



Early-onset CMT1B due to the MPZ mutation c.320A>T associated with collateral inclusion body myopathy and Deafness

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Authors' contributions

This work was carried out in collaboration between all authors. Author JF designed the study, performed the evaluation of the data, and wrote the first draft of the manuscript. Author CH was responsible for the nerve and muscle biopsy analysis. Author MAG carried out the genetic studies. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To present the case of a patient with early-onset demyelinating neuropathy due to a MPZ-mutation, associated with deafness and inclusion-body-myopathy.

Methods: Nerve conduction studies, electromyography, muscle biopsy, genetic testing.

Results and Discussion: In a 46yo male with slowly progressive weakness and wasting since childhood initially of the lower and later also of the distal upper-limbs, ptosis, recurrent hyper-CK-emia, and progressive hearing impairment, nerve conduction studies revealed mixed demyelinating and axonal polyneuropathy and electromyography revealed neurogenic motor unit architecture. Nerve biopsy disclosed diffuse loss of myelinated fibers, reduced diameter of non-myelinated fibers, and fibers with hypomyelination and variable internodal myelination. Muscle biopsy revealed classical features of inclusion-body-myopathy. Upon genetic diagnostic work-up the MPZ-mutation c.320A>T, p.Glu107Val was detected. Since his son presented with a similar phenotype, inclusion-body-myopathy was interpreted as secondary to the neuropathy.

Conclusions: CMT1B may show secondary axonal loss and mild clinical manifestations

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despite early onset. CMT1B may be associated with severe hearing impairment and collateral inclusion-body-myopathy.

Keywords: Hereditary neuropathy; charcot-marie-tooth; sensorimotor polyneuropathy; genetics; myelin protein zero.

1. INTRODUCTION

Mutations in the myelin protein zero (MPZ) gene cause hereditary, autosomal dominant demyelinating sensorimotor polyneuropathy Charcot-Marie-Tooth (CMT) 1B [1], late-onset, mixed demyelinating and axonal polyneuropathy [2,3], late-onset autosomal dominant, axonal sensorimotor polyneuropathy CMT 2I/J [3,4], early-onset Dejerine-Sottas syndrome [5], or congenital hypomyelinating polyneuropathy [6,7,8,9]. Though MPZ-mutations have been reported to cause deafness [10,11,12] and may go along with elevated creatine-kinase (CK) [13], the association of an MPZ-mutation with early-onset demyelinating neuropathy, hypoacusis and neuropathological features of inclusion-body-myopathy (IBM), as in the following case, has not been reported.

2. METHODS

Methods applied were the clinical neurologic examination, blood tests, nerve conduction studies, electromyography, nerve and muscle biopsy, and genetic tests.

3. RESULTS AND DISCUSSION

The patient is a 46yo Caucasian male, height 174cm, weight 72kg, who experienced slowly progressive wasting of the lower-legs since childhood, later accompanied by distal lower-limb weakness. Since age 18y he developed slowly progressive hearing impairment, and since age 24y bilateral tinnitus. At age 33y he experienced a muscle rupture of the left calve. Gait disturbance and hyperhidrosis became apparent since age 38y and since then the foot drop required a peroneal splint. Since at least age 39y he noted muscle cramps of the lower-limbs. Since age 39y he experienced recurrent falls, this is why he used a wheelchair for longer distances since age 40y. Since age 42y he complained about paresthesias and dysesthesias in a stocking-type distribution up to the knees and in a glove-type distribution up to the ankles. Since the same age, stiffness of the fingers became apparent. Gabapentin (1200mg/d) was prescribed. Because of unsteady gait and a tendency to fall he started to use a crutch. Since age 45y, slowly progressive weakness of the distal lower-arm muscles developed. The family history was positive for a similar presentation as in the index case in the grandfather from the mother's side, in the sister of this grandfather, and in his son. The 21yo male had developed slowly progressive lower-limb weakness since age 6y and complained about easy fatigability. At the age of 14y he presented with left-sided ptosis and weakness of the lower-limbs (M5-). Nerve conduction studies at that time were normal. He had refused nerve / muscle biopsy and genetic testing so far. The mother of the index patient was clinically unaffected.

Clinical examination of the index patient revealed facial dysmorphism, bilateral ptosis (Fig. 1), protruding eye bulbs, dysarthria, severe hypoacusis, and weakness for right-sided finger straddling (M5-), bilateral hip flexion (M5-), foot extension (M0), and foot flexion (M1). Tendon reflexes were reduced on the upper-limbs and absent on the lower-limbs. Muscle

wasting was evident on the distal upper-limbs and severe on the lower-legs (Fig. 2). Sensory testing revealed reduced vibration sense on the right hand and stocking-type hypesthesia bilaterally for all modalities. There was no pupillary anomaly but pes planus, blotchy hyperemia, and hyperkeratosis of the planta pedis (Fig. 2).

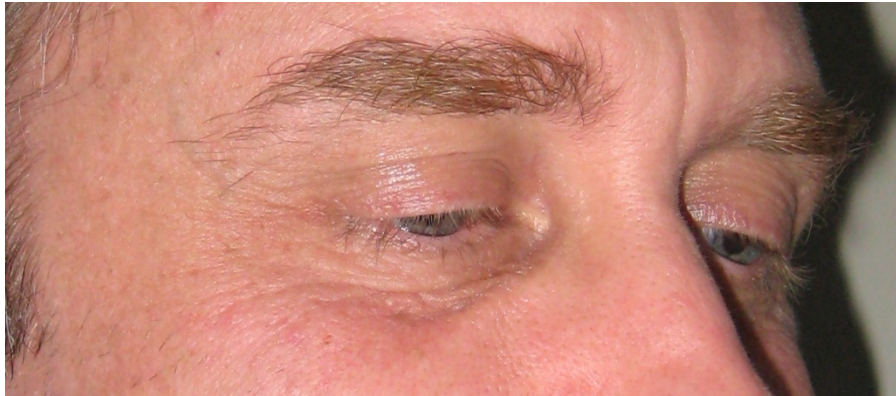


Fig. 1. Myopathy manifested clinically as bilateral ptosis with right-sided predominance

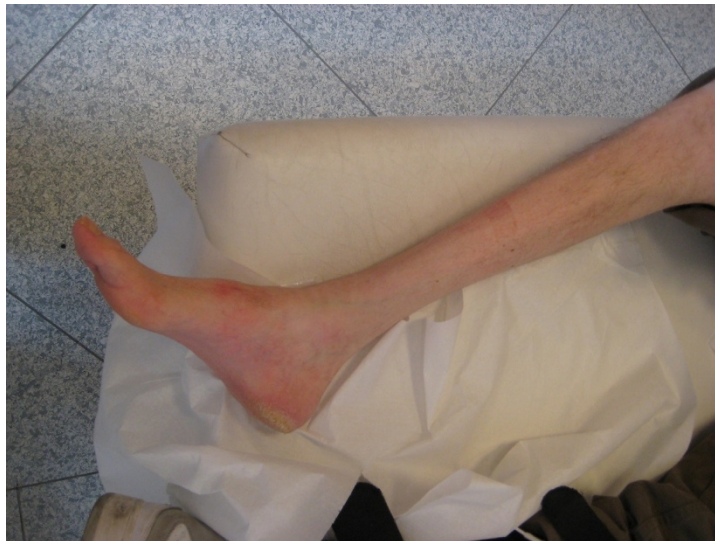


Fig. 2. Severe wasting of the lower limb muscles and foot deformity in the described patient with early-onset CMT1B. Affection of vegetative fibers may be responsible for trophic abnormalities resulting in blotchy hyperaemia on the feet and hyperkeratosis on the heels

