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Case report

A special association between Charcot-Marie-Tooth type 1A disease and relapsing remitting multiple sclerosis

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ABSTRACT

Background: Central nervous system involvement has been reported in different subtypes of Charcot-Marie-Tooth (CMT) diseases. The increasing number of cases with CMT and MS may provide further information about the common pathway of demyelination and MS pathogenesis.
Case presentation: We report the case of a 21-year-old woman with CMT1A and MS. Bilateral rest and intention tremor, steroid associated psychotic episodes, and severe disability at an early age were unexpected aspects of this case.
Conclusion: PMP22, the target protein in CMT1A, shares partial homology with other CNS proteins. PMP22 gene might be relevant to a common pathway of the demyelinating process.

1. Introduction

Charcot-Marie-Tooth (CMT) disease is a heterogeneous group of inherited demyelinating neuropathies mainly characterized by distal limb weakness and muscle atrophy, sensory loss, and decreased or absent deep tendon reflexes.

The central nervous system involvement in the form of clinical symptoms or magnetic resonance imaging (MRI) white matter lesions have been occasionally reported, mainly for CMT1X (Kleopa and Scherer, 2006; Isoardo et al., 2005). Also, data from literature reported the association between CMT1A/1B and MS, supported by genetic studies and clinical investigations showing a possible demyelinating process (Cortese et al., 2016).

On the other hand, multiple sclerosis (MS) is a chronic, neurodegenerative autoimmune disease attacking to the central nervous system (Milo and Kahana, 2010). Relapsing remitting multiple sclerosis – the most common initial form – is characterized by periods of stability following clearly defined attacks of new or increasing neurologic symptoms. Although there are many different clinical symptoms, the most commonly reported physical and cognitive effects include: weakness, fatigue, ataxia, bladder complaints, intestinal problems, sensory effects and visual impairment (Richards et al., 2002).

2. Case presentation

A 21-year-old woman was admitted to our department for rehabilitation with a 6-year history of gait disorder and a 3-year history of multiple sclerosis. She had a family history of peripheral neuropathy with dominant inheritance. She declared pes cavus since childhood, but her complaints about gait disorder was exacerbated 6 years ago. The patient was initially referred to the neurology department because of a history of diplopia, amnesia episodes and headache. She also reported an episode of right hemibody dysesthesias and motor weakness. She also referred a history of acute psychosis at the age of 18 years, and stated her mental state worsened after multiple doses of intravenous methylprednisolone for multiple sclerosis attack. Acute psychosis episode recovered after treatment with aripiprazole (30 mg/daily) and valproic acid (750–1250 mg/daily). For this reason, the patient was consulted to the psychiatry department before treatment and medicine doses were adjusted according to blood values. The patient was treated with high-dose intravenous methylprednisolone (1 g daily for seven consecutive days) and subsequently, the patient was started on immunomodulatory treatment with glatiramer acetate. After initiation of treatment, fampridine was added to the treatment and remains well tolerated. Long-term drug tolerance and results of the treatment continue to be evaluated by the neurology department.

On clinical examination, she had difficulty with tandem gait,

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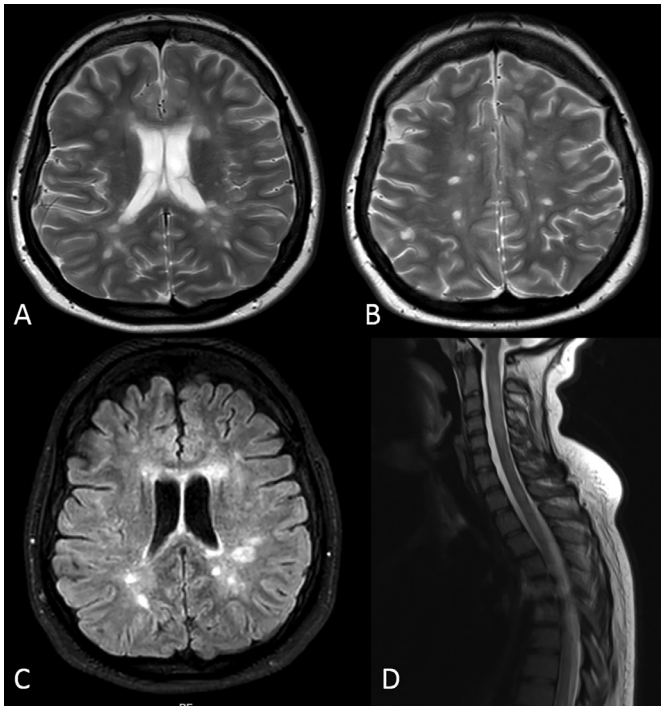

