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Case report

Charcot-Marie-Tooth disease with pyramidal features due to a new mutation of *EGR2* gene

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Summary. *Background and aim of the work:* Childhood-onset peripheral neuropathies are often of genetic origin. Charcot-Marie-Tooth (CMT), is considered the commonest neuromuscular disorder. Due to its high clinical heterogeneity, especially in the pediatric age, the co-existence of central and peripheral symptoms and signs does not necessarily rule out a diagnosis of hereditary peripheral neuropathy. *Methods:* We describe the clinical, neurophysiological and genetic findings in a teen-age patient evaluated for acquired toe-walking and progressive difficulties in walking since the age of 5. Genetic testing was carried out with a targeted NGS panel. Identified variants are analyzed using Variant Studio program (Illumina). Rare variants and variants considered as pathogenic were analyzed by Sanger direct sequencing. *Results:* The coexistence of peripheral and pyramidal signs in the lower limbs, the absence of a significant pre/perinatal history, the unremarkable brain and spine MRI, together with the presence of a sensory-motor polyneuropathy in all four limbs, prompted the execution of genetic investigations with an NGS panel covering hereditary spastic paraplegias, motor neuron disease and Charcot-Marie-Tooth. We identified a previously undescribed variant (c.1142G>T, p.Arg381Leu) in the *EGR2* gene. *Conclusions: ERG2* gene has been described as a cause of various phenotypes, including a rare autosomal dominant form of CMT (CMT type 1D) representing approximately 1% of all CMT subgroups. We describe a novel pathogenic variant in *EGR2* gene leading to the development of a complex association of peripheral and central neurological signs, underscoring the genetic and clinical heterogeneity of hereditary neuropathies of pediatric onset. (www.actabiomedica.it)

Key words: *EGR2*, Charcot-Marie-Tooth, CMT-1D, hereditary polyneuropathy, pediatric, sensory-motor neuropathy

Introduction

Childhood-onset peripheral neuropathies are frequently genetically determined. Charcot-Marie-Tooth (CMT), is considered as the commonest neuromuscular disorder, typically presenting with distal wasting and weakness, decreased deep tendon reflexes, contractures and skeletal deformities (1). Exceptionally, pes cavus has been described as an isolated finding in congenital CMT1A (2). The presence of additional clinical signs, such as marked sensory or upper limbs involvement, visual/hearing impairment, pyramidal signs or intellectual disability results in a need to extend the differential diagnoses to complicated forms of hereditary spastic paraplegia, inborn errors of metabolism or neurodegenerative disorders (3-5). Conversely,

the coexistence of central and peripheral nervous system involvement does not exclude a diagnosis of hereditary peripheral neuropathy (6).

Case report

Our patient is a 16-years-old boy born at term after uneventful pregnancy and delivery, from non-consanguineous, healthy parents. Following a normal early psychomotor development, since 5 years of age he has started to toe walk, with constant, progressive difficulties in walking.

His last neurological examination shows distal lower limbs hypertonus, bilaterally brisk tendon reflexes in his lower limbs and extensor plantar reflexes, no clonus, cavovarus supinated feet, postural/intention tremor in his upper limbs, hypotrophy of the intrinsic hand muscles and of the peroneal and extensor digitorum brevis (EDB) muscles. MRC muscle strength is mildly reduced (4/5) in the peroneal/extensor, thumb abductor/adductor, intrinsic and orbicularis oculi muscles. EMG/ENG shows a sensori-motor polyneuropathy in all four limbs.

The patient has undergone serial, non-contributory diagnostic investigations, including brain and spine MRI, full ocular examination, audiometric evaluation, array-CGH, vitamin E dosage, urinary organic acids profile, molecular testing for *SPG3A*. Somatosensory evoked potentials (SSEP) in the lower limbs are in keeping with bilateral central conduction delay.

