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Letter to the Editor

Widening the phenotypical spectrum of *EGR2*-related CMT: Unusual phenotype for R409W mutation

Mutations in *EGR2* are associated with a wide spectrum of inherited neuropathies: congenital hypomyelinating (MIM 605253)/Dejerine-Sottas (MIM 1459000) syndromes, Charcot-Marie-Tooth type 1 D (CMT1D) (MIM 607678) with variable onset and severity (Shiga et al., 2012), CMT1 with susceptibility to vincristine (Nakamura et al., 2012), and mild adult-onset axonal CMT (Sevilla et al., 2015). Herein, we report a 46-year-old man who had presented, since his late thirties, a slowly progressive symmetric distal limb weakness and atrophy, associated with mild distal sensory loss. He had no family history of neurological complaints or pes cavus. At neurological examination, a bilateral, symmetric weakness was detected on tibialis anterior, extensor hallucis longus, gastrocnemius and hand interossei muscles (MRC 1/5), as well as on wrist extensors and flexors (MRC 3/5). Proximal muscle strength was normal in upper and lower limbs. Deep tendon reflexes were diffusely absent. Mild bilateral distal light touch hypoesthesia was also present. Results of nerve conduction study (NCS) are shown in Fig. 1A. Median, peroneal, tibial and sural nerves were all bilaterally unexcitable. Ulnar nerves showed a bilateral reduction of motor conduction velocity (MCV), marked reduction of compound muscle action potential (cMAP) amplitude, no conduction blocks, non-recordable F wave and non-recordable sensory nerve action potential (SNAP). Superficial radial nerve showed bilaterally reduced SNAP amplitude and sensory conduction velocity. Needle electromyography (EMG) of first dorsal interosseus and tibialis anterior muscles showed denervation activity, reduced number of motor unit action potentials, which had increased duration, amplitude and polyphasicity. EMG of proximal muscles (vastus medialis and deltoid) was normal. An extensive diagnostic workup for acquired peripheral neuropathies, including CSF analysis, infectious, immune, and metabolic serum panels, as well as a total-body CT-scan, was unremarkable. Nerve high-resolution ultrasound (HRUS) showed a diffuse and bilateral enlargement of brachial plexus, cervical roots, and median nerve at arms (Fig. 1B–E). Despite the silent family history, a genetic etiol-

Motor conduction study

Nerve	cMAP amp (mV)	DL (ms)	CV (m/s)	F-wave (ms)
R ulnar	1.6/1.6	4	36.6	abs
L ulnar	1.9/1.9	3.65	40.6	abs
R median	abs	-	-	-
L median	abs	-	-	-
R fibular	abs	-	-	-
L fibular	abs	-	-	-
R tibial	abs	-	-	-
L tibial	abs	-	-	-

Sensory conduction study

Nerve	SAP amp (μV)	CV (m/s)
R ulnar	abs	-
L ulnar	abs	-
R median	abs	-
L median	abs	-
R radial	2.9	38.2
L radial	2.8	35,2
R sural	abs	-
L sural	abs	-

