Charcot-Marie-Tooth type 1C disease coexisting with progressive multiple sclerosis: a study of an overlapping syndrome

Anna Potulska-Chromik1, Elena Sinkiewicz-Darol1, Anna Kostera-Pruszczyk1, Hanna Draci, Dagmara Kabzińska1, Beata Zakrzewska-Piechowska1, Marek Gołębiewski1, Andrzej Kołnaski2

*These authors contributed equally to the study

1Department of Neurology, Medical University of Warsaw, Poland, 2Neuromuscular Unit, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland, 3Department of Radiology, Medical University of Warsaw, Poland


Abstract

Charcot-Marie-Tooth type 1C disease (CMT1C) is a rare form of hereditary demyelinating neuropathy caused by mutations in the LITAF (lipopolysaccharide-induced tumor necrosis factor-α) gene. CMT1C disease was mapped to chromosome 16p12-p13.3. To date only a few mutations in the LITAF gene have been reported. Due to a small group of CMT1C reported patients, the phenotype of CMT1C is poorly characterized. CMT1C disease is a pure demyelinating neuropathy limited to the peripheral nervous system with a mild clinical course, manifesting without any additional symptoms. To the best of our knowledge, in this study, for the first time we present a three generational CMT1C family in which in the proband, CMT1C disease coexists with central demyelination fulfilling criteria of primary progressive multiple sclerosis (PPMS). The coexistence of PPMS and CMT1C in one family may not result from a common pathogenetic trait, however only in the proband with central demyelination and CMT1C we have detected a –308G>A sequence variant in the promoter of the TNF-α gene.

Key words: CMT1C, primary progressive multiple sclerosis, overlapping syndrome LITAF, TNF-α.

Introduction

CMT1C disease is caused by mutations in the lipopolysaccharide-induced tumor necrosis factor-α (LITAF) gene on chromosome 16p12-16p13.3 [1,18,19]. To date only nine pathogenic mutations in the LITAF gene have been reported [6].

All to-date reported CMT1C patients harbouring mutations in the LITAF gene manifest with a phenotype of mild, slowly progressive demyelinating neuropathy, which is not accompanied by additional features/symptoms [16,18].

Some sequence variants identified in the LITAF gene perfectly segregate with the CMT1C phenotype, whereas other variants are found in the patients suffering from chronic acquired neuropathies. Thus, the Ile92Val sequence variant was reported in the familial case of multifocal, acquired, demyelinating sensory and motor polyneuropathy (MADSAM) and was also considered to contribute to the phenotype of CMT1A disease caused by duplication of the PMP22 gene [10,17].

Central demyelination caused by multiple sclerosis is rare in patients with genetic neuropathies. Similarly to the GJB1 and Mfn2 genes responsible for CMTX1 and CMT2A forms for which central demyelination has been proved, mutations in the LITAF gene expressed in the brain, cerebellum and spinal cord

Communicating author:
Andrzej Kołnaski, Neuromuscular Unit, Mossakowski Medical Research Centre, Polish Academy of Sciences, Pawłańskiego 5, 02-106 Warsaw, Poland, phone +48 22 608 65 36, e-mail: andko@cmdik.pan.pl
might be expected to mediate central demyelination in a molecular mechanism independent from peripheral neuropathy [2,12].

In all to-date reported CMT1C-affected patients harbouring the Gly112Ser mutation, a homogenous phenotype of mild slowly progressive demyelinating neuropathy was present without symptomatic central nervous system involvement [8,16,18].

The role of genetic factors in development of multiple sclerosis is still debated. The published results are conflicting. Grey et al. suggested a role of TNF-α in the outcome of multiple sclerosis [5]. The results of the association of MS with DRB1*15(2) and TNF-α in the Russian population, reported by Favorova et al. indicate the interplay of three loci in susceptibility to multiple sclerosis [3].

To the best of our knowledge, we present for the first time a patient with CMT1C disease and clinical picture dominated by symptoms of central demyelination, fulfilling diagnostic criteria of primary progressive multiple sclerosis (PPMS).