Methods

Based on the coexistence of peripheral and central neurological sings, a targeted next generation sequencing (NGS) panel evaluating 185 genes associated with hereditary spastic paraplegias, motor neuron and the most common forms of Charcot-Marie-Tooth diseases was performed. Identified variants were analyzed using Variant Studio (Illumina), enabling verification of the frequency of occurrence of each variant in dedicated databases (dsSNP and ExAC), their association with known diseases (OMIM, HGMD) and their impact on protein structure and function (SIFT and Polyphen2 software). All potentially pathogenic variants (based on the scientific literature or databases) and rare variants resulting in either an aminoacidic substitution, the creation of a stop codon or a change in a splicing site were verified by Sanger sequencing.

Results

Three variants were identified. Two involved the *EGR2* (Early Growth Response 2) gene. The first variant (NM_000399.3 c.1142G>T, leading to the protein variant NP_000390.2 p.Arg381Leu), is not reported in ExAC database and is predicted to be potentially damaging, while the second variant (NM_000399.3 c.736C>T, leading to the protein variation NP_000390.2 p.Arg246Cys) is reported with a frequency of 0.001% by the ExAC database (dbSNP ID rs774391305). An additional heterozygous variant in the BSCL2 (seipin lipid droplet biogenesis associated) gene was identified: c.116A>G (NM_001122955.3) which leads to the protein variation p.Gln39Arg (NP_001116427.1. This variant is reported in the ExAC database (dbSNP ID rs 531137749) with a frequency of 0.03% and is predicted to be potentially damaging. Segregation analysis in the parents indicated that only the *EGR2*-p.Arg381Leu is a likely *de novo* variant, while *EGR2*- p.Arg246Cys and *BSCL2*- p.Gln39Arg are inherited from one of the parents.

Discussion

EGR2 mutations have been associated with the development of different inherited neuropathic phenotypes, including dominant and recessive forms of Dejerine-Sottas disease (severe early-onset hereditary neuropathy with motor delay, very low nerve conduction velocities, nerve hypertrophy, severe dysmyelination (1, 7)), congenital neuropathy with hypomyelination (7) and an autosomal dominant form of severe CMT (CMT type 1D), representing less than 1% of all CMT subgroups, in which cranial nerve involvement has also been described (1). This characteristic involvement in peripheral demyelinating and dysmyelinating disorders can be explained by the high expression of the EGR2 gene product (a zinc-finger transcription factor) in Schwann cells, where it activates the transcription of several myelin-associated genes. It is also implicated in myelin development and maintenance (1). How-

ever, cases of adult-onset axonal Charcot-Marie-Tooth disease with variable disease severity have also been exceptionally reported, and have been related to specific mutations leading to mild conformational protein changes disrupting axon-myelin interactions (8).

In this wide range of clinical features, genotype-phenotype correlations have started to be recognized. An association between a different pathogenic variant affecting the same Arg381 residue (p.Arg381His) and CMT1 with sensorineural hearing loss, third cranial nerve palsy and vocal cord palsy has been published (9). Cranial nerve involvement has also been described in association with respiratory compromise and multiple disabilities in a case with the p.Arg359Trp pathogenic variant (10), while the p.Asp383Tyr pathogenic variant has been reported in severe (Dejerine-Sottas syndrome) phenotype (11). Finally, an association with scoliosis has been noted in individuals with the p.Arg359Gln pathogenic variant (12).

Although the presence of pyramidal signs, to the best of our knowledge, has never been reported in association with pathogenic variants in the *EGR2* gene, it has been reported in the context of various genetic mutations causing Charcot-Marie-Tooth disease (6, 13).

The *BSCL2* variant, p.Gln39Arg, may likely contribute to some extent, to our patient's clinical picture, as this gene has been associated with SPG 17 (Sylver syndrome) and with a hereditary distal motor neuropathy (14).

We described a novel heterozygous mutation in the *EGR2* gene in a patient with a complex clinical picture of peripheral and central neurological signs, further underscoring the genetic and clinical heterogeneity of hereditary neuropathies, especially of pediatric onset.

Conflict of interest: None to declare

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