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Revisiting the SPG8 phenotype – the first European case of L619F WASHC5 hereditary spastic paraplegia

Přehodnocení fenotypu SPG8 – první případ L619F WASHC5 hereditární spastické paraplegie v Evropě

Dear editor,

Hereditary spastic paraplegia (HSP) is a rare disease, with prevalence estimated at a few cases per 100,000, characterized by slowly progressive spasticity, clinically expressed by gait disorder, often with sensory deficits [1,2].

A clinical and phenotypical classification of HSP differentiates uncomplicated (pure) HSP, characterized only by spastic syndrome, from complicated HSP, which includes additional neurological manifestations such as amyotrophy, ataxia, peripheral neuropathy, optic atrophy, and psychiatric disorders [1,3].

Genetically, an increasing number of relevant genes (spastic paraplegia genes; SPG) have been identified, the most recent being SPG83 in 2020 [4].

SPG8 is a pure, autosomal-dominant HSP condition, linked to several missense mutations in *WASHC5* (strumpellin, formerly *KIAA0196, SPG8*). It has been described in 23 families worldwide so far, being associated with 20 different point mutations [5].

Our paper presents the second unrelated case of SPG8 (NM_014846.4(WASHC5):c.1857G>T:p.(Leu619Phe); ClinVar ID: 39008) in the literature, which stands out from the previous report of Rocco et al [6] (further explored by Valdmanis et al [7]), and from SPG8 in general, by its noticeably milder phenotype and minimal associated symptoms.

We present the case of a 54-year-old man with a neurologically unremarkable medical history, complaining of gait disturbances, muscle weakness and sensory abnormalities in the lower extremities. The first symptoms appeared 4 years ago (in 2016) and consisted of muscle weakness associated with gait disturbances and slowly progressive lower limb spasticity. A cranial MRI performed that year showed no important pathological changes.

Furthermore, the patient reported that his mother had suffered from chronic spastic paraparesis. Moreover, the maternal grandfather, one maternal aunt and one maternal uncle apparently displayed similar phenotypes, presumably HSP.

On neurological examination, pyramidal signs limited to the lower limbs were identified – spastic, scissor gait, bilateral Babinski sign – while deep tendon reflexes were symmetrically brisk. The patient could walk unassisted, but could not run due to spasticity, and complained of fatigue after walking at least 500 m. He was able to climb stairs and rise from a chair. Sensory impairment was present, with diminished proprioception, vibratory sensitivity and bilateral plantar paresthesias. Clonus was present. On the other hand, clinical examination excluded cognitive disorders, loss of coordination, dysarthria, involuntary movements and signs of meningeal and cranial nerve damage.

Results of laboratory tests were unremarkable, apart from a mild folate deficiency. Creatine kinase and aspartate aminotransferase values were within reference values, excluding myopathy. Urinalysis revealed leukocyturia and hypersthenuria, with a negative culture.

Electromyography assessment of the lower and upper limbs revealed normal motor and sensory nerve conduction studies, while evoked motor potentials in the upper and lower limbs were distorted, consistent with a bilateral pyramidal tract lesion located above C7. Another sagittal brain and cervical spine MRI did not show any signs of focal lesion in the supratentorial and cerebellar region, nor compression or narrowing of the spinal cord (Fig. 1).

A blood sample was analyzed using the Invitae Hereditary Spastic Paraplegia panel (GeneDx, Gaithersburg, MD, USA), a next-generation sequencing (NGS) panel which comprised of HSP genes *SPG1* to *SPG78*. The test identified, in a heterozygous state, the above-mentioned missense mutation in *WASHC5* (*SPG8*), a variant which is pathogenic according to the American College

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Fig. 1. Dorsal and cervical sagittal T2-weighted MRI (FRFSE). Mild aging-associated changes of intervertebral discs without signs of the spinal cord compression and with normal spinal canal structure and size.
FRFSE – fast-recovery fast spin-echo

Obr. 1. Sagitální T2-vážený snímek MR (FRFSE) dorzální části krční páteře. Mírné změny meziobratlových plotének v důsledku stárnutí bez známek komprese míchy při normální struktuře a velikostí páteřního kanálu.
FRFSE – fast-recovery fast spin-echo

of Medical Genetics (ACMG) criteria [8] and ClinVar. Additionally, one more heterozygous, missense variant in *DDHD1* (formerly *SPG28*) was identified: NM_001160148.2 (DDHD1):c.976G>C:p.(Asp326His), ClinVar ID: 576186. The latter mutation is classified as a variant of unknown significance (VUS) according to ClinVar and the ACMG criteria [8].

Considering the clinical evidence of pathogenicity of the first mutation, the final diagnosis of the patient is SPG8 HSP.

Despite its rarity, HSP is notably heterogeneous, genetically and phenotypically.

Regarding the latter, SPG8, while conventionally classified as a pure HSP, stands out due to an earlier onset of symptoms (typically, but not exclusively, in the patients' 20s or 30s), a more severe prognosis (patients are in need of physical therapy and become wheelchair-bound at an earlier age), as well as more obvious associated signs (e.g., decreased distal vibration sense, reduced bladder control, amyotrophy); these can lead to confusion with complicated HSP [5,7].

In our case, the patient's presentation has some overlap with previously described features of SPG8, namely adult onset and diminished vibration sense [5,7]. On the other hand, the patient denied urinary dysfunction, a common complaint in this type of HSP [5,7], with the only pathological finding – sterile leukocyturia. Another difference between our patient and other cases of SPG8 is a milder phenotype in the former (onset at the age of 50, compared to 20–30 in other cases of SPG8) [6].

It should be noted that another case of *WASHC5* p.(Leu619Phe) has been reported by Rocco et al [6] in a Brazilian family. Despite general similarities, there are considerable differences between our patient and the above-mentioned case. Namely, all members of the Brazilian family had an early onset (at the age of 18–26 years) and a more accelerated degradation of motor functions, being wheelchair-bound at the age of 30–40 years [6]. A comparison between the case series of Rocco et al and the present case is outlined in Tab. 1.

The *DDHD1* (SPG28) mutation, on the other hand, despite a considerable rarity in the gnomAD 2.1.1 database [9], is not known to be linked to HSP, in which case all pathogenic mutations described so far affect the phospholipase domain, unlike the present mutation [10]. Finally, SPG28 shows autosomal recessive inheritance [1] and cannot be responsible for the patient's phenotype on its own, in whose case a single variant allele was identified.

In conclusion, practicing neurologists should keep in mind that classification into pure HSP by mutational analysis is not necessarily incompatible with a limited degree of autonomic and sensory dysfunction, and likewise the age of onset and motor impairment can differ considerably from the previously described clinical picture, especially in the case of rarer forms of HSP. Subsequently, for a disease of such genetic heterogeneity as HSP, and especially in the context of overlapping and incompletely understood clinical features, comprehensive NGS panels or whole-exome / whole-genome sequencing, become essential for an accurate diagnosis.

Tab. 1. Phenotype comparison between cases reported by Rocco et al [6] and the present case.

	Rocco et al [6]	Present case
Age of onset (years)	21.2 ± 3.2	50
Walking aids	4 of 12 wheelchair-bound at the age of 33–40 2 of 12 require cane at the age of 44–50	walks unassisted the age of 54
Spastic gait	all patients	yes
Hyperreflexia	all patients	yes
Vibration sensitivity	not described	decreased
Urinary dysfunction	all patients	denies

Declaration of patient consent

The authors declare that they have received all necessary patient permission forms. The patient has provided his agreement in the form for his diagnostic features to be published in the journal. The patient understands that his name and initials will not be published, and that his identity will be hidden, but anonymity cannot be guaranteed.

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