Vestibulo-ocular reflex impairment in SPG7 hereditary spastic paraplegia

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Hereditary spastic paraplegia (SPG) can be due to many different mutations in at least 9 different genes, one of which is SPG7 (Hewamadduma et al. 2020). Patients with homozygous SPG7 mutations are usually male and present in the 4th decade with ataxia and are then found to have pyramidal signs in the lower limbs. We tested vestibular function with video head impulses (vHIT) (Halmagyi and Curthoys, 2018) in 3 patients from 3 families with 3 different novel autosomal recessive SPG7 mutations to find out if vestibular impairment (Strakov et al. 2020) might be contributing to their ataxia.

Patient 1 is a 48 years old man who presented with progressive imbalance starting after 40. In his 20s he completed military service as a commando. On examination he had mild dysarthria and spastic-ataxic gait, heel-shin ataxia, brisk tendon reflexes with extensor plantar reflexes, bilateral gaze-evoked nystagmus, normal horizontal and vertical saccades and bilaterally impaired vestibulo-ocular reflex (VOR) on impulsive testing (Table 1, Figure 1). His hearing was clinically normal. MRI showed only cerebellar atrophy. He has a brother and a half-brother (common mother) without similar complaints. His unaffected parents are second-degree cousins. Hereditary spastic paraplegia panel analysis using Next Generation Sequencing (Celemics®) revealed a pathogenic (PM1, PM2, PP2, PP5), homozygous c.2228T>C (chr16:89623341) (p.Ile743Thr, rs752623413) mutation in exon 17 of the SPG7 gene. Pathogenicity scoring is according to American College of Medical Genetics (ACMG) guidelines (Richards et al. 2015).

Patient 2 is a 35 years old man who presented with progressive imbalance and slurred speech starting in his 20s, during military service. On examination he had mild dysarthria and spastic-ataxic gait, heel-shin ataxia, brisk tendon reflexes with extensor plantar reflexes, bilateral gaze-evoked nystagmus, normal horizontal and vertical saccades and bilaterally impaired VOR on impulsive testing (Table 1). His hearing was clinically normal. MRI showed only cerebellar atrophy. He has 11 siblings. His unaffected parents are second-degree cousins. He thinks 2 of his brothers have the same problems as he has, but they refuse to be examined. Whole exome sequencing revealed a novel homozygous variation (c.G1176A) in exon 13 of the SPG7 gene, leading to p.Thr588Met missense mutation in the paraplegin protein. The substitution is predicted to be damaging with a Combined Annotation Dependent Depletion (CADD) score of 24.6. The presence and segregation of the homozygous variant was validated with Sanger sequencing in Patient 2 and on his asymptomatic mother who is, as expected, a heterozygous carrier.

Patient 3 is a 37 years old man who presented with progressive imbalance starting in his 20s. On examination he had mild dysarthria and spastic-ataxic gait, heel-shin ataxia, brisk tendon reflexes with ankle clonus and extensor plantar reflexes, bilateral gaze-evoked nystagmus, normal horizontal and vertical saccades and bilaterally impaired VOR on impulsive testing. His hearing was clinically normal. MRI showed only cerebellar atrophy. His parents are second-degree cousins. He has two siblings. His father and a sister are affected. Whole exome sequencing revealed a homozygous and novel c. G1972A mutation was found in Exon 13 of the SPG7 gene, resulting in a missense change (p.Ala658Thr) in the paraplegin protein. The mutation is predicted to be damaging with a CADD score of 23.5. Segregation analysis of the family members confirmed the expected presence of the same variant in homozygosity in Patient 3 and in his affected father and affected sister. His unaffected mother, sister, two nieces and nephew are heterozygous carriers of the variant. One nephew does not carry the mutation.

All 3 patients had mild to moderate impairment of the VOR from 5 or from all 6 semicircular canals (SCC) on vHIT.

Table 1. Vestibulo-ocular reflex gain in SPG7.

	VOR gain					
Patient	LL	RL	LA	RA	LP	RP
1	0.41[a,b]	0.48[a,b]	0.40	0.62	0.69	0.57
2	0.75	0.73	0.61	0.75	0.52	0.64
3	0.67[a]	0.72[a]	0.48	0.56	0.59	0.46

Semicircular canals: LL = Left Lateral; RL = Right Lateral; LA = Left Anterior; RA = Right Anterior; LP = Left Posterior; RP = Right Posterior. Vestibulo-ocular reflex (VOR) gain < 0.80 for lateral canals and < 0.70 for vertical canals was considered abnormal; a = low VOR gain with overt saccade; b = low VOR gain with covert saccade.

For example, in Patient 1, the VOR was impaired from all 6 SCCs, the 2 lateral SCCs more severely than the 4 vertical SCCs (Figure 1). The site of lesion responsible for the vestibular impairment cannot be determined from the vestibular function testing alone but in the absence of hearing impairment it is most likely to be at the level of the vestibular ganglia as in CANVAS (Szmulewicz et al. 2014) and perhaps in Charcot-Marie-Tooth disease (Akdal et al. 2020). Testing vestibular function with vHIT is easy, quick, reliable and reproducible (McGarvie et al. 2020). Testing vestibular function in response to low angular accelerations will give inconclusive results (Milenkovic et al. 2019).

In conclusion, testing vestibular function in hereditary SPG patients using vHIT should give a clear idea of which genotypes can cause vestibular impairment and whether this impairment is static or progressive.

Conflict of interest

The authors have no conflicts of interest. All testing was approved by local ethics committee.

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Figure legend

Figure 1. Video Head Impulse Test (Natus Otometrics®) of the vestibulo-ocular reflex (VOR). Low gain from each semicircular canal (SCC) in Patient 1. Rightward head velocity in blue; leftward head velocity in orange, VOR eye velocity (inverted) in green; catch-up saccades in red.