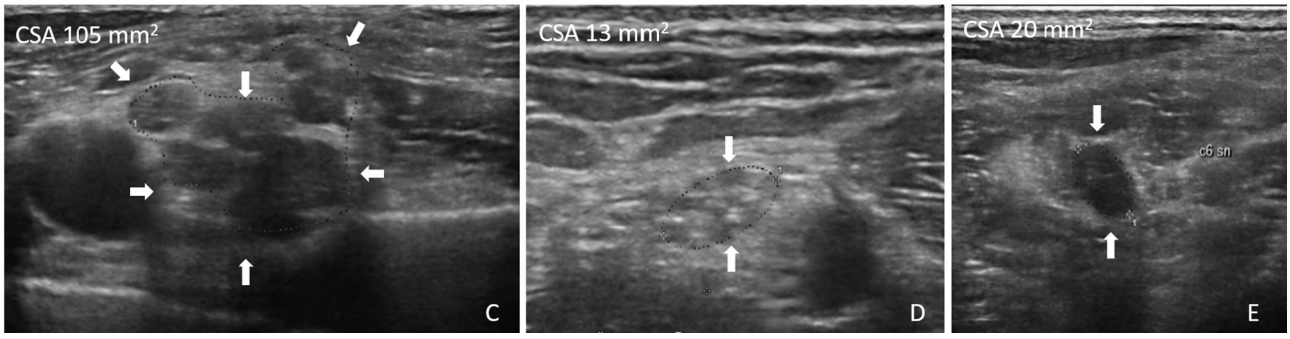

Fig. 1. (A) Nerve conduction study. DL: distal latency, CV: conduction velocity, R: right, L: left, abs: absent, amp: amplitude, cMAP: compound muscle action potential (expressed as wrist amplitude/under elbow amplitude), SAP: sensory action potential. (B–E) High resolution nerve ultrasonography. Diffuse enlargement of cervical roots, brachial plexus and median nerve at the arm bilaterally. (B) Left C5 root (long axis). (C) Left brachial plexus at supraclavicular space (short axis). (D) Right median nerve at arm (short axis). (E) Right C6 root (short axis). CSA: cross sectional area. d: diameter.

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ogy was evaluated by an extensive next generation genetic panel, including 75 axonal and intermediate CMT genes. A heterozygous c.1225C > T (R409W) mutation on *EGR2* gene was detected.

Heterozygous R409W mutation has been associated with childhood/juvenile-onset demyelinating CMT1D (Nakamura et al., 2012). Despite carrying the same R409W mutation, our patient presented an adult-onset sensory-motor neuropathy, characterized by electrophysiological evidence of severe sensory and motor fiber loss in distal nerve segments and conduction velocities with "intermediate" values according to Saporta et al. (2011) [ulnar MCV > 35 m/s and $\leq$ 45 m/s]. Interestingly, a different amino acid change (R409Q) in the same residue R409 has been recently reported in a family with intermediate-axonal dominant CMT (Sevilla et al., 2015). Probably, the genotype-phenotype correlations in *EGR2*-related neuropathies are conditioned by more complex phenomena than the impact of single amino acid substitution in a specific residue.

Worth of note, extreme variability of both age at onset and neurophysiological features, which seem to characterize *EGR2*-related CMT, have been also reported in *MPZ*-related CMT (Sevilla et al., 2015). *EGR2* encodes, interestingly, for a zinc-finger transcription factor, which regulates myelin genes, comprising MPZ (Sevilla et al., 2015), explaining the phenotypical overlap of these two CMTs. To this regard, in a large cohort of *MPZ*-related CMT patients, HRUS revealed increased cervical root, brachial plexus and proximal upper limb nerve cross sectional area in 9 patients with "slow-very/slow" MCV (Fabrizi et al., 2018), in contrast to our patient who showed similar HRUS changes, but "intermediate" MCV and severe axonal damage. A myelin involvement prevailing in proximal nerve sites, associated with a secondary distal axonal loss could be hypothesized as explanation of this phenotype.

Declaration of interest

None of the authors have potential conflicts of interest to be disclosed. There are no sources of funding to be declared.

Ethical standards

This study has been performed in the accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. A written informed consent was obtained from the patient.

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Luca Leonardi *
Matteo Garibaldi
Laura Fionda
Fiammetta Vanoli
Simona Loreti
Stefania Morino
Giovanni Antonini
Neuromuscular Diseases Centre, Department of Neurosciences Mental Health and Sensory Organs (NESMOS), SAPIENZA University of Rome, Sant'Andrea Hospital, Rome, Italy
* Corresponding author at: Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, SAPIENZA University of Rome, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Roma, Italy.
E-mail address: luca.leonardi@uniroma1.it (L. Leonardi)

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