

CASE REPORT

X-linked Charcot-Marie-Tooth type 1: stroke-like presentation of a novel *GJB1* mutation

Anna Sagnelli¹, Giuseppe Piscosquito¹, Luisa Chiapparini², Claudia Ciano³, Ettore Salsano¹, Paola Saveri¹, Micaela Milani⁴, Franco Taroni⁴, and Davide Pareyson¹

¹Clinic of Central and Peripheral Degenerative Neuropathies Unit, Department of Clinical Neurosciences; ²Unit of Neuroradiology, Department of Diagnostic and Applied Technology; ³Neurophysiopathology and Epilepsy Centre, Department of Diagnostic and Applied Technology; and ⁴Unit of Genetics of Neurodegenerative and Metabolic Diseases, Department of Diagnostic and Applied Technology, IRCCS Foundation, "C. Besta" Neurological Institute, Milan, Italy

Abstract X-linked Charcot-Marie-Tooth type 1 (CMTX1) is the second most common type of CMT and is caused by mutations in the Gap-Junction Beta-1 gene (*GJB1*), encoding connexin 32 which is expressed in Schwann cells as well as in oligodendrocytes. More than 400 *GJB1* mutations have been described to date. Many mutation-carrier males have subclinical central nervous system (CNS) involvement, a few show mild CNS clinical signs, whereas only rarely overt though transient CNS dysfunction occurs. We report a 29-year-old man with CMTX1 who, at 16 years, showed short-lived CNS symptoms with transitory white matter abnormalities on cerebral magnetic resonance imaging (MRI) as first clinical presentation of a novel *GJB1* mutation (p.Gln99_His100insGln). He had three consecutive episodes of right hemiparesis, together with sensory loss in the paretic limbs and expressive aphasia, all lasting a few hours, over a 2-day period, with concurrent white matter hyperintensity on MRI. These "stroke-like" episodes occurred just after arriving at sea level, after travelling from home at 700 m of altitude. Only a few years later did symptoms of peripheral neuropathy appear. In conclusion, CMTX1 should be included in the differential diagnosis of diseases characterized by transient CNS symptoms and white matter abnormalities on MRI.

Key words: central nervous system symptoms, connexin 32, *GJB1* gene, magnetic resonance imaging, X-linked Charcot-Marie-Tooth disease

Introduction

X-linked Charcot-Marie-Tooth type 1 (CMTX1) accounts for approximately 10% of CMT cases (Murphy *et al.*, 2012a) and is associated with mutations in the Gap-Junction Beta-1 gene (*GJB1*) encoding connexin 32 (Cx32), a gap-junction (GJ) forming protein expressed by Schwann cells and oligodendrocytes (Kleopa *et al.*, 2012).

CMTX1 usually manifests within the second life decade in hemizygous males, with a relentless progressive course, and nerve conduction velocities (NCV) commonly in the intermediate range (30–45 m/s) (Pareyson and Marchesi, 2009); heterozygous women are generally less affected because of the random X-inactivation phenomenon (Murphy *et al.*, 2012b).

More than 400 *GJB1* mutations, all causing CMT, are known. Affected males often have subclinical central nervous system (CNS) involvement, with increased latency of central components of multimodal evoked potentials (EPs), and sometimes mild clinical signs such as extensor plantar responses and increased deep tendon reflexes (DTRs). Rarely, overt

Address correspondence to: Dr. Davide Pareyson, Clinic of Central and Peripheral Degenerative Neuropathies Unit, Department of Clinical Neurosciences, IRCCS Foundation, "C. Besta" Neurological Institute, via Celoria 11, 20133 Milan, Italy. Tel: +39-02-2394-3001; Fax: +39-02-2394-2293; E-mail: davide.pareyson@istituto-besta.it

though transitory CNS dysfunction occurs and brain magnetic resonance imaging (MRI) demonstrates transient white matter abnormalities (Abrams and Scherer, 2012).

We observed a young adolescent with transient CNS symptoms as first presentation of a novel *GJB1* mutation, who only later developed clear-cut polyneuropathy.

Case Report

We observed a 29-year-old man with a 9-year history of slowly progressive hand weakness and mild gait disturbance. Family history was suggestive of X-linked neuropathy because his mother and maternal grandmother had clinical and electrophysiological evidence of mild CMT.

Remarkably, at 16 years, he had three attacks of right hemiparesis, with sensory loss in the paretic limbs and expressive aphasia, over a 2-day period. Episodes lasted a few hours with severe paresis in two episodes and normal examination between attacks. Such “stroke-like” episodes occurred just after arrival at the sea level, after travelling from home at 700 m of altitude.

