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Letter to the Editor

Sensory-motor neuropathy in a case with SPG35: Expanding the phenotype

Dear Editor,

1. Introduction

SPG35 is a complicated form of hereditary spastic paraplegia (HSP) caused by biallelic mutations in the fatty acid 2-hydroxylase (FA2H) gene [1]. FA2H protein is involved in the synthesis of 2-hydroxy fatty acid galactolipids, which belong to the most abundant lipids in the myelin sheath [2]. Mouse model of FA2H deficiency has demonstrated that FA2H protein is indispensable for long-term myelin sheath and axon maintenance. Mice deficient in FA2H develop structural and functional normal myelin, but aged FA2H-deficient mice show axon and myelin sheath degeneration in the central nervous system (CNS) and peripheral nerves [3,4]. Similar findings are described in humans with FA2H deficiency who display a normal early development, but as they mature, they begin to manifest a range of CNS demyelinating phenotypes including SPG35 [1,5,6]. In contrast to the mice deficient in FA2H which show late-onset peripheral demyelinating and axonal neuropathies, peripheral neuropathy is uncommon in affected humans. So far, only 1 case has been reported to have an axonal sensory neuropathy [7]. We report a case of SPG35 with the severe phenotype associated with FA2H deficiency that also developed a sensory-motor neuropathy. In addition, in this case the finding of abnormal lipid storage in macrophages on a rectal biopsy is described contributing new potential information about this complicated form of HSP. Soehn et al., who simultaneously analyzed the DNA of this patient (family 4), revealed uniparental disomy (UPD) as mutational mechanism [8].

2. Case report

The patient was born to healthy non-consanguineous parents and there was no family history of neurological disease. She developed normally until age 4, when she began to manifest pyramidal tract signs in lower limbs. Over the next years the patient suffered a progressive neurological decline and by the age 8 the examination disclosed dysarthria, spastic quadriparesis, upper and lower limbs ataxia and oculomotor impairment with saccadic ocular pursuit and a non-persistent ocular apraxia. Cognitive function was preserved until age 8 when she began showing deteriorating academic performance. Brain MRI was normal at age 5 and 7 years; however, at 11 years of age it revealed slight T2 hyperintensity in the periventricular and deep white matter that extended to the centrum semiovale, and mild cortical and corpus callosum atrophy (unavailable to show). At age 13 years, these changes developed into a diffuse atrophy and residual peritrigonal leukopathy (Fig. 1a1–a4). Electrophysiological studies were normal until 13 years, when the nerve conduction studies indicated that motor and sensory responses (CMAPs and SNAPs, respectively) had decreased amplitudes and slightly decreased conduction velocity in lower limbs consistent with a mostly axonal sensory-motor neuropathy (Fig. 1b). In addition, concentric needle electromyography (EMG) of the right tibialis showed the presence of denervation potentials. At 13 years of age, ophthalmologic examination (previously normal) revealed signs of optic atrophy. By the age 18 the examination showed a severe neurological impairment with anarthria, dysphagia, dystonic posture of upper limbs, upper limbs ataxia, and spastic quadriparesis. At this age, the brain MRI revealed a severe atrophy (Fig. 1a5–a8).

Laboratory investigations, genetic analysis for trinucleotide repeat expansions causing ataxias, as well as biopsies of different tissues (skin, conjunctiva, and bone marrow medulla) performed at age 13 years were all negatives. However, the histological analysis of the rectum showed a great number of large macrophages that took up the mucosa, submucosa and muscularis. The ultrastructural analysis by electron microscopy revealed lipid storage although there were no signs suggestive of lysosomal disease in these cells or other cell types (Fig. 1c). Follow-up testing of lysosomal enzymes was normal.

Finally, the analysis of all coding exons and flanking introns of an autosomal recessive HSPs gene panel by next-generation sequencing (platform Illumina HiSeq 2000/2500) carried out when the patient was 18-years-old, detected a likely pathogenic homozygous mutation in exon 5 of FA2H gene (c.785A>C, p.K262T). The mutation was confirmed by Sanger sequencing. Soehn et al., who simultaneously analyzed the DNA of this patient (family 4), revealed uniparental disomy (UPD) as mutational mechanism [8].

3. Discussion

The clinical and radiological manifestations described in our patient are consistent with the previously reported severe phenotypes associated with FA2H deficiency [9]. In addition, electrophysiological tests showed a late-onset axonal sensory-motor neuropathy. So far, the involvement of the peripheral nerves in humans with FA2H deficiency has only been reported in 1 case with an axonal sensory neuropathy [7]. In our patient, unlike the previous case, there was also a motor involvement. Interestingly, these findings are similar to those described in the fa2h knockout mice presented by Zoller et al. emphasizing the role of the FA2H in myelin sheath and, especially in axon maintenance [3].

As seen in this case, the involvement of cerebellum is a frequent manifestation in the SPG35. Similarly, about a half of the previous reported cases presented additional signs of cerebellar deterioration [9]. In this sense, histological and behavioral analysis of the mutant mice has revealed that disruption of the cerebellum is an early sign of the neurological abnormalities that can be seen in this disorder [4].

Previous biopsies performed in patients with FA2H deficiency have been negatives with the exception of the case described by Kruer et al. that showed PAS-positive granular cytoplasm in macrophages in a bone marrow biopsy [5,6,9]. We speculate that the lipid storage observed in macrophages of the rectal mucous in our patient

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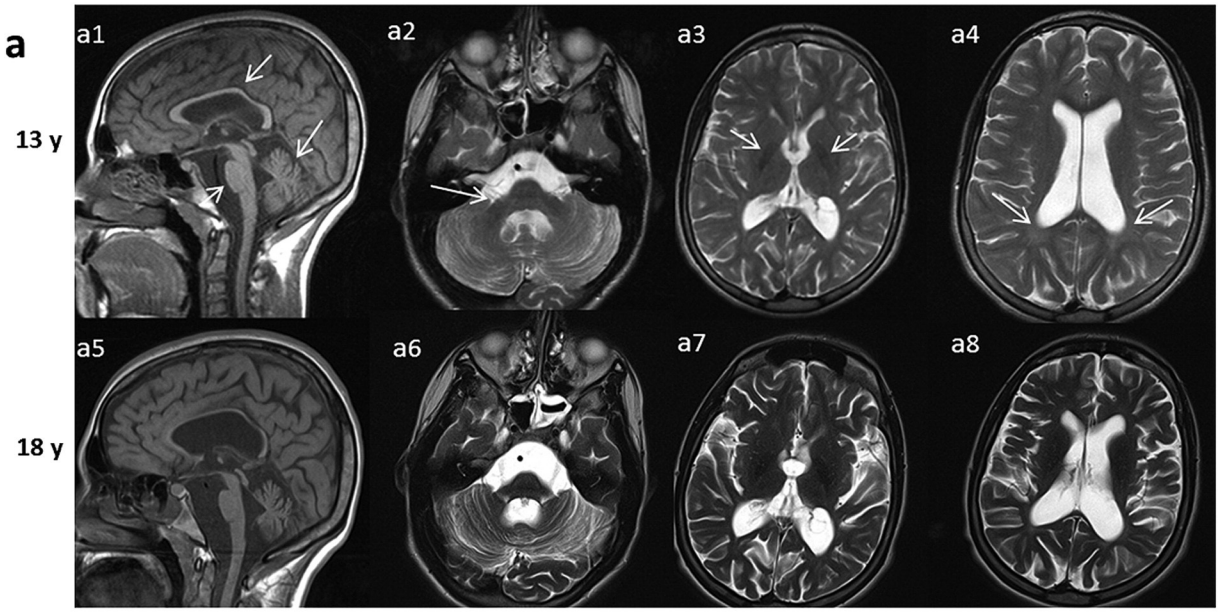

b

MNCS	R/L	DL (ms)	CV (m/s)	A (mV)
Medianus (wrist)	R	3.1 (<4.2)	60 (>48)	10 (>3.5)
Peroneus (ankle)	R	5.0 (<5.5)	**36** (>40)	**1** (>2.5)
Peroneus (ankle)	L	4.7 (<5.5)	55 (>40)	**1.2** (>2.5)
Tibialis (ankle)	R	5.0 (<6)	**39** (>41)	6 (>2.9)
SNCS	**R/L**	**DL (ms)**	**CV (m/s)**	**A (μV)**
Medianus (2nd finger)	R	2.6 (<3.5)	57 (>44)	25 (>19)
Sural (Stim site 14 cm)	R	3 (<3.5)	41 (>40)	**2.6** (>4)

c

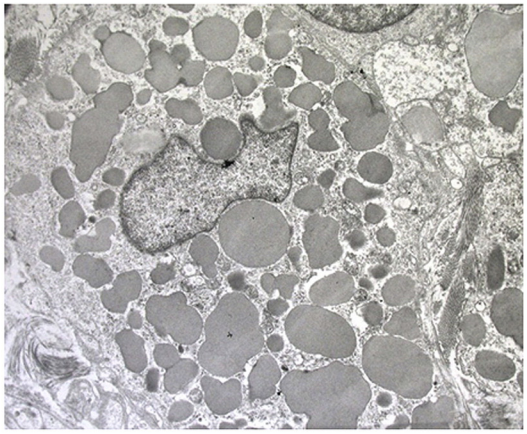

Fig. 1. Radiological, electrophysiological, and pathological findings of the patient with SPG35. 1a: Brain MRI at age 13 (a1–a4): sagittal T1 indicating flat pons, vermian atrophy and thin corpus callosum (a1); axial T2 showing pons and cerebellar atrophy with enlargement of the IV ventricle (a2), mild hypointensity of the globus pallidus (a3), and mild cortical atrophy and slight peritrigonal hyperintensities (a4). Brain MRI at age 18 years (a5–a8): a severe thinning of corpus callosum and a profound pontocerebellar atrophy are seen on sagittal T1 and axial T2 images (a5, a6); hypointensity of the globi pallidus is similar (a7), but the white matter signal abnormalities are not seen whereas the cortical and subcortical atrophy with enlargement of the lateral ventricles is more prominent (a8). 1b: Data of the motor nerve and sensory nerve conduction studies (MNCS and SNCS): right/left (R/L), distal latency (DL), conduction velocity (CV) and amplitude (A). Abnormal values are in bold. Normal range is in brackets (*Reference: Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice, 3rd ed. J. Kimura New York: Oxford University Press, 2001*). 1c: Histological analysis of the rectum: (standard electron microscopic techniques, fixation in glutaraldehyde, postfixation in osmium tetroxide, embedding in araldite, staining with uranyl acetate and lead citrate): macrophage containing vacuoles with a neutral lipid material. These vacuoles seem to be surrounded by a membrane. The electron density of these structures is average in terms of their osmium staining. Their size ranges from 0.50 to 1.5 μm (scale bar: 5 μm). Lamellae structures or other findings of lysosomal pathology are not observed.

might be related to a FA2H deficiency in this tissue leading to substrate storage and this finding might be useful as a potential biomarker of the disease.

In summary, the involvement of the peripheral nervous system may be part of the clinical spectrum of SPG-35. Determining the consistency and relevance of the histological findings discovered in our patient will require identification of additional cases. Future postmortem tissue studies are necessary to analyze the neuropathological features of FA2H deficiency.

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