, vitamin deficiencies, and metabolic disorders. Among the hypomyelinating leukodystrophies reported with onset in adolescence, hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum (due to *TUBB4A* mutations), Pelizaeus–Merzbacher disease, Pelizaeus–Merzbacher-like disease, and *POL3*-related disorders are seen.[2]

Variants in the *TMEM63A* gene have recently been identified as an extremely rare cause of hypomyelinating leukodystrophy [Supplementary Table 1]. In a cohort of 20 patients with unexplained hypomyelinating leukodystrophy, two pediatric patients with *TMEM63A* as a causative variant were identified with a clinical phenotype of motor and intellectual impairment.[3] *TMEM63A* variants have been reported to be a cause of a Pelizaeus–Merzbacher-like disease in infants.[4,5] Infantile-onset transient hypomyelination leading to spinal cord involvement and paroxysmal event has also been reported.[6]

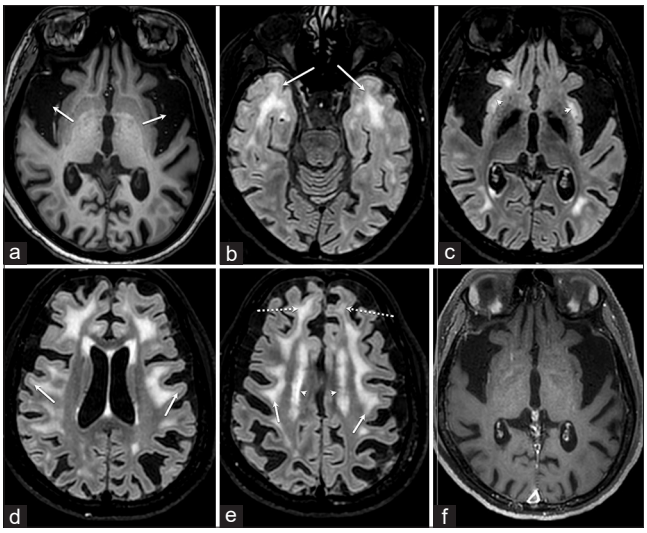

Figure 1: Axial T1-WI shows bilateral enlargement of the sylvian fissure. (a) Axial Fluid attenuated inversion recovery (FLAIR) images (b–e) show bilateral symmetrical hyperintensities in the temporal pole white matter (WM) (arrows in b), external capsules (short arrow in c), subcortical WM (arrows in d and e), and periventricular WM (arrowheads in e). No enhancement is seen following gadolinium administration in axial T1-WI (f) T1-WI = T1-weighted image

Transmembrane protein 63A (TMEM63A) belongs to the family of ion channels, with *TMEM63B* and *TMEM63C* being the other members.[5] These are mechanically activated. *TMEM63A* plays a role in early development of myelin, which may be also influenced by the two other family members, although they have not been reported to play a pathogenic role so far. In contrast to the pediatric onset in published cases so far who had hypomyelination, our patient had an adult-onset leukodystrophy. This suggests that TMEM63A may play a role not only in myelin development, which accounts for hypomyelination in infancy, but also in maintenance of normal myelin structure, the disruption of which may lead to a leukodystrophy pattern in older patients.

We expand the phenotypic spectrum of *TMEM63A*-related syndrome with our patient, who had several atypical clinical features, including onset of symptoms in adulthood, and the development of parkinsonism. Functional analysis of the variant identified may potentially provide an explanation for lack of development of symptoms at an early age.

Our case serves to highlight that variants in the *TMEM63A* gene may rarely lead to adult-onset leukodystrophy with rapidly progressive cognitive impairment in combination with parkinsonism, expanding the list of differentials for this symptom conglomerate of dementia–parkinsonism.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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