

Coexistent Charcot-Marie-Tooth type 1A and type 2 diabetes mellitus neuropathies in a Chinese family

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doi: 10.4103/1673-5374.167771
<http://www.nrronline.org/>

Accepted: 2015-07-10

Abstract

Charcot-Marie-Tooth disease type 1A (CMT1A) is caused by duplication of the peripheral myelin protein 22 (PMP22) gene on chromosome 17. It is the most common inherited demyelinating neuropathy. Type 2 diabetes mellitus is a common metabolic disorder that frequently causes predominantly sensory neuropathy. In this study, we report the occurrence of CMT1A in a Chinese family affected by type 2 diabetes mellitus. In this family, seven individuals had duplication of the PMP22 gene, although only four had clinical features of polyneuropathy. All CMT1A patients with a clinical phenotype also presented with type 2 diabetes mellitus. The other three individuals had no signs of CMT1A or type 2 diabetes mellitus. We believe that there may be a genetic link between these two diseases.

Key Words: nerve regeneration; PMP22 duplication; demyelinating degeneration; hereditary disease; phenotype; axonal loss; electrophysiology; concentric structure; multiplex ligation-dependent probe amplification; neural regeneration

Sun AP, Tang L, Liao Q, Zhang H, Zhang YS, Zhang J (2015) Coexistent Charcot-Marie-Tooth type 1A and type 2 diabetes mellitus neuropathies in a Chinese family. *Neural Regen Res* 10(10):1696-1699.

Introduction

Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system with an estimated average prevalence of 1 in 1,214 (Braathen et al., 2011). The most frequent genetic form of CMT is CMT type 1A (CMT1A) which constitutes about 70% of CMT1 and 50% of all CMT cases (Nelis et al., 1996). CMT1A is caused by a duplication on chromosome 17p11.2–p12 containing the PMP22 gene that encodes peripheral myelin protein 22 (Lupski et al., 1991; Raeymaekers et al., 1991). Most patients with CMT1A have a typical phenotype characterized by onset in childhood, distal weakness, sensory loss, foot deformities, and absent reflexes (Thomas et al., 1997; Krajewski et al., 2000).

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia. Diabetic neuropathy is the most common and troublesome complication of diabetes with a prevalence of 50–60% (Said et al., 1998; Sima, 2006). We describe the clinical, electrophysiologic, and neuropathologic features of a Chinese family with CMT1A and type 2 diabetes mellitus (type 2 DM).

Subjects and Methods

Subjects

We studied a pedigree that includes seven affected subjects over three generations (Figure 1). Patients were clinically evaluated by taking a detailed history. Muscle power was evaluated manually using the Medical Research Council scale (5/5) (O'Brien, 2010). Electrophysiological studies were

performed on participants with symptoms of neuropathy. Conduction studies of the median, ulnar, tibial, peroneal, and sural nerves were performed by conventional procedures using a Key point electromyography instrument (Dantec, Copenhagen, Denmark). Parameters measured included distal motor latency, motor nerve conduction velocity, compound motor action potential, sensory nerve conduction velocity, and sensory nerve action potential. A measurement deviating from the standard range by $\pm 20\%$ was considered abnormal. The study was approved by the Hospital Ethics Committee of Peking University Third Hospital in China.

The proband (II-1) was a 64-year-old man who presented with an 8-year history of slowly progressive weakness and sensory loss in the distal extremities, especially the lower limbs. He was diagnosed with type 2 DM at the age of 44 years. Physical examination revealed pes cavus and hammer toes. Neurological examination showed hands with evident wasting, weakness (2/5 on the Medical Research Council scale) of the interossei and thenar muscles, and hypotrophy of the distal lower limbs with associated weakness (3/5). Steppage gait was caused by weakness of the distal lower extremities. There was mild weakness (4/5) in the muscle groups of both forearms and in the extension and flexion of both knees. Atrophy was noted in the thenar, hypothenar, interosseous, peroneal, and anterior tibial muscle groups. Vibration and position sensations were decreased in the upper extremities, and absent in the lower extremities. Glove and stocking hypoesthesia were detected bilaterally. Deep tendon reflexes were absent in all extremities. Electrodiagnostic examination revealed a diffuse demyelinating neuropathy with

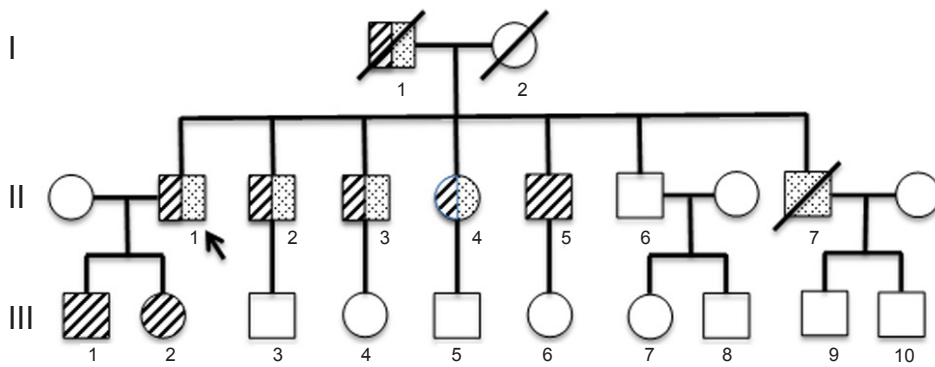


Figure 1 Pedigree of CMT1A + DM family.

▨: CMT1A male patient; ▩: CMT1A female patient; ▤: DM male patient; ▥: CMT1A + DM male patient; ▦: CMT1A + DM female patient; □: healthy male; ○: healthy female; /: death; ↑ proband; CMT: Charcot-Marie-Tooth disease; DM: diabetes mellitus.

Table 1 Electrophysiologic studies of four family members with both CMT1A and DM

Patient	Side	Motor nerves						Sensory nerves			
		Median nerve		Ulnar nerve		Peroneal nerve		Median nerve		Sural nerve	
		CMAP (mV)	CV (m/s)	CMAP (mV)	CV (m/s)	CMAP (mV)	CV (m/s)	SNAP (μV)	CV (m/s)	SNAP (μV)	CV (m/s)
II-1	Left	0.7	24.4	0.4	26.6	A	A	0.5	35	A	A
	Right	0.1	17.7	0.7	20.9	A	A	A	A	A	A
II-2	Left	0.6	21.2	0.5	22.1	A	A	A	A	A	A
	Right	0.4	18.6	0.8	23.8	A	A	A	A	A	A
II-3	Left	2.3	20.9	0.5	21.2	A	A	A	A	A	A
	Right	–	–	–	–	–	–	–	–	–	–
II-4	Left	1.7	22.5	1.6	15.9	A	A	A	A	A	A
	Right	1.3	20.1	0.9	20.3	A	A	A	A	A	A

CMAP: Compound motor action potential; SNAP: sensory nerve action potential; CV: conduction velocity; A: absent evoked response; –: not measured; CMT: Charcot-Marie-Tooth disease; DM: diabetes mellitus.

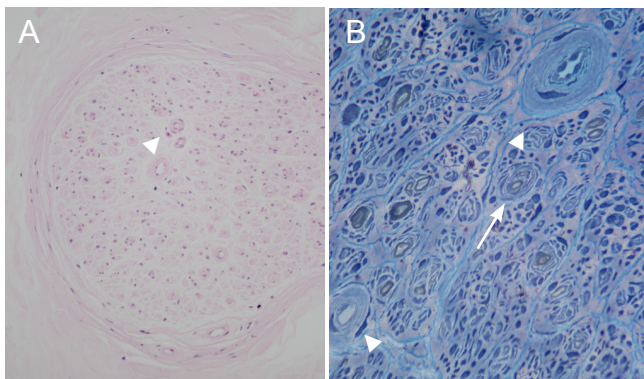


Figure 2 Nerve biopsy of the proband with Charcot-Marie-Tooth disease and diabetes mellitus.

Photomicrograph of a sural nerve biopsy showing loss of large myelinated fibers, abundant onion bulb formations (arrow), and thickened capillary walls (arrowhead) with no inflammation. (A) Hematoxylin-eosin staining (× 400); (B) toluidine blue staining (× 1,000).

severe axonal loss.

Two male relatives (II-2 and II-3) had CMT phenotypes similar to the proband. Bilateral hypotrophy and mild weakness of the distal upper and lower muscles were noticed in patient II-2 (a 58-year-old man) at the age of 40 years, and

he was diagnosed with type 2 DM at 38 years. Patient II-3, a 56-year-old man, experienced similar symptoms at the age of 44 years and developed type 2 DM at 41 years. Atrophy and weakness of the distal extremities progressed gradually. Both had sensory loss in a stocking-glove distribution and absence of deep tendon reflexes in all extremities.

Patient II-4, the proband’s 54-year-old sister, was diagnosed with type 2 DM at the age of 51 years. At that time, she had no symptoms of CMT, but electrophysiological studies showed slowing of motor conduction velocity, especially in the lower extremities. Sensory-nerve action potentials of the bilateral median, ulnar, and sural nerves could not be elicited. Two years later, at the age of 53 years, she began to suffer from numbness and weakness of the toes, which progressed to the lower legs and hands. Neurologic examination showed mild wasting of the hands, weakness (4/5) of the interosseus and thenar muscles, and distal lower limb hypotrophy with weakness (3⁺/5). Sensory loss was detected in a stocking-glove distribution. All tendon reflexes were absent.

Patient II-5, the proband’s 49-year-old brother, presented with slight atrophy and weakness of the interosseus and thenar muscles (5⁻/5). Sensation was normal. He had no history of type 2 DM. Patient II-7 died in a traffic accident at the age of 46; he had been diagnosed with type 2 DM at the age of

38. Patients III-1 (34 years old) and III-2 (28 years old) had no symptoms of CMT or type 2 DM.

The proband's father also had symptoms of both CMT1A and type 2 DM according to his history, but as he was deceased he could not be included in the study group.

Nerve biopsy

A sural nerve biopsy was obtained from the proband. One piece of the nerve was fixed in 4% formaldehyde, paraffin-embedded, cut into 8- μ m-thick sections, and stained with hematoxylin and eosin. For ultrastructural observation, 3% glutaraldehyde-fixed tissue was post-fixed with 1% osmium. After dehydration and epoxy resin embedding, ultrathin sections were cut and stained with uranyl acetate and lead citrate solution, and observed under an electron microscope (JEM-100; Hitachi, Japan).

Molecular genetic studies

Genetic testing was performed at the Department of Genetics, Medical Center, Peking University, China. DNA samples were extracted from peripheral whole blood using a Chemagic DNA Blood Kit (Chemagen, Baesweiler, Germany), according to the manufacturer's instructions. Multiplex ligation-dependent probe amplification was employed to analyze duplications of the *PMP22* gene on chromosome 17p11.2, using a SALSA multiplex ligation-dependent probe amplification P033 CMT1 kit (Medical Research Council, Amsterdam, Holland).

Results

Electrophysiological findings

Electrophysiological examination was performed in the proband, patients II-2, II-3, and II-4 (the other members declined) and the findings are shown in **Table 1**. All four individuals had symptoms of neuropathy. The results revealed a diffuse demyelinating neuropathy with severe axonal loss. No conduction block was detected. Motor-nerve conduction studies demonstrated decreased amplitudes of compound muscle action potentials and slowing of motor conduction velocities in the bilateral median, ulnar, peroneal, and tibial nerves, which were more severe in the lower extremities. Sensory action potentials and F-waves could not be elicited.

Neuropathological findings

A sural nerve biopsy of the proband revealed severe loss of myelinated fibers with abundant "onion bulb" formations. Ultrastructurally, well developed onion bulbs had the typical appearance of concentrically proliferated Schwann cells surrounding a central myelinated axon or a small cluster of regenerating axons. The capillary walls showed thickening and no evidence of inflammation; this is characteristic of DM (**Figure 2**).

Molecular findings

The proband possessed a duplication of the *PMP22* gene on chromosome 17p11.2, confirming CMT1A (data not

shown). Patients II-1, II-2, II-3, II-4, II-5, III-1, and III-2 also had the *PMP22* duplication. Among these, II-1, II-2, II-3, and II-4 had both CMT1A and type 2 DM, but II-5, III-1, and III-2 had no history of type 2 DM and no symptoms of CMT1A.

We hypothesize that the duplication was inherited from the proband's father, who had symptoms of weakness and numbness in the distal extremities suggestive of CMT1A, although he died from type 2 DM-related ketoacidosis.

Discussion

CMT is a genetically heterogeneous hereditary neuropathy that is phenotypically variable even between monozygotic twins (Garcia et al., 1995; Marques et al., 1999). As the most common form of CMT, CMT1A has been reported to be associated with several other disorders, such as type 2 DM, myotonia congenita, myotonic dystrophy, facioscapulohumeral muscular dystrophy, chronic inflammatory demyelinating polyneuropathy, adrenomyeloneuropathy, and CMTX (Çelik et al., 2001; Ota and Osawa, 2003; Hodapp et al., 2006; Koç et al., 2006; Kim et al., 2010; Kurt et al., 2010; Carvalho et al., 2013; Schreiber et al., 2013). In a literature search, we identified several reports of patients with CMT1A and DM (Çelik et al., 2001; Ota and Osawa, 2003; Koç et al., 2006; Carvalho et al., 2013). It is worth noting that there were two families with co-occurrence of CMT1A and DM (Çelik et al., 2001; Koç et al., 2006), similar to our report. It is likely that if both diseases run in the family, an individual is likely to have both conditions. The fact that three families (including the one described here) with both CMT1A and type 2 DM have been reported raises the possibility of a chance association between CMT1A and type 2 DM. Moreover, in these three families, the symptoms of CMT1A were not apparent until the fourth decade or later. It is widely known that the onset of symptoms is most frequently within the first decade (over 60%) (Harding and Thomas, 1980; Thomas et al., 1997). In the families with co-occurring CMT1A and type 2 DM, the late onset is notable, and is more similar to the usual onset age of type 2 DM (after 35–40 years old). Although there is no known genetic link between them, this might be interesting to explore in the future. Late onset in a CMT1A family is rare. As we know, CMT1A mostly affects childhood, and with the progression of the disease, disabilities become evident. Further studies may look for genetic modifiers that could account for a later age of onset; this might identify new therapeutic targets.

CMT1A and DM are both common causes of peripheral neuropathy. CMT1A is an inherited demyelinating neuropathy, with *PMP22* gene duplications resulting in abnormal myelin adhesion, while diabetic neuropathy is the most common complication of DM. The pathogenesis of diabetic neuropathy is considered to be multifactorial, with contributions from both metabolic and vascular factors. The common pattern of diabetic neuropathy is associated with a progressive distal axonopathy. The role of microangiopathy in the development of diabetic neuropathy has been highlighted (Estrella et al., 2008). Capillary basement membrane

thickening is the classical pathological feature of diabetic microangiopathy. A sural nerve biopsy from our proband showed loss of large myelinated fibers, abundant onion bulb formation, and thickened capillary walls. These pathological features demonstrate coexistent changes caused by CMT1A and type 2 DM, suggesting that these two conditions might cause compound injuries to the peripheral nerves, exacerbating the severity and progression of the phenotypes. Clearly, having two diseases that directly affect the peripheral nerves will likely have a cumulative negative effect. Sheth et al. (2008) observed a trend for CMT1A patients with diabetes to have low compound muscle action potentials and sensory nerve action potentials, indicating, in accordance with our findings, that DM exacerbates motor and sensory impairment in CMT1A.

All family members with symptoms of polyneuropathy had type 2 DM, except patient II-5 who displayed a mild phenotype with slight atrophy and weakness of the interossei and thenar muscles (5/5). Genetic testing showed *PMP22* duplication. In addition, patients III-1 and III-2 had *PMP22* duplication, but no symptoms of CMT1A or DM. Unfortunately, these individuals declined electrophysiological examination, which might have demonstrated subclinical evidence of polyneuropathy. The number of affected individuals in our pedigree who were first diagnosed with DM and then with CMT was considerable. As DM is the most common cause of neuropathy, this might lead to clinical referral. The most common pattern of diabetic neuropathy is length-dependent polyneuropathy with symptoms of distal, symmetrical neuropathy. Sensory disturbances are the main clinical manifestations, including numbness, burning and tingling sensations, and intractable pain. However, our patients with neuropathy presented distal weakness and atrophy, which are rare symptoms in DM. Thus, further genetic studies were performed, which eventually demonstrated CMT1A.

In conclusion, we describe the coexistence of CMT1A and type 2 DM in a Chinese family. Both are common causes of neuropathy that are likely to have a cumulative negative effect on peripheral nerves. There might be an as-yet-unknown genetic linkage between CMT1A and type 2 DM. Further studies will yield insights into the pathogenesis of neuropathy.

Author contributions: APS collected the clinical features of family members, performed genetic analysis and wrote the paper. LT carried out extraction of DNA samples from blood. QL performed the neuropathological staining. YSZ and HZ analyzed the electrophysiological results. JZ was responsible for subject design and closely reviewed the paper. All authors approved the final version of the paper.

Conflicts of interest: None declared.

References

Braathen GJ, Sand JC, Lobato A, Høyer H, Russell MB (2011) Genetic epidemiology of Charcot-Marie-Tooth in the general population. *Eur J Neurol* 18:39-48.

Carvalho MA, Secchin JB, Lourenço CM, Leal RCC, Bueno KC, Barreira AA, Marques W (2013) Coexistence of CMT1A and diabetes mellitus in a young woman with a severe and progressive neuropathy and respiratory insufficiency. *Muscle Nerve* 47:141-142.

Çelik M, Forta H, Parman Y, Bissar-Tadmouri N, Demirkirkan K, Battaloglu E (2001) Charcot-Marie-Tooth disease associated with Type 2 diabetes mellitus. *Diabetic Med* 18:685-686.

Estrella JS, Nelson RN, Sturges BK, Vernau KM, Williams DC, LeCouteur RA, Shelton GD, Mizisin AP (2008) Endoneurial microvascular pathology in feline diabetic neuropathy. *Microvasc Res* 75:403-410.

Garcia CA, Malamut RE, England JD, Parry GS, Liu P, Lupski JR (1995) Clinical variability in two pairs of identical twins with the Charcot-Marie-Tooth disease type 1A duplication. *Neurology* 45:2090-2093.

Harding AE, Thomas PK (1980) The clinical features of hereditary motor and sensory neuropathy types I and II. *Brain* 103:259-280.

Hodapp JA, Carter GT, Lipe HP, Michelson SJ, Kraft GH, Bird TD (2006) Double trouble in hereditary neuropathy: concomitant mutations in the *PMP-22* gene and another gene produce novel phenotypes. *Arch Neurol* 63:112-117.

Kim H, Chung K, Kang S, Choi S, Cho S, Koo H, Kim SB, Choi BO (2010) Myotonic dystrophy type I combined with X-linked dominant Charcot-Marie-Tooth neuropathy. *Neurogenetics* 11:425-433.

Koç F, Sarica Y, Yerdelen D, Baris İ, Battaloglu E, Sert M (2006) A large family with Charcot-Marie-Tooth Type 1a and Type 2 diabetes mellitus. *Int J Neurosci* 116:103-114.

Krajewski KM, Lewis RA, Fuerst DR, Turansky C, Hinderer SR, Garbern J, Kamholz J, Shy ME (2000) Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A. *Brain* 123:1516-1527.

Kurt S, Karaer H, Kaplan Y, Akat I, Battaloglu E, Eruslu D, Basak AN (2010) Combination of myotonic dystrophy and hereditary motor and sensory neuropathy. *J Neurol Sci* 288:197-199.

Lupski JR, de Oca-Luna RM, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, Barker DF, Killian JM, Garcia CA, Chakravarti A, Patel PI (1991) DNA duplication associated with Charcot-Marie-Tooth disease type 1A. *Cell* 66:219-232.

Marques W, Hanna MG, Marques SR, Sweeney MG, Thomas PK, Wood NW (1999) Phenotypic variation of a new P0 mutation in genetically identical twins. *J Neurol* 246:596-599.

Nelis E, Van Broeckhoven C, De Jonghe P, Löfgren A, Vandenberghe A, Latour P, Le Guern E, Brice A, Mostacciolo ML, Schiavon F, Palau F, Bort S, Upadhyaya M, Rocchi M, Archidiacono N, Mandich P, Bellone E, Silander K, Savontaus ML, Navon R, et al. (1996) Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type I and hereditary neuropathy with liability to pressure palsies: a European collaborative study. *Eur J Hum Genet* 4:25-33.

O'Brien M (2010) *Aids to the Examination of the Peripheral Nervous System*. London: Saunders Ltd.

Ota T, Osawa K (2003) Marked improvement of glycaemic control with pioglitazone in a Type 2 diabetic patient associated with Charcot-Marie-Tooth disease. *Diabet Med* 20:420-421.

Raeymaekers P, Timmerