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Short Communication

A Novel *CSF1R* Mutation in a Patient with Clinical and Neuroradiological Features of Hereditary Diffuse Leukoencephalopathy with Axonal Spheroids

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Abstract. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is an autosomal dominant cerebral white matter degeneration leading to progressive cognitive and motor dysfunction. The peripheral nervous system is generally spared. Recently, mutations in the colony-stimulating factor-1 receptor (*CSF1R*) gene have been shown to be associated with HDLS. Here we report a new case of HDLS, carrying a mutation in *CSF1R* and manifesting rapidly progressive dementia and peripheral neuropathy.

Keywords: *CSF1R*, HDLS, leukoencephalopathy, presenile dementia

INTRODUCTION

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is a rare autosomal dominant disorder characterized by cerebral white matter degeneration with focal swellings of axons. Since the original HDLS kindred identified in Sweden [1], both hereditary and sporadic cases have been described. Onset is usually in the fourth to fifth decade of life. The clinical picture is characterized by behavioral and cognitive changes [2], often associated with unsteady gait, urinary incontinence, seizures, and involuntary movements. Dementia, abulia, dysphagia, and severe motor dysfunction appear later. Brain magnetic resonance imaging (MRI) shows nonspecific frontotemporal leukoencephalopathy with concomitant cerebral atrophy. Cerebral white matter abnormalities are initially patchy and asymmetrical, and later become confluent and symmetrical. Neuropathology shows a loss of myelin and axons, gliosis, and macrophages in the presence of axonal swellings (spheroids) [3]. The peripheral nervous

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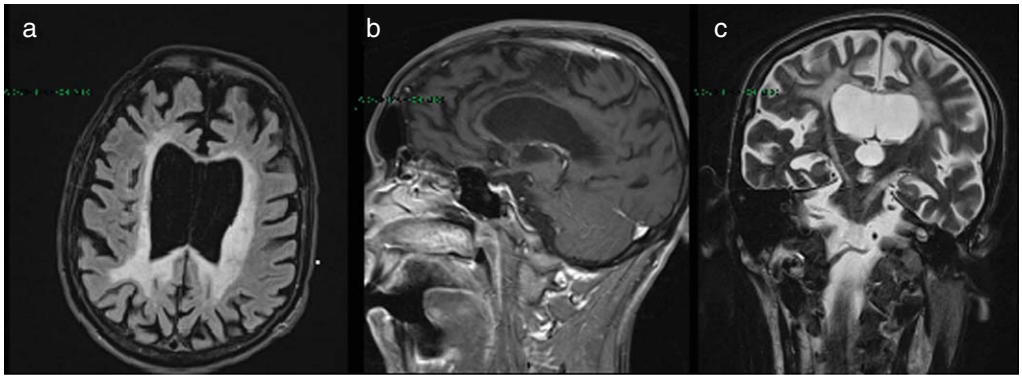

Fig. 1. MRI: Neuroimaging of the patient. a) Fluid attenuated inversion recovery axial magnetic resonance image (MRI) shows brain atrophy, ventriculomegaly, and symmetrical hyperintensity of the periventricular white matter, with predominant parieto-occipital involvement. Subcortical U-fibers are relatively spared. b) T1-weighted sagittal MRI shows brain atrophy and severe thinning of the corpus callosum. c) T2-weighted coronal MRI shows a hyperintense signal in the pyramidal tracts.

system is generally spared. Recently, mutations in the colony stimulating factor 1 receptor (*CSF1R*) gene were identified as the genetic basis of HDLS [4]. Most consist of missense substitutions within the protein tyrosine kinase domain, predicted to lead to a loss of autophosphorylation. To date, more than 20 different mutations have been detected in familial cases, among which, three unrelated Italian patients with HDLS, described by our group [5].

Here we report a new case of HDLS, with a novel *CSF1R* mutation, in which the classical symptoms were associated with peripheral neuropathy

CASE REPORT

The index case was a 35-year-old man with a one-year history of depression, abulia, and apathy, followed by left hemiparesis. A few months into his illness, he manifested early signs of cognitive impairment, with deficits in short term memory, concentration, and logical sequencing. Language and long term memory were spared.

The patient's father had suffered a similar neurological illness, beginning in his third decade and leading to progressive mental and motor deterioration with death at age 34.

The patient was first hospitalized at age 34: brain MRI showed multifocal leukoencephalopathy and severe atrophy of the corpus callosum. Cerebrospinal fluid analysis revealed slight protein elevation and an absence of oligoclonal IgG bands. A diagnosis of primary progressive multiple sclerosis was entertained and the patient received immunotherapy with intravenous methylprednisolone and interferon beta-1a (IFNβ-1a). However, his cognitive functions rapidly declined and he developed incontinence and dysarthria. He stopped working and became inconsistent in performing regular daily activities.

When he was admitted to our hospital at age 35, his condition was further worsened. He was bedridden, mute, unable to perform purposeful movements, and had severe mixed dysphagia requiring percutaneous endoscopic gastrostomy. Neurological examination showed spastic tetraparesis with large joint contractures, cortical blindness, and bowel incontinence. Tendon reflexes were diffusely weak and all four distal limbs were severely atrophic. Laboratory tests, including lactate, lysosomal enzymes, ceruloplasmin, urinary oligosaccharides, and urinary sulfatides, were all negative. A thrombotic risk profile and autoantibody screening were also negative. Brain MRI revealed severe T2/ FLAIR-hyperintensities in the periventricular deep white matter, thinning of the corpus callosum and marked cortical atrophy (Fig. 1). Electroencephalography showed frontotemporal slowing. A peripheral nerve conduction study and electromyography revealed marked sensorimotor axonal neuropathy with predominant involvement of the motor nerves (Supplementary Table 1). To date the patient is in a vegetative state.

GENETIC ANALYSIS

After obtaining informed consent, genomic DNA was extracted from peripheral blood leukocytes using the Puregene DNA isolation kit or the Qiamp blood kit (Qiagen, Mannheim, Germany). Genomic DNA was amplified by PCR using sets of specific primers,

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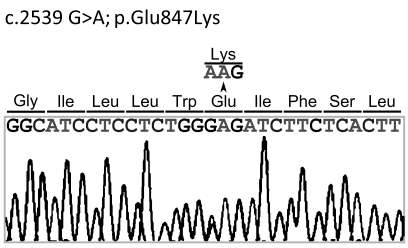

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	847		
Human	LLWEIFS	CSF1R	LLWEIFS
Rhesus	LLWEIFS	PDGFRA	LLWEIFT
Mouse	LLWEIFS	FLT3	LLWEIFS
Rabbit	LLWEIFS	RET	LLWEIVT
Cow	LLWEIFS	FGFR1	LLWEIFT
Elephant	LLWEIFS		
Opossum	LLWEIFS		
Chicken	LLWEIFS		
X-tropicalis	LLWEMFS		
Zebrafish	LLWEIFS		

C

Software	Description	Value output	Range of reference	Bibliography
SIFT	deleterious	0.00	(≤ 0.05 pathogen)	Ng and Henikoff (2001)
PolyPhen-2	Probably damaging	0.999	(benign -damaging: 0-1)	Adzhubei IA et al. (2010)
I-Mutant 2.0	decrease stability	3	(> 0: decrease stability; < 0: increase stability)	Capriotti et al. (2005)
Mutation t@sting	disease causing	1.00	(Probability of pathogenicity: 0-1)	Schwarz et al., (2010)
PMUT			(> 0.5 pathogenic)	Ferrer-Costa et al. (2005)
SNAP-F	non neutral	4	(> 0 non neutral)	Bromberg and Rost (2007)
PON-P	pathogenic	0,625	(Probability of pathogenicity: 0-1)	Olatubosun A et al. (2012)
PHD-SNP	disease	n.a	n.a	Capriotti et al. (2006)

Fig. 2. Identification of the c.2539G>A *CSF1R* mutation. A) Sequencing chromatogram showing the heterozygous c.2539G>A missense mutation in the exon 19 of the *CSF1R* gene. The mutation changes a Glutamic acid codon into Lysine at position 847. B) Glutamic acid 847 (p.E847) conservation among CSF1R orthologues and CSF1/PDGF receptor paralogues. C) Mutation pathogenicity of the p.Glu847Lys was assessed using eight software programs: SIFT, PolyPhen-2, I-Mutant 2.0, Mutation Tasting, PMUT, SNAP-F, PON-P, and PHD-SNP.

in order to investigate the coding sequences and intron/exon boundaries of *CSF1R* (NM_005211.3). Sequence analysis was carried out using SeqScape version 2.5 software (Applied Biosystems).

A novel mutation c.2539G>A, leading to the amino acid substitution p.Glu847Lys, was revealed in exon 19 of the *CSF1R* gene. This amino acid is located within the conserved intracellular tyrosine kinase domain of the *CSF1R* gene and has not been reported previously (HGMD® Human Gene Mutation Database, dbSNP, 1000Genomes, EVS). p.Glu847Lys mutation, investigated by *in silico* analysis, was predicted to be pathogenic (Fig. 2).

CONCLUSION

We report a patient with a genetically confirmed HDLS initially presenting with behavioral changes, followed by rapid progressive cognitive and motor decline. Peripheral neuropathy was evident at electrophysiological examination. Involvement of the peripheral nervous system has never been previously reported in HDLS. In our patient, the most common toxic and metabolic causes of polyneuropathy were ruled out, even if we could not perform a nerve biopsy. Interestingly, axonal spheroids have recently been found in the skin nerves of HDLS patients, suggesting a more widespread nervous system involvement and possibly providing new insights into the etiopathology of HDLS [6].

Another point of interest was the MRI findings, which showed cerebral atrophy with parieto-occipitally predominant T2 white matter hyperintensity and areas of restricted diffusion, a lack of gadolinium enhancement, thinning of the corpus callosum, and cortico-spinal involvement along the whole length of the pyramidal tract, which correlated with motor deterioration toward tetraplegia [7]. The clinical and neuroimaging findings were very similar to those of previously reported cases of HDLS. However, our patient presented a more severe involvement of the parieto-occipital white matter, responsible of the cortical blindness, as previously described in only another case in the literature [8].

The c.2539G>A missense mutation identified in our patient results in a missense change Glu847-to-Lys. As all the other mutations in CSF1R gene described to date, this substitution affects a highly evolutionary conserved residue located in the intracellular tyrosine kinase domain. Bioinformatics analyses and the conservation among paralogues gene support a pathogenic role of the c.2539G>A.

Finally, we want to underline that all the described Italian families originated from the South of Italy. This patient is from Puglia; the three previously reported families [5] included one from Puglia and the other two from Campania and Sicily, respectively. The different mutations in all families exclude common ancestors.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0097r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-150097.

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