Blood tests revealed repeatedly elevated cholesterol, glutamat-pyruvat dehydrogenase and CK up to 298U/l (n, <177U/l). Lactate stress testing was normal (lactate: 1.9, 2.2, 2.2, 2.4, 1.6 mmol/l). The cerebrospinal fluid was non-informative. Audiograms and acoustically-evoked potentials were highly abnormal indicating sensori-neural hearing loss. Nerve-conduction studies revealed demyelinating and axonal polyneuropathy and lower-limb predominance (Table 1). Needle electromyography revealed a neurogenic motor-unit

architecture with denervation and re-innervation. Nerve biopsy of the right sural nerve at age 40y disclosed diffuse loss of myelinated fibers and reduced diameter of unmyelinated fibers. Several fibers showed hypomyelination and variable internodal myelination, being interpreted as demyelinating neuropathy with secondary axonal loss. Muscle biopsy revealed increased fiber-size variability, grouped and non-grouped fiber atrophy, occasionally fiber necrosis, endomysial fibrosis, and repeatedly rimmed vacuoles (Fig. 3). These vacuoles reacted with antibodies against phosphorylated neurofilament, cellular prion-protein, and ubiquitin. Additionally, there were autophagic vacuoles, and intra-nuclear tubulo-filamentous inclusions (Fig. 3). IBM was suspected. Genetic testing revealed the mutation c.320A>T, p.Glu107Val in exon 3 of the MPZ gene affecting the V-like domain (MPZ RefSeq NM 000530). The mutation was equivalent to the previously described c.290A>T, p.Glu97Val mutation [14] based on the MPZ sequence D10537 (<http://www.ncbi.nlm.nih.gov/entrez/>) [15]. The mutation has not been found in 10000 investigated alleles according to the database of the NHLBI Exome Sequencing Project (ESP). At the last follow-up at age 46y he had discontinued gabapentin. He did not use hearing devices and refused to consider cochlear device implantation. Capsaicin ointment and paracetamol were prescribed. Testing for this mutation and muscle biopsy were offered to the index-patient's son but refused by him so far.

Table 1. Results of nerve conduction studies carried out in the described patient at ages 39, 40 and 43y

AI (y)	Nerve	Fiber type	DL	NCV	CMAP(mV)/SNAP(μ V)
39	Right median	Motor	5.6	23.5	6.7/2.6
	Right median	Motor	4.5	26.1	11.2/3.2
	Right median	Motor	5.8	31.8	5.4/2.6
	Right median	Sensory	NPR	NPR	NPR
	Right median	Sensory	NA	39.7	1.8/1.8
	Left median	Motor	6	24.4	0.9/0.4
	Right peroneal*	Motor	9.9	13.3	0.1/0.1
	Left peroneal	Motor	NA	18.9	0.2/0.1
	Left peroneal*	Motor	2.7	41.9	0.3/0.3
	Left peroneal*	Motor	5.6	37.1	0.9/0.6
40	Left median	Motor	6.4	24.2	7.7/3.4
	Left median	Sensory	NPR	NPR	NPR
	Left ulnar	Motor	3.4	31.7	5.8/7.0
	Left ulnar	Sensory	NPR	NPR	NPR
	Right peroneal	Motor	NA	15.7	0.3/0.1
	Right sural	Sensory	NPR	NPR	NPR
43	Right median	Motor	6.3	22.7	2.0/0.3
	Right median	Sensory	NA	30.8	9.5
	Right ulnar	Motor	2.8	34.0	6.9/5.4
	Right ulnar	Sensory	NA	53.6	5.2
	Right peroneal*	Motor	14.7	NA	8.5/NA
	Right tibial	Motor	NPR	NPR	NPR
	Right sural	Sensory	NPR	NPR	NPR

AI: Age at investigation, DL: distal latency, NCV: nerve conduction velocity, CMAP: compound muscle action potential, SNAP: sensory nerve action potential, NPR: no potential recordable, *: recording from the anterior tibial muscle, NA: not available.