Fig. 1. Brain MRI showing multiple T2- hyperintense lesions in the white matter of both hemispheres (A, B). Axial FLAIR image demonstrating periventricular lesions characteristic of MS (C). Sagittal T2-weighted image showing a hyperintense lesions on cervical spinal cord at C2-5 level and thoracic spinal cord at T1, T6, T10 levels (D).

extensor plantars, hypoactive upper limb tendon reflexes, reduced knee jerks, absent ankle jerks, mild peripheral atrophy in upper and lower limbs, pes cavus, and hammer toes. There was also a moderate decrease in sensation of vibration in the lower limbs, mild bilateral rest and intention tremor and urinary incontinence. Examination of the cranial nerves exposed a right intranuclear ophthalmoplegia with endpoint nystagmus along with right abducens nerve paresis.

Blood tests results including serum vitamin B12 and vitamin D level were normal. The autoimmune/infection serological tests were negative when she was diagnosed with multiple sclerosis. Cerebrospinal fluid(CSF) analysis showed a mild increase in IgG index (1.22 normal < 0.85) and positive intrathecal oligoclonal bands.

Electrophysiological investigations confirmed the presence of a hereditary neuropathy with intermediate velocities. Electroencephalogram and visual evoked potentials study were not meaningful because of artifacts (probably result from tremor and mental situation of the patient). Brain MRI revealed multiple focal periventricular, callosal, juxtacortical, and brainstem lesions, some contrast-enhancing, strongly suggestive of the primary demyelinating disease (Fig. 1A–C). In addition, spinal cord MRI revealed nonenhancing hyperintense lesions on T2-weighted images at C2–C5 level and T1, T6, T10 levels (Fig. 1D).

The family history showed dominant inheritance at the three generation pedigree (Fig. 2). On neurological examination of family members, the mother presented bilateral pes cavus, gait disorder and a severe distal sensory loss in lower limbs. She also informed that the brain MRIs were normal, except the patient. Additionally, her uncle had a CMT diagnosis.

Her genetic tests were revealed and the CMT1A diagnosis was confirmed with multiplex ligation-dependent probe amplification (MLPA) [duplication of peripheral myelin protein 22 gene (PMP22) is detected].

In the first evaluation of the patient, the Kurtz Expanded Disability Status Scale (EDSS) score was 6.5 and the Mini-Mental State Exam (MMSE) score was 25. During the hospitalization period, a rehabilitation program including occupational therapy procedures, stretching, walking and balance-coordination exercises was applied. Although she had difficulty in performing coordinated actions on upper extremities at the beginning of the treatment, she started making her daily living activities more independent day by day. According to tests and clinical follow ups, there was no significant improvement in the balance-coordination skills of the patient, but there was an increase in walking distance compared to the patient's first state. In the subsequent follow-up, botulinum toxin administration in the department of neurology revealed a decrease in the tremor.

3. Discussion

Our patient is one of the rare cases with CMT1A that developed a demyelinating illness fulfilling the diagnostic criteria for MS. Previously reported cases included typical CMT disease and relapsing forms of MS with MRI evidence of inflammatory demyelination and positive CSF analysis. The first case in literature is a 44-year-old man with CMT, MS and glioma reported by Mathews and Moosey in 1972 (Mathews and Moossy, 1972). As far as an association between CMT1A and MS is concerned, four case reports were present in the literature (Koros et al., 2013; Almsaddi et al., 1998; Frasson et al., 1998). Our patient had not remarkable distal sensory loss and did not complain of any difficulty in walking until 3 years before. Additionally, in our patient, the central nervous system (CNS) involvement started earlier and had different manifestations than other cases. Significant bilateral intention tremor probably caused from central neuropathy and acute psychosis episodes were unexpected presentations of this case. This case is unique and important because of having these features. The increasing number of cases with CMT and MS may point to the relationship between the two diseases. These case reports defined the coexistence of peripheral neuropathy and CNS involvement (Isoardo et al., 2005; Cortese et al., 2016; Koros et al., 2013; Almsaddi et al., 1998; Frasson et al., 1998). For CMT1X, this association was explained by the expression of connexin32 (Cx32) both in the Schwann cells and oligodendrocytes, as well as by other tissues, and the gap junction formed by Cx32 play an important role in the homeostasis of myelinated axons (Kleopa and Scherer, 2006; Parman et al., 2007). On the other hand, previous case reports about CMT1A and MS support the possibility of a special relationship and common pathogenetic mechanism -resulting from duplications on the protein 22 gene (PMP22)- between the two diseases (Koros et al., 2013; Almsaddi et al., 1998; Frasson et al., 1998). The PMP22 gene is expressed in myelinating Schwann cells of the peripheral nervous system (PNS) and the central nervous system myelination remains the responsibility of oligodendrocytes. Also, there is evidence to support that PMP22, a component of myelin, shares partial homology with other CNS proteins like the proteolipid protein (PLP) (Koros et al., 2013; Frasson et al., 1998). Therefore, another genetic aberration could be responsible from the phenotype of the case. Five percent of the patients present with more than one genetic variation (Posey et al., 2017). A series of 6 cases were reported by Thomas and McDonald in 1987. The authors found clear parallels, both clinical and histopathological, between the events in chronic animal models of experimental allergic neuritis (EAN) and experimental allergic encephalomyelitis (EAE) with combined PNS/CNS demyelination. And they concluded that; since there are clear differences in disease mechanisms, further studies might illuminate the pathogenesis of the clinical syndrome, the relationship to chronic idiopathic demyelinating neuropathy and MS (Thomas et al., 1987). In conclusion, although the simultaneous existence of CMT1A and MS in our patient could be coincidental, we suggest that inherited peripheral demyelination may trigger an autoimmune reaction against CNS myelin.

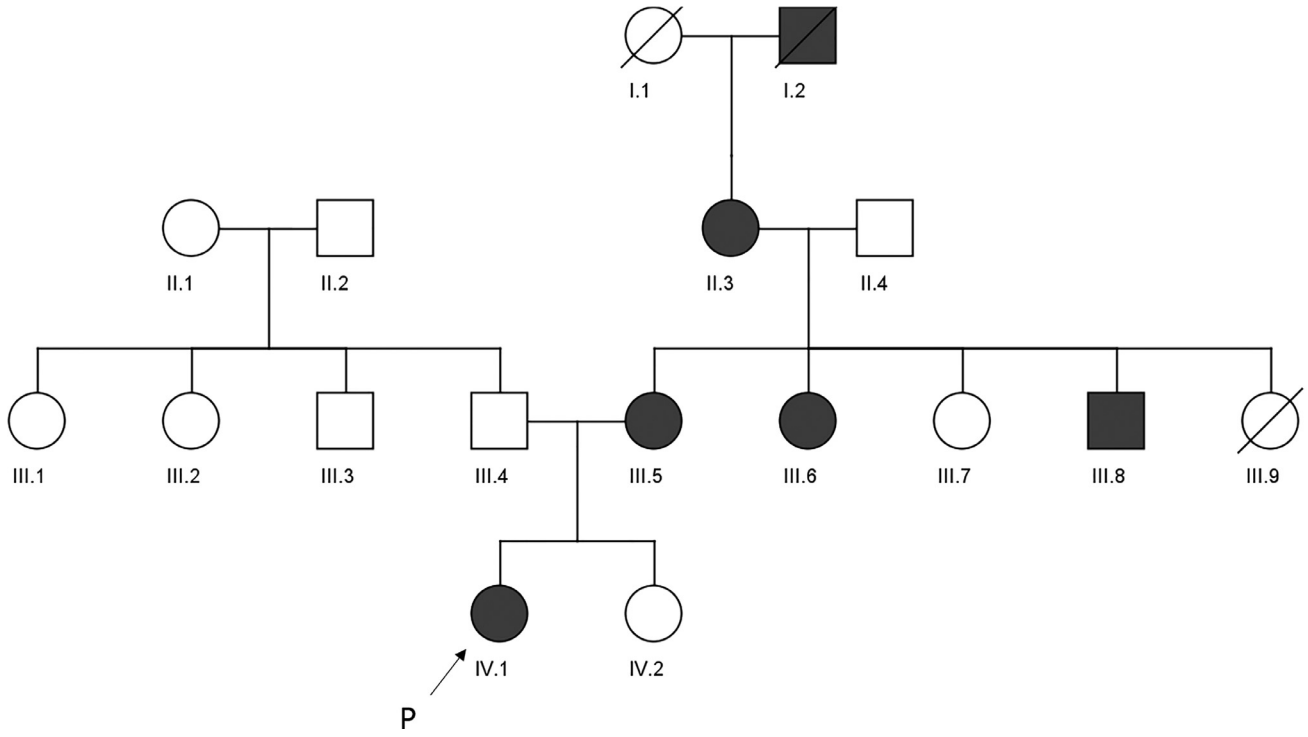

Fig. 2. Pedigree analysis of the patient shows the autosomal dominant inheritance at the three generations.

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