Cerebral MRI during the acute phase showed confluent hyperintense white matter abnormalities in the posterior portion of cerebral hemispheres, splenium of the corpus callosum, corticospinal tracts, and middle cerebellar peduncles (Figs. 1, a–g); diffusion-weighted imaging was not performed. Routine blood tests, cerebrospinal fluid (CSF) analysis, metabolic and genetic investigations (plasma lactate and pyruvate, very-long-chain fatty acids, aryl-sulfatase A, beta-hexosaminidase, alpha-fucosidase, beta-galactosidase, beta-glucuronidase, alpha-mannosidase, plasmatic and urinary amino acids, A3243G and T8993 mtDNA mutations) were normal. Somatosensory EP latencies were prolonged, whereas brainstem auditory and visual EPs were normal. There was minimal NCV slowing with slight decrease of compound muscle action potential amplitude (CMAP) in lower limbs; he had absent DTRs but no definite foot deformities. The already known neuropathy of the mother and grandmother was mild and was overlooked. After 18 months MRI had greatly improved (Figs. 1, h–k).

On examination at age 29, we observed pes cavus, mild gait difficulties, moderate distal muscle weakness and wasting (more marked on median-innervated muscles), absent DTRs, distal proprioceptive sensory loss, without clinical signs of CNS involvement. Motor and sensory NCV were slightly-to-moderately reduced (37.8–44.8 m/s range in upper limbs), and all

CMAPs and sensory action potentials (SAPs) were reduced in amplitude, with median (CMAP amplitude 1.4–1.7 mV, absent SAPs) more severely affected than ulnar nerve (CMAP amplitude 13–13.3 mV, SAP amplitude 2.2–2.4 μ V). Brain MRI was normal.

Preceding CNS dysfunction in a CMT male with prominent median nerve involvement was suggestive of CMTX1. Therefore, we directly sequenced *GJB1* and found a novel CAA in-frame insertion (c.297_298insCAA) introducing a glutamine between Gln99 and His100 (p.Gln99_His100insGln), absent in >200 controls and in the Exome Variant Server database (<http://evs.gs.washington.edu/EVS/>). *In silico* analysis (<http://www.mutationtaster.org/>) does not predict a pathogenic role. We could neither clinically examine nor test for mutation segregation in his mother and grandmother.

Discussion

The first clinical manifestations in the patient were three consecutive “stroke-like” episodes related to acute brain dysfunction, whereas only years later did symptoms of peripheral neuropathy appear.

CNS involvement in CMTX1 is known to occur with subclinical abnormalities of EPs and sometimes mild clinical signs (Nicholson and Corbett, 1996; Bähr et al., 1999). However, an increasing number of reports describe transient CNS dysfunction in CMTX1 males, sometimes dramatic, manifesting as hemiplegia, tetraplegia, sensory loss, dysarthria, ataxia, aphasia, and even confusion, accompanied by transient white matter MRI abnormalities. These symptoms last hours to weeks and rarely can precede clinical onset of CMT, whereas MRI changes often resolve completely in a few months (Paulson et al., 2002; Schelhaas et al., 2002; Hanemann et al., 2003; Anand et al., 2010; Al-Mateen et al., 2014). Brain MRI abnormalities are symmetrical and confluent, especially in the posterior white matter and splenium of the corpus callosum, associated with restricted diffusion, and thought to be caused by intramyelinic edema and subsequent reduction of the extracellular space (Taylor et al., 2003; Anand et al., 2010; Al-Mateen et al., 2014).

Different Cx32 mutations display CNS involvement, and a CMTX1 family showed varying brain dysfunction patterns (Hanemann et al., 2003); however, there is no consistent genotype–phenotype correlation (Abrams and Scherer, 2012). In myelinating Schwann cells, Cx32 forms reflexive GJs allowing radial diffusion of ions and small molecules across myelin lamellae. In the CNS, both Cx32 and Cx47 form GJs between oligodendrocytes, but the mechanism by which *GJB1* mutations cause CNS dysfunction is

