Familial Spastic Paraparesis: A Novel Mutation in a 4-Year-Old Girl

Sir,

Hereditary/Familial spastic paraparesis (HSP) or Strumpell-Lorrain syndrome constitutes a heterogeneous group of neurodegenerative disorders involving predominantly the corticospinal tracts and dorsal columns.[1] We saw a 4-year-old girl with toe-walking, abnormal gait, and frequent falls for the past two and a half years. The symptoms were non-progressive and she continued ambulation with difficulty. There was no history of vision impairment, alteration in sensorium, seizures, fluctuations in symptoms, incoordination, or bowel or bladder disturbances. She was born to non-consanguineously married parents by a term vaginal delivery and uneventful perinatal transition. She was immunized for age and showed motor and mild language delay. Father had similar complaints since early childhood and had undergone several surgical procedures for gait improvement. He was currently employed and ambulatory with a waddling gait. Remaining family members were not affected and normal. On examination, she had signs of vitamin D deficiency (frontal bossing and wrist widening), a single café-au-lait macule over the left side of the trunk, platynychia, unclear speech, bilateral talipes varus, spastic paraparesis, diminished vibration sense, extensor plantar, ankle contractures, waddling gait, normal head size, and absence of organomegaly. Father also demonstrated toe-walking, spastic paraparesis, and knee and ankle contractures. Clinical diagnoses of familial, inherited spastic paraparesis, or neurometabolic disorders such as arginase deficiency**,** biotinidase deficiency, and abetalipoproteinemia were considered. Magnetic resonance imaging (MRI) of the spine revealed hydromyelia with mild spinal cord atrophy. MRI brain in the child was normal. MRI spine of father was normal. Tandem mass spectrometry, gas chromatography-mass spectrometry, serum ammonia, lipid profile, nerve conduction, and electromyography studies were normal. Whole exome sequencing for the child revealed an autosomal-dominant, heterozygous, missense, pathogenic variation in exon 8 (NM_015915) of *ATL1* gene (chr14:51081116.c.T749A/p.Leu250Gln), which was confirmed by Sanger sequencing. Parental testing was not done due to financial constraints. She was offered supportive care and anti-spasticity drugs.

Familial HSP can occur as an autosomal dominant (70% in pure forms) or recessive, and rarely as X-linked inherited disorder. Overall, the age of onset, disease severity, and rate of progression differ among different types of autosomal dominant HSP. To date, nearly 20 genetic loci for autosomal dominant HSP have been identified, but only 12 genes are known.[2] *SPG3A*/Atlastin-1 mutations represent approximately 30–50% of autosomal dominant HSP cases and are the most frequent cause of HSP with onset before the age of 10 years.[3] The reported genetic variations are predominantly of missense type, as in the index patient. However, this was a novel mutation, which has not been observed in 1000 genome database and ExAC database. The protein product Atlastin-1 helps in neurite outgrowth and axon elongation during neuronal development. The age of onset is commonly at around 4 years of life.[4] The diagnosis is usually suspected on the basis of characteristic clinical presentation, family history of similar illness, and

absence of progressive neuroimaging changes. In pure forms, MRI spine can be normal; however, spinal cord atrophy and hydromyelia has been reported in cases with *SPG56* variation.[5] We propose that hydromyelia seen in the index child may be an incidental finding and cannot explain the entire spectrum of clinical symptoms seen in this child. Hence, it probably is not the cause of spastic paraparesis in the index child. MRI brain may reveal white matter abnormalities on corticospinal tracts with thinning of corpus callosum.[6] Common clinical differential diagnoses include spastic diplegic cerebral palsy, subacute combined degeneration of spinal cord, copper deficiency, Segawa disease, Friedreich's ataxia, mitochondrial respiratory chain disorders, organic acidurias such as biotinidase deficiency, and methylmalonic aciduria, arginase deficiency, and structural abnormalities of brain and spinal cord.[7] Family history may give a clue to the diagnosis, prompting a genetic confirmation. The rate of progression in *ATL1*-related HSP is slow, and wheelchair dependency is relatively rare as exhibited by the disease course in the father who suffers from disability but is able to carry out his activities of daily living and preserved intellect.

In conclusion, in any child presenting with early onset toe-walking and spasticity with similar family history, a differential diagnosis of autosomal-dominant HSP due to *ATL1* (*SPG3A*) must be considered. Timely diagnosis will help to initiate early rehabilitation and prevent unnecessary diagnostic evaluations.

Consent

Written informed consent was obtained from parents.

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Conflicts of interest

There are no conflicts of interest.

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