Neurodegeneration with Progressive Dystonia: Juvenile-Onset Tay–Sachs Disease

Dear Editor,

Juvenile-onset Tay–Sachs Disease (TSD) is a rare form of GMII gangliosidoses presenting between 2–10 years of age. We describe a 5-year-old boy born to consanguineous parents, with progressive familial dystonia, regression of language and cognitive decline. Diagnostic evaluation of TSD involves enzyme assay and genetic sequencing in patients with characteristic clinical symptoms. We report a novel mutation in *HEXA* gene in Indian population and elaborate the differentials involving neurodegeneration and worsening dystonia.

A 5-year-old boy, born to third-degree consanguineous parents, presented with frequent falls, voice change, and gradually progressive inability to walk for the past 2 years. The falls were associated with abnormal twisting postures of the limbs, which gradually became more severe. He also had a slow decline in cognition and memory. The illness progressed to complete absence of speech, abnormal gait with toe-walking, and generalized dystonia. Birth and perinatal period were normal. There were no seizures, vision impairment, episodic encephalopathy, fluctuating symptoms, abnormal startle or organomegaly. Mother had three abortions in the past and one previous child who died at 6 years of age with a similar illness.

On examination, he was oriented to time, place, and person but could not respond by meaningful words; speech was incomprehensible and slurred. He indicated most of his needs by gestures. He had generalized dystonia with gait instability [Video 1], intermittent opisthotonic posturing, spasticity, brisk reflexes, bilateral ankle clonus and extensor plantar responses, normal fundi, normal head circumference, and absence of organomegaly. A clinical diagnosis of neurodegeneration with progressive familial dystonia secondary to gangliosidosis, neuroacanthocytosis, Wilson's disease, dopa-responsive dystonia, inborn errors of metabolism such as late-onset organic aciduria, mitochondrial spectrum disorders, and biotin-responsive basal ganglia disease were considered.

Investigations showed normal peripheral blood film, liver functions, biotinidase level, and acylcarnitine and amino-acid profile in the blood and urinary organic acids. Magnetic resonance imaging (MRI) of the brain revealed subtle hyperintensities in peritrigonal white matter and bilateral centrum semi-ovale. Clinical exome analysis showed a homozygous, missense variation c.G1511A (p.Arg504His) at exon 13 in the *HEXA* gene (chromosome 15) associated with TSD (HEXA, OMIM #272800). This variant has not been observed in 1000 Genome and ExAC databases and was reported as pathogenic by ClinVar Database, dbSNP Database, and HGMD Database. It was predicted to be deleterious by Bioinformatics algorithms. Parents did not consent for their genetic testing as they were not planning further conception. The child received supportive care for severe dystonia and continued to follow up with the involvement of multidisciplinary teams.

TSD (GM-II gangliosidosis type 1) is a rare, autosomal recessive neurodegenerative disorder caused by reduced/absent activity of hexosaminidase, an enzyme, leading to accumulation of gangliosides within neuronal and retinal cells. Sandhoff disease and hexosaminidase activator deficiency are the other two related GMII gangliosidoses that slightly differ clinically and can be differentiated only on basis of an enzyme or genetic test.[1] TSD is caused by the mutations in *HEXA* gene. It is located on chromosomes 15q23-q24 encompassing 14 exons. Among the large spectrum of mutations causing TSD, mutations causing gross alterations in Hex alpha subunit result in severe infantile form, whereas missense mutations causing amino acid substitutions result in both infantile and late-onset subtypes.[2]

Infantile-onset TSD is the most prevalent form and exhibits characteristic neuroregression associated with hyperacusis, seizures, and cherry-red spot in the first 2 years of life. On the other hand, juvenile-onset TSD has an onset between 2–10 years of age with progressive gait instability, prominent movement disorder, impaired intellect, and speech. The classic cherry-red spots are rarely seen, rather optic atrophy develops gradually.[1] The movement disorder may manifest as progressive generalized dystonia, Parkinsonism, ataxia, tremors, and dysarthria.[3-7] Common differential diagnoses for neurodegeneration associated with movement disorders in this age group include mitochondrial disorders, Wilson's disease, neurodegeneration with brain iron accumulation, and Huntington's disease.[8] The spectrum of movement disorders tends to vary among different storage disorders and most of the patients exhibit more than one disorder. However, the important thing for a pediatrician is to recognize the phenotype of childhood-onset progressive neurodegeneration associated with movement disorders. A normal MRI excludes several of these disorders and further genetic testing is warranted for confirmation as well as prenatal counseling. Treatment is mainly supportive.

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Conflicts of interest

There are no conflicts of interest.

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