**Family report**

A 25-year-old right-handed woman was admitted five years ago to our Department for a 2-year history of gait disorder.

On admission her cranial nerves were normal. The motor function was normal in the upper limbs. The deep tendon reflexes in the upper limbs were hypoactive and the abdominal reflexes were absent. There was bilateral foot drop and pes cavus. She had moderate weakness and wasting of the anterior tibial and peroneal muscles, with bilateral foot drop. The knee and ankle jerks were absent. The plantar responses were extensor. There was a distal sensory loss for all modalities (vibration > proprioception) in the lower limbs. She also presented mild slowing of fine coordinated movements and a wide-based unsteady gait. The results of nerve conduction studies showed demyelinating neuropathy with uniform slowing of conduction velocities. Motor conduction velocity of her median nerve was 22.3 m/s. Somatosensory evoked potentials revealed prolonged latency from the right median nerve and lack of any response from the right tibial nerve. The right sural nerve biopsy showed demyelination and remyelination with the form of “onion” bulb formation, there were no inflammatory infiltrates (Fig. 1). The MRI T2-weighted sequences showed both abnormal hyperintense pathological focal lesion in white matter and brain atrophy. The level of very long chain fatty acid was not elevated.

The latencies of visual evoked responses and brainstem auditory evoked responses were prolonged. Fundus and anterior segment of the eyes were normal. On the psychological examination she scored 57 (71) 85 points in Wechsler Intelligence Scale (WAIS-R). She presented a tendency to decline of her cognitive function.

The family history showed the pedigree of only three consecutive generations. Although the mother and brother of the patient did not complain of any difficulty in walking, on neurological examination they presented bilateral pes cavus and a slight distal sensory loss in lower limbs. The ankle jerks were absent. In both cases, nerve conduction studies showed demyelinating neuropathy with uniformly slowed conduction velocity. The patient’s brother’s MRI scan was completely normal.

At that time the preliminary diagnosis of demyelinating CMT1 with coexisting central nervous system involvement was made.

Four years later the patient was readmitted to our Department because of progression of her gait disorder and incontinence of the urine.

Neurological examination revealed prominent gait ataxia, intention tremor in the upper and lower limbs. She had, similar to the previously reported, moderate weakness and wasting of the anterior tibial and peroneal muscles and the toe extensors. She had also wide-based unsteady gait and neurogenic bladder.

The laboratory tests were again irrelevant. The results of the electrophysiological studies did not show
any significant difference from the previously obtained ones. The MRI T2-weighted sequences showed much more pronounced cortical atrophy and hyperintense pathological demyelinating lesions in brain white matter with the corpus callosum atrophy (Fig. 2). The demyelinating lesions were also present in the cervical part of the spinal cord. Visual evoked responses and brainstem auditory evoked responses were more prolonged comparing to the previously obtained results. Her psychological examination did not show any further decline of her cognitive function.

CSF parameters were within normal limits, however detailed analysis detected oligoclonal bands.

Dominant clinical features e.g. progressive cerebellar ataxia and neurogenic bladder as well as results of MRI scan of the brain and spinal cord strongly suggested diagnosis of multiple sclerosis. After exclusion of similar condition resembling MS, according to the McDonald criteria, primary progressive multiple sclerosis (PPMS) was diagnosed [14].

Discussion

Our proband presented with symptoms attributable to two coexisting disorders – Charcot-Marie-Tooth type 1C disease with primary progressive multiple sclerosis (PPMS), while her brother and mother, who carry only the LITAF gene mutation, presented with mild peripheral neuropathy symptoms only.

Although our patient may represent the random coincidence of both disorders (an overlapping syndrome), a possible role of LITAF and TNF-α genes mutations in their development cannot be excluded.