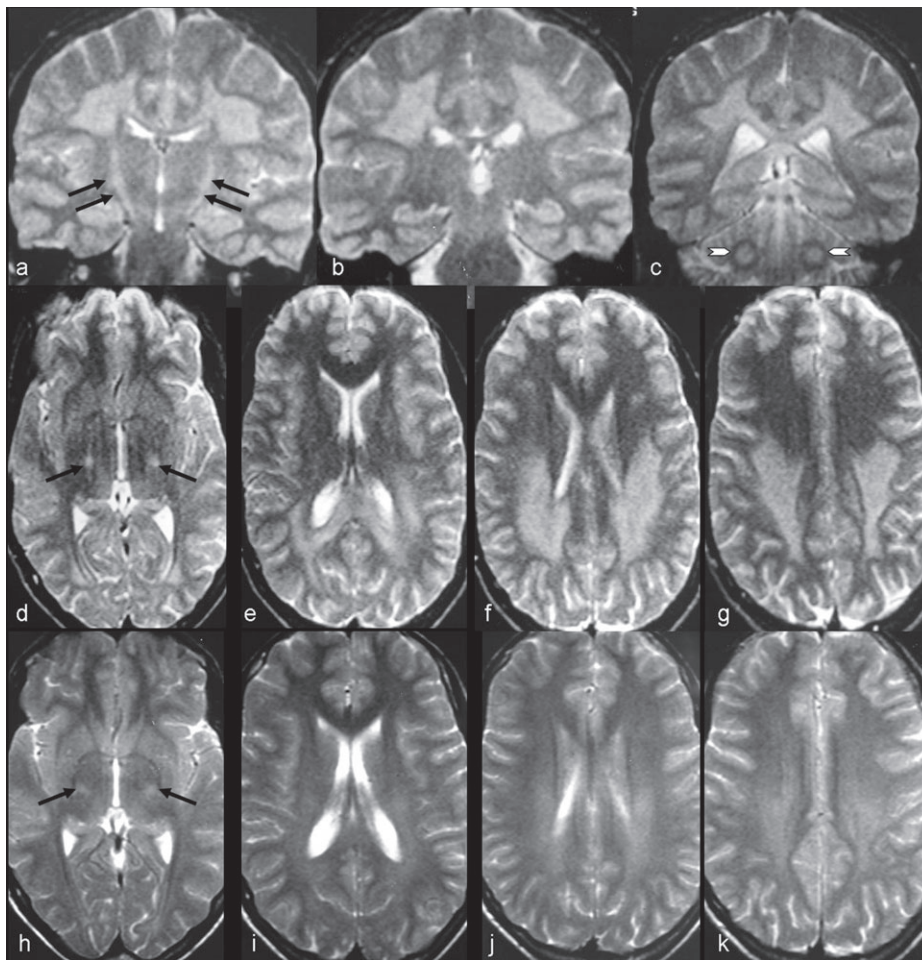


Figure 1. Brain MRI. First (a–g) and second examination (h–k). Coronal (a–c) and axial (d–g) T2-weighted images show confluent, bilateral, and symmetric marked hyperintensities in the fronto-parietal, parietal, and occipital white matter and in the corticospinal tracts in the posterior limb of internal capsule (arrows in a and d). Note the involvement of the splenium of the corpus callosum. In addition, signal abnormalities were found in both middle cerebellar peduncles (arrowheads in c). After 1.5 years (h–k), the lesions in the white matter and along the corticospinal tracts (arrows in h) were almost completely vanished.

not completely understood. Proposed mechanisms include either a loss of function with intracytoplasmic retention of mutated Cx32, unable to reach the cell surface and form functional channels (Sargiannidou et al., 2009), or a gain of abnormal function, possibly causing reduced Cx47 activity (Abrams and Scherer, 2012; Nualart-Marti et al., 2013).

We identified a novel Cx32 mutation associated with a CNS phenotype, with a glutamine codon insertion between codons Gln99 and His100 resulting in the addition of a third glutamine following glutamines 98 and 99 in the intracellular loop. Although *in silico* analysis does not predict a pathogenic role, this variant was not found in controls nor is reported in databases, and occurs within a four-polar amino acid sequence (HisGlnGlnHis) highly conserved from chicken to humans; moreover, a missense mutation affecting codon 100 (His100Tyr) causes CMTX1 (Bone et al.,

1997). There is evidence for a major role of the intracellular loop in pH and CO₂-induced voltage gating sensitivity (Peracchia et al., 2000). Thus, the insertion of an extra-glutamine in the four-amino acid polar stretch raises the interesting possibility of a gain-of-function effect that may cause CNS dysfunction in the presence of pH stressors.

Indeed, the patient had the “stroke-like” episodes when just arrived at sea level travelling from 700 m of altitude. Transient CNS symptoms have often been associated with metabolic stress such as febrile illnesses, exercise, or, as in this case, return to lower altitudes after adapting to higher altitudes. It is not known how these stressors induce CNS symptoms; a decrease of CSF pH, secondary to altitude change, might reduce GJ coupling (Abrams and Scherer, 2012).

CNS involvement may occasionally precede the clinical signs of neuropathy. Therefore, CMTX1 enters

into the differential diagnosis of diseases with transient CNS symptoms and white matter abnormalities (*Al-Mateen et al., 2014*), even if clear-cut clinical signs of CMT neuropathy are lacking. Conversely, peripheral neuropathy should be considered in males with acute, transient CNS involvement and reversible T2-weighted MRI abnormalities, and accurate family history can be a clue to the right diagnosis.

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