A Sibling Pair with Autosomal Recessive Charcot–Marie–Tooth Disease Due to Novel Ganglioside-induced Differentiation-associated Protein 1 Mutation

Sir,

Charcot–Marie–Tooth disease (CMT) due to ganglioside-induced differentiation-associated protein 1 (GDAP1) mutations is rare. The GDAP1 expression in the Schwann cells and in the outer mitochondrial membrane is responsible for the complex interplay whereby it can cause axonal as well as demyelinating neuropathy. Although GDAP1 is also expressed in the brain, no clinical involvement has been documented so far in any patient. The purpose of this letter is to report an Indian family with a novel GDAP1 mutation which also appears to be the first report in literature.

The index case was a 12-year-old boy with delayed motor milestones, bilateral foot drop, and frequent falls. At presentation, he was ambulatory independently, but he had been using ankle orthoses for few years. On examination, there was distal wasting in a length-dependent manner without sensory loss, hypotonia, and diffuse areflexia. Higher mental functions and cranial nerves were intact. No dysmorphism was noted. Electrodiagnostic (EDX) study suggested a generalized sensorimotor mixed, i.e., axonal and demyelinating type of polyneuropathy, with severe active denervation in the right tibialis anterior. Family history was relevant for his 14-year-old sister who had a similar clinical and EDX profile. On screening, the father had attenuated superficial peroneal sensory nerve action potential amplitude (3–4 uV). Both parents showed a reduced sural: radial SNAP amplitude ratio suggestive of sensory axonopathy affecting the feet. The siblings showed a homozygous missense variation c. 3G>A.p in the start codon of GDAP1 gene and both parents showed a heterozygous mutation for the same. The start codon mutation would abolish the protein translation causing complete loss of

Table 1: Summary of the clinical, electrodiagnostic, and genetic profile of the family

Family member	Index case	Sister	Mother	Father
Age (years)	12	14	40	39
Phenotype	Motor delay, walking with ankle orthoses for 2 years	Motor delay, walking with ankle orthoses for 2-3 years	Asymptomatic	Asymptomatic
DML (ms)	5.18 (left tibial, NR<7)	6.76 (right ulnar, NR<5)	Normal	Normal
CMAP amplitude (mV)	0.79 (left tibial, NR>5)	0.91 (right ulnar, NR>5)	Normal	Normal
CV (m/s)	21.3 (left tibial, NR>40)	35.7 (right ulnar, NR>50)	Normal	Normal
SNAP amplitude (uV)	All absent	All absent	Normal	Reduced in both superficial peroneal nerves (NR>5)
Sural: Radial SNAP amplitude ratio	NA	NA	0.21 (NR>0.36)	0.16 (NR>0.36)
Mutation	GDAP1 c. 3G>A.p Homozygous missense variation	GDAP1 c. 3G>A.p Homozygous missense variation	GDAP1 c. 3G>A.p Heterozygous	GDAP1 c. 3G>A.p Heterozygous

DML = Distal motor latency, CMAP = Compound muscle action potential, CV = Conduction velocity, SNAP = Sensory nerve action potential, NR = Normal range, NA = Not applicable, GDAP1 = Ganglioside-induced differentiation-associated protein 1

GDAP1 function. Table 1 is a summary of the clinical, EDX, and genetic profile of the family.

In the evaluation of children with early foot deformities and delayed motor milestones without a significant history during birth and neonatal period, testing for FGD4, PRX, MTMR2, SBF2, SH3TC2, and GDAP1 was recommended by Baets *et al*.[1] The three most common genes associated with autosomal recessive CMT are GDAP1, SH3TC2, and HINT1, GDAP1 being the most frequent.[2,3] Mutations in the GDAP1 can occur with dominant and recessive inheritance patterns. The early onset and severe phenotype in the siblings with unaffected parents and negative family history suggest an autosomal recessive mode of inheritance. Since both parents showed early sensory axonopathy affecting the lower limbs, it may be appropriate to postulate that the demyelination seen in the siblings may be secondary to axonal degeneration.

The diagnostic protocol for a suspected recessive inheritance pattern suggests initial screening for mutations in NDRG1 which is responsible for CMT4D. If negative or if not of Gypsy ethnicity, then screening for GDAP1 is recommended.[4]

CMT is genetically and clinically heterogeneous. Careful attention to phenotype combined with good electrophysiological evaluation of patient and unaffected parents helped us to narrow the diagnosis to the possible subtype.

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Conflicts of interest
There are no conflicts of interest.

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References

1. Baets J, Deconinck T, De Vriendt E, Zimoń M, Yperzeele L, Van Hoorenbeeck K, *et al.* Genetic spectrum of hereditary neuropathies with onset in the first year of life. Brain 2011;134:2664-76.
2. Meuleman J, Pou-Serradell A, Löfgren A, Ceuterick C, Martin JJ, Timmerman V, *et al.* A novel 3'-splice site mutation in peripheral myelin protein 22 causing hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord 2001;11:400-3.
3. Nelis E, Erdem S, Van Den Bergh PY, Belpaire-Dethiou MC, Ceuterick C, Van Gerwen V, *et al.* Mutations in GDAP1: Autosomal recessive CMT with demyelination and axonopathy. Neurology 2002;59:1865-72.
4. Berciano J, Sevilla T, Casasnovas C, Sivera R, Vílchez JJ, Infante J, *et al.* Guidelines for molecular diagnosis of Charcot-Marie-Tooth disease. Neurologia 2012;27:169-78.

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