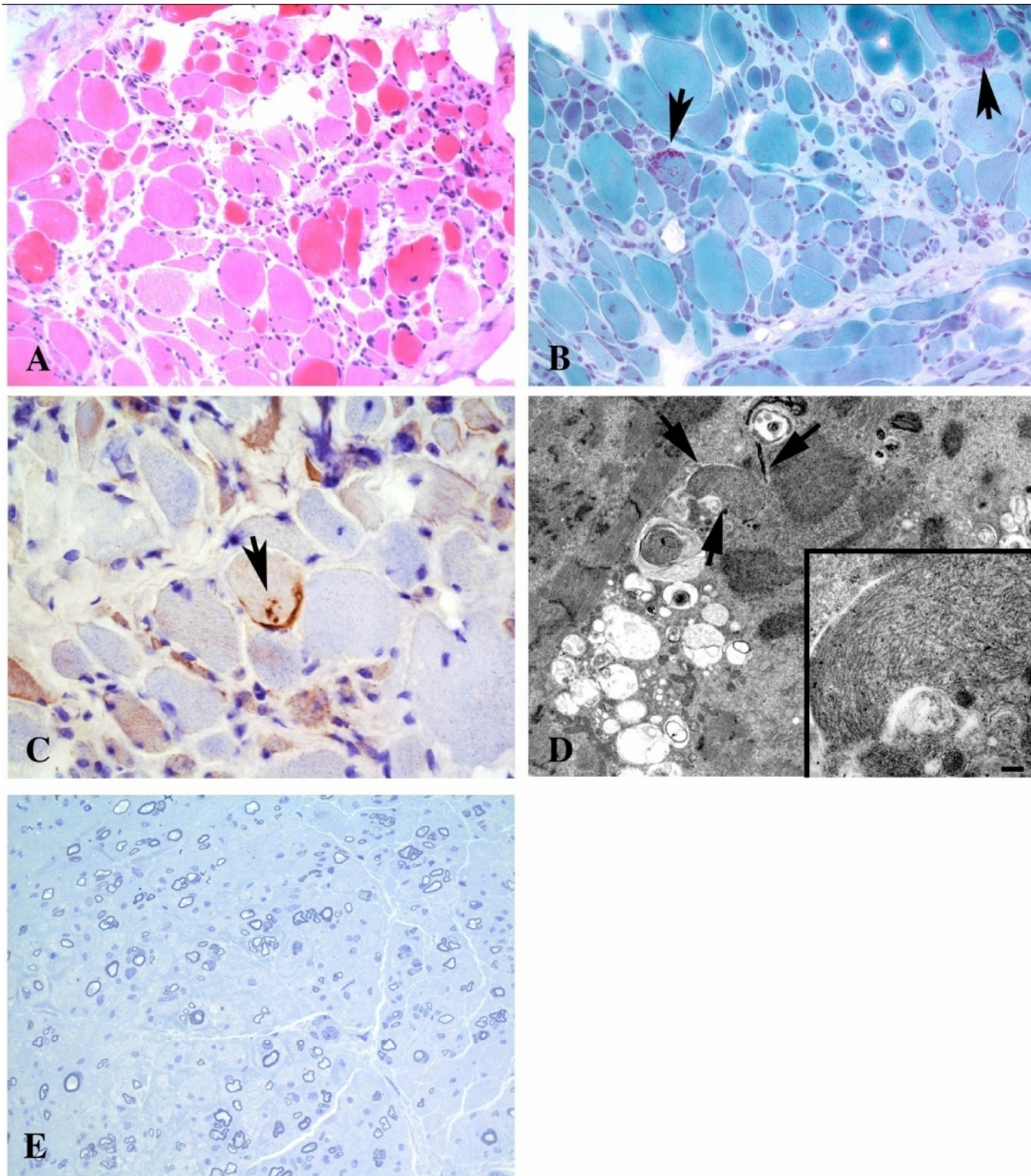


Fig. 3. Biopsy from the right gastrocnemius muscle showing fiber size variation, atrophic fibers, endomysial fibrosis, regenerating and necrotic fibers (A; HE staining, x20) and rimmed vacuoles (B arrows; Gomori Trichrome staining, x20). Within the rimmed vacuoles SMI31 positive deposits are detectable (C arrow; anti-SMI31 immunostaining, x40). Ultrastructural examination reveals rimmed vacuoles and tubulo-filamentous inclusions sized 18nm (arrows and inset) (D, x3000, inset x20000, scale bar indicates 250nm). Nerve biopsy shows diffuse loss of large and small myelinated Ia fibers (E; semi-thin section, x20)

The presented case is unique for two aspects: first, the MPZ-mutation detected caused early-onset, demyelinating sensorimotor polyneuropathy with secondary axonal loss, and second, the neuropathy was associated with the histological features of IBM.

Since neuropathy was of the demyelinating type and since the transmission followed an autosomal dominant trait-of-inheritance, the presented case was diagnosed as CMT1B, which has been repeatedly reported in the literature [16,17,18,19]. CMT1B patients present either with severe early-onset (prior to stage of walking) demyelinating neuropathy or with late-onset (>40y of age), demyelinating sensorimotor polyneuropathy with prominent axonal loss [2,17]. There is lower limb-predominance of weakness, wasting, and sensory disturbances, and foot deformity but hardly pupil anomalies, or deafness in early-onset CMT1B. Early-onset CMT1B results from multiple abnormal gain-of-function pathways whereas late-onset CMT1B results from partial loss of function of the MPZ protein [17]. Early-onset CMT1B due to MPZ-mutations is assumed to be attributable to disruption of the tertiary structure of the protein affecting MPZ-mediated adhesion and myelin compaction [20,21]. Secondary axonal degeneration due to MPZ-mutations is generally attributed to disruption of the glial-axon interaction by protein aggregates or by alterations in the molecular architecture of internodes or paranodes [22]. Whether immune mechanisms contribute to the pathogenicity of MPZ-mutations is under debate [23]. The variable phenotype of MPZ-mutations has been attributed to modifying genes regulating MPZ-gene expression, to mRNA instability, or to post-translational protein modification [22]. MPZ-mutations may not only manifest as sensorimotor neuropathy but also as multiple sclerosis-like phenotype [10], with Adie's pupil [4] or other abnormal pupillary reaction [14], autonomic dysfunction [24], recurrent nerve compression [1], with isolated spinal root hypertrophy [25], respiratory failure [24], CK-elevation [4], or impaired hearing [4,10,11,12]. MPZ mutations contribute to 5% of the CMT cases [2]. MPZ mutations most frequently manifest as CMT1B, but only rarely as CMT2I/J, Dejerine-Sottas syndrome, or congenital hypomyelination [18]. Auditory impairment in the presented patient was attributed to axonal neuropathy of the cochlear nerve [12] but it cannot be excluded that it was due to mutations in genes other than the MPZ-gene. Contrary to what is described in the literature our patient did not present with severe clinical manifestations despite the early onset. Contrary to previous descriptions the patient presented with marked axonal loss despite early-onset [17].

Hyper-CK-emia has been occasionally reported in association with MPZ-mutations [4,13,26]. Whether IBM was causally related to the neuropathy or a second trouble independent of the neuropathy remains speculative. Arguments for a causal relation are that single previous reports indicate that familial IBM may be associated with polyneuropathy [27,28], that MPZ-mutations may go along with hyper-CK-emia [4,13,27,29], and that immune mechanisms are suspected to contribute to the pathogenicity of MPZ-mutations [23]. Arguments against a causal relation, however, are that the clinical presentation was not typical for IBM (ptosis is an uncommon feature of IBM), that IBM has not been reported in association with hereditary neuropathy, and that CK-elevation is not unusual in cases with denervation from neuropathy [30]. Most likely, features of IBM on muscle biopsy were secondary to the axonal loss. A further argument for an association between hereditary neuropathy and IBM is that also the index patient's son had developed features of muscle disease but it cannot be definitively excluded that both, father and son, suffered from a second genetic trouble. Unfortunately, systematic analyses of muscle biopsies in patients with hereditary neuropathy are lacking. Stiffness of the fingers was attributed to secondary IBM.

Limitations of the study are that no other clinically affected family members were tested for IBM or the mutation and that no investigations for IBM mutations were carried out. Due to the first limitation pathogenicity of the mutation is so far unproven but quite likely [14].

4. CONCLUSIONS

This case shows that early-onset CMT1B may show secondary axonal loss and mild clinical manifestations despite early onset. Early-onset CMT1B may be associated with severe hearing impairment and coincidentally associated with collateral IBM.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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