Leukodystrophy-Like Presentation in a Child: A Case of Hereditary Spastic Paraparesis-35

To the Editor,

Our index child is a 14-year-old boy, who was symptomatic from 5 years of age. According to his mother, he was developmentally normal till 5 years of age after which he developed difficulty in walking. This was associated with swaying from one side to the other and dragging of both feet during walking. There were no associated falls, seizures, or loss of consciousness. Over the course of next 1 year, he had further deterioration in his ability to walk and he could walk only with support. Gradually, his other domains of development were also affected as he had difficulty in eating food without spilling, dysarthria, and reduction in speech output. This was slowly progressive and by 10 years of age, he was bedridden and was completely dependent on his mother for all activities of daily living. He was able to indicate bladder and bowel movements till 12 years of age. His speech output completely declined and he was only able to vocalize. He was also not able to reach out for objects due to associated tremor. He had difficulty in swallowing and had history of aspiration of food. However, his cognition, emotion, and sleep–wake cycle were relatively preserved. There were no associated seizures, sensory disturbance, visual, or hearing problems. There was a family history of similar illness in two of the maternal cousins (both male), who were developmentally normal till 4 years of age and then had neuroregression involving all domains. One of the siblings expired due to aspiration pneumonia and other sibling was bedridden for the last 6 years. At admission, he was minimally conscious, was able to vocalize meaningful sounds, and had stable hemodynamics. General examination revealed generalized wasting, horizontal nystagmus, oromandibular dystonia, callosities over both lower limbs, and fixed flexion deformity in bilateral ankles. Neurological examination showed relatively preserved higher mental function, pseudobulbar palsy manifested by exaggerated jaw jerk, decreased bulk, spasticity in all four limbs (lower limb more than upper; Ashworth scale 4), power 3/5 in all 4 limbs, and exaggerated reflexes. His Babinski reflex was positive. Ophthalmological examination showed early features of optic atrophy and hearing assessment was normal. His respiratory, cardiovascular, and abdominal examination was normal. The initial differential diagnoses considered were neurodegenerative disorders—Adrenoleukodystrophy, metachromatic leukodystrophy, Pelizaeus-Merzbacher syndrome, or Juvenile GM1 gangliosidosis. Initial investigations revealed normal hematological and biochemical parameters. Magnetic resonance imaging of the brain with contrast revealed periventricular white matter paucity with relative sparing of U fibers and signal changes predominantly in the bilateral parieto-occipital regions, diffuse cerebral and cerebellar and brain stematrophy with thinning of corpus callosum [Figure 1]. Visually evoked potential showed decrease in amplitude and delay in latency. Subsequently, a clinical exome sequencing was done to confirm the diagnosis, which revealed a likely pathogenic homozygous missense variation in exon 5 of the fatty acid hydroxylase (FA2H) gene (chr16:g. 74719070C > T; Depth: 135x) that resulted in the amino acid substitution of Histidine for Arginine at codon 235 (p.Arg235His; ENST00000219368.8), consistent with **Autosomal recessive Spastic paraplegia-35 with neurodegeneration.** The child was provided neurorehabilitation in the form of physiotherapy and muscle relaxants for control of spasticity and genetic counseling was provided to the mother.

Hereditary spastic paraplegia (HSP), also known as familial spastic paraparesis or Strumpell-Lorrain syndrome, is a group

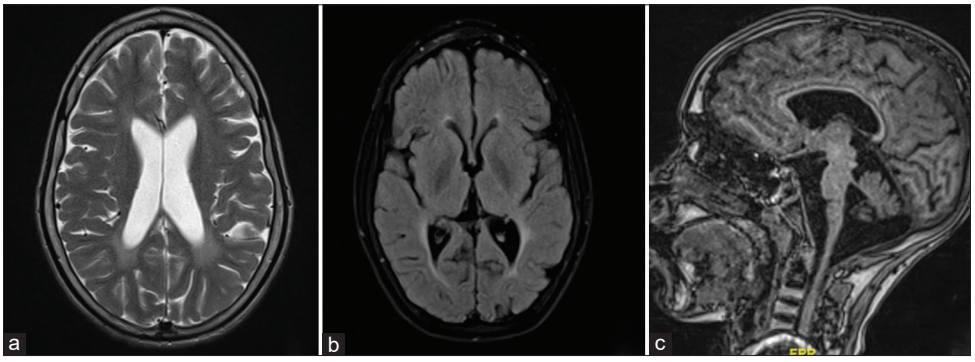

Figure 1: Magnetic resonance imaging of the brain with (a) T2 axial image showing hyperintensities in bilateral posterior periventricular parietal region with relative sparing of U fibers. (b) T2/FLAIR axial sequence showing periventricular white matter loss and ex vacuo dilatation of occipital horn of lateral ventricles. (c) T1 sagittal image showing diffuse thinning of corpus collosum with brain stem and cerebellar atrophy

of rare inherited disorders, characterized by progressive weakness and spasticity of the lower limbs.[1] HSP can be of early childhood onset with non-progression of symptoms, mimicking spastic diplegic cerebral palsy, or of late onset with progressive symptoms. HSP can be further classified as uncomplicated (pure spastic weakness of the lower extremities) or complicated form (associated with other features like seizures, intellectual disability, visual impairment, and extrapyramidal involvement).[2] Of the various genes causing HSP, FA2H gene is responsible for HSP-35. FA2H gene product participates in the synthesis of the fatty acids of myelin galactolipids, which when defective affects myelination.[3] The clinical spectrum of FA2H deficiency includes FA2H associated neurodegeneration, which is a subtype of neurodegeneration with brain iron accumulation, hereditary spastic paraparesis type-35, and leukodystrophy with spasticity and dystonia.[3] HSP-35 is autosomal recessive in inheritance and is characterized by childhood onset gait difficulties, dystonia, seizures, optic atrophy, and cognitive decline.[4]

The differential diagnoses include adrenomyeloneuropathy, mitochondrial disorders, hereditary motor-sensory neuropathy, and spinal cord lesions, which can present with spastic paraplegia.[5] The same were considered in the index case also, which were ruled out by the neuroimaging and genetic analysis. The neuroimaging findings in HSP-35 include T2 white matter hyperintensities, T2 globus pallidi hypointensity, thinning of corpus callosum, and atrophy of cerebellum and brain stem, as in our case.[6] The clinical features of HSP-35 mimic other leukodystrophies and the diagnosis is strictly by genetic analysis. There is no specific treatment and the management aims at reducing the spasticity by physiotherapy, anti-spasmodic drugs, botulinum toxin injection, and baclofen pump therapy.[7]

The literature on HSP-35 is sparse and is limited to a few case reports. Cao *et al.*[8] described two siblings with clinical features of spastic paraplegia, and neuroimaging findings of cerebral and cerebellar atrophy. Soehn *et al.* and Liao *et al.*[9,10] described FA2H homozygous mutations with clinical presentation of seizures, spasticity, and dystonia, respectively. A demyelinating form of neuropathy was described by Incecik *et al.*[11] in a 16-year-old boy with HSP-35. Bektaş *et al.*[5] reported that homozygous mutations in FA2H gene involving p.Asp57Glyfs*48 had an early and severe presentation. Our child had mutation involving p.Arg235His, which presented at around 5 years of age. A similar variant was reported by Magariello *et al.*[12] in one of the siblings of an Italian family.

There is an increasing need for the awareness to think beyond well-known leukodystrophies in a child with white matter degeneration, as in our case. FA2H mutations are associated with a progressive neurodegenerative disorder characterized by spasticity, dystonia, and white matter degeneration, due to a defect in myelinogenesis.

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Conflicts of interest

There are no conflicts of interest.

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