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F.J. Ros Forteza[a,b,*], H. Cabrera[b,c], M. Bousende[d]

[a] *Serviço de Neurologia, Unidade Local de Saúde da Guarda, EPE, Guarda, Portugal*

[b] *Departamento de Ciências Médicas, Faculdade de Ciências da Saúde (UBI), Covilhã, Portugal*
[c] *Serviço de Medicina Interna, ULS-Guarda, EPE, Guarda, Portugal*
[d] *Serviço de Neurorradiologia, Centro Hospitalar São João, EPE, Porto, Portugal*

[*] Corresponding author.
E-mail address: javierros40@hotmail.com
(F.J. Ros Forteza).

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New mutation in a patient with Charcot-Marie-Tooth disease[☆,☆☆]

Nueva mutación genética en un caso de enfermedad de Charcot-Marie-Tooth

Dear Editor:

Charcot-Marie-Tooth disease (CMT) is a type of hereditary sensorimotor polyneuropathy which may be caused by a great variety of genetic alterations[1]; new alterations continue to be identified.

We present the case of a 39-year-old patient diagnosed with CMT type 1 during childhood. His mother also has the disease but with mild clinical symptoms.

Examination of the patient revealed distal amyotrophy with weakness, steppage gait, and arreflexia. Neurophysiological studies have always shown decreased conduction velocity and amplitudes of motor potentials; sensory potentials could not be elicited. At the time, the patient and his partner were trying to conceive.

A genetic study was conducted in 2015. Proceeding gradually, the study began with genotyping with polymerase chain reaction and allele-specific oligonucleotide of a battery of polymorphisms distributed throughout the CMT1/HNPP region (17p11.2), with no evidence of duplication or deletion. Massively parallel sequencing was performed for 7 genes from the panel associated with autosomal dominant CMT type 1; this did not reveal any clearly pathogenic variant associated with the disease. The study was subsequently expanded to 42 genes, which revealed a mutation of the *SBF1* gene (c577C>T [pArg193Trp]) in heterozygosis and a mutation of the *GJB1* gene (c.476_481del [pGly159_Tyr160del]) in hemizygosis; since these are not pathogenic variants clearly associated with CMT disease, we conducted a Sanger confirmation and a cosegregation study in the patient's mother.

We confirmed presence of the mutation (c.476_481del [pGly159_Tyr160del]) and the mother was found to be a carrier of the mutation in heterozygosis.

We describe a new mutation of the *GJB1* gene, located at Xq13.1 and coding for gap junction beta-1 protein (or connexin 32),[2] in a patient with demyelinating CMT with an X-linked dominant inheritance pattern. Variations of this gene are the second most frequent genetic alteration observed, following duplication of the *PMP22* gene at chromosome 17p11.2-p12.[2,3]

Curiously, in these X-linked forms, motor conduction velocities are not homogeneous in different nerves; nor are they as decreased as in autosomal dominant forms.[3,4] These forms can also be associated with disorders of the central nervous system[5]; we therefore requested a brain magnetic resonance imaging scan in our patient, which yielded normal results.

In conclusion, we deem it important to characterise and communicate these alterations, both for the purpose of genetic counselling (as illustrated by our patient) and with a view to the potential prognostic and therapeutic implications of future research.

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F.J. Domínguez Díez*, J.T. López Alburquerque

Servicio de Neurología, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain

*Corresponding author.
E-mail address: javierdominguezdiez@gmail.com
(F.J. Domínguez Díez).

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Coeliac disease and neuromyelitis optica: a rare but possible association☆

Enfermedad celíaca y neuromielitis óptica: una rara pero posible relación

Dear Editor:

Coeliac disease (CD) is an enteropathy of autoimmune origin, triggered by the intake of foods containing gluten. The condition not only affects the digestive system, but also presents a broad clinical spectrum, including various neurological manifestations.[1] Neuromyelitis optica (NMO) is a chronic, inflammatory, autoimmune, demyelinating disease of the central nervous system, characterised by severe spinal cord and optic nerve involvement; it can be monophasic or display relapses and remissions, and is a cause of disability in young and adult patients.[2] Given the limited published information on the relationship between these 2 entities, we decided to report the present case.

Our patient is a 9-year-old boy with a family history of CD (mother and a maternal aunt) and personal history of foetal distress, meningitis during lactation, severe sensorineural hearing loss diagnosed at 4 years and treated with cochlear implants, mild intellectual disability, and CD diagnosed at the age of 5. Diagnosis was based on high levels of anti-transglutaminase IgA antibodies and anti-gliadin IgG and IgA antibodies, HLA-DQ2 expression, and compatible duodenal biopsy findings. He was admitted to hospital due to a 4-week history of subacute symptoms of lower limb pain and gait disorder with falls. During the examination the patient was alert and oriented, and displayed developmental delay with poverty of speech and dyslalias, visual deficit, and sensorineural hearing loss. He presented predominantly distal weakness of all 4 limbs, with generalised hyporeflexia, bilateral extensor plantar response, and no clear sensory alterations, although he did have difficulties completing the assessment. The patient displayed positive Romberg sign and difficulty toe and heel walking. The brain MRI scan was of little value due to the cochlear implants, but showed no significant alterations; a spinal MRI scan revealed increased signal intensity from C1 to T2, with patchy distribution and no contrast uptake (Fig. 1). We also requested analyses of lactate, ammonia, amino acids, and organic acids in the blood and urine; very long-chain fatty acids; phytanic, guanidinoacetic, and pristanic acids; alpha-fetoprotein; neuron-specific enolase; human chorionic gonadotropin; creatine; vitamins B_{12} and B_6; folic acid; and immunoglobulins. An autoimmunity test and viral serologic testing were also performed. All results were normal. CSF study results were as follows: 8 cells, proteins 68 mg/dL, glucose 60 mg/dL, and weakly positive oligoclonal bands. An electromyography study showed signs of demyelinating sensorimotor polyneuropathy. Visual evoked potentials revealed bilateral retrobulbar optic neuropathy. The study was expanded with tests for anti-NMO and anti-MOG antibodies, which yielded negative results. The patient was initially treated with immunoglobulins dosed at 0.4 g/kg/day, with no response; he subsequently received methylprednisolone at 1 g/day for 5 days, which achieved favourable outcomes. When interviewed, the mother admitted that the patient was not strictly following a gluten-free diet; in the absence of any other possible aetiology, NMO symptoms were attributed to CD. The patient was discharged and prescribed a tapered dose of the corticosteroid and a strict gluten-free diet. On 2 occasions over the following months, symptoms worsened in association with fever, and the patient was treated with corticosteroids, although radiology studies identified no new lesions; outcomes were excellent after resolution of the infectious symptoms.

Neurological complications are estimated to be present in 10% to 22% of cases of CD.[3,4] Reported manifestations include ataxia, epilepsy, myopathy, migraine, cognitive impairment, and, as observed in our patient, axonal or demyelinating peripheral neuropathy, sensorineural hearing loss, and demyelinating diseases.[1,5—7]

The association between NMO and CD has very rarely been reported in the literature.[8—13] Given that CD is relatively common, it would be difficult to demonstrate the cause of this relatively rare neurological syndrome. However, the excellent response to methylprednisolone and the introduction of a strict gluten-free diet suggest an inflammatory process in which gluten plays a fundamental role. Indeed, some authors have proposed that the pathophysiological mechanism may be an autoimmune process in which circulating IgG anti-neuronal

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