The LITAF gene was identified as a transcription factor of the tumor necrosis factor α gene many years before its characteristics as a gene responsible for CMT1C disease. In the experimental approach, inhibition of the LITAF mRNA expression resulted in the reduction of the TNF-α transcription [11]. The Gly112Ser mutation in the LITAF gene detected in the CMT family may act in our patient at least in two independent ways. In the peripheral nerve, the mutated LITAF gene causes a typical course of mild peripheral demyelinating neuropathy seen in our proband’s affected family members, and was previously described in other CMT1C patients harbouring Gly112Ser mutation [1,8,16,18].

In CMT1X disease caused by mutations in the GJB1 gene numerous patients with transient demyelinating central nervous system changes were demonstrated [7]. Similarly to the LITAF gene, the GJB1 gene is also expressed in the central nervous system [7]. Some CMTX1-affected patients displayed demyelination in
Fig. 2. MRI T2-weighted images in the proband III:3. Axial and coronal MRI brain images demonstrate subcortical and periventricular bilateral white matter lesions with pronounced corpus callosum and cortical atrophy.

Fig. 3. A) A four-generation pedigree of a CMT family with an autosomal dominant mode of inheritance. The arrow indicates the proband. DNA available for analysis is marked with asterisks. The affected individuals are represented by black symbols and the unaffected family members are indicated by open symbols, B) wild type LITAF sequence, C) heterozygous transversion 334G>A in the LITAF gene (Gly112Ser) found in II:5, III:1 and III:3, D) wild type TNF-α promoter sequence, E) heterozygous sequence variant −308G>A in TNF-α promoter region found in III:3.
the white matter of the cerebral hemispheres visible in MRI investigation [12]. Parman et al. reported on CMTX1/CMT1X family in which peripheral neuropathy coexisted with multiple sclerosis in the proband. The patient harbouring the R164W mutation in the GJB1 gene had also disseminated white matter cerebral—cerebellar brain stem and spinal lesions typical of MS [13].

In the most frequent form of CMT2 – CMT2A disease, some mutations in the Mitofusin-2 gene have been reported to segregate with periventricular and subcortical hyperintense lesions in the central nervous system [2]. Brain white matter lesions observed in five CMT1A Italian family members were recognized as central demyelination due to genetic neuropathy, and did not meet the diagnostic criteria for multiple sclerosis [15].

In the currently reported family, the symptoms of CNS involvement were observed only in our proband, but not her mother or brother. His MRI was also normal.

Our proband carried not only the LITAF mutation, but also a polymorphism in the promoter sequence of the TNF-α gene. We hypothesize that in the central nervous system, the Gly112Ser mutation in the LITAF gene may have triggered the inflammatory reaction leading to PPMS, by influencing expression of the TNF-α gene. The 308G>A polymorphism was detected in the promoter sequence of the TNF-α gene. The TNF-α gene promoter region polymorphism was previously investigated in different MS populations with conflicting results. Although the –308G>A polymorphism has been shown to occur in similar frequencies in the MS-affected patients and in the control groups, its functional relevance has not been proven [9]. In the MS-affected patients harbouring the –308G>A polymorphism, a significantly higher TNF-α mRNA expression level was detected [9]. Functional relevance of the –308G>A polymorphism was also confirmed by an in vitro approach, in which high transcriptional activity of the TNF-α gene harbouring –308G>A allele was found [20].

The possible LITAF gene mutation influence on development of immune matter reaction in the peripheral nervous system has been recently suggested. The Ile92Val polymorphism in the LITAF gene was previously found in a family with demyelinating motor and sensory polyneuropathy with conduction block responsive to prednisone treatment [17]. The TNF-α gene was not tested in this family. A clinical course resembling acquired neuropathy, and electrophysiological pattern of motor and sensory neuropathy with conduction block was also reported in a German family with (c.430G>A p.V144M) mutation in the LITAF gene [4].

Recognition of this genetic-inflammatory association is difficult and based only on the clinical case reports. We conclude that coexistence of demyelinating peripheral neuropathy and primary progressive multiple sclerosis is not necessarily coincidental. Central and peripheral involvement in our proband can result from interplay of mutations of two genes related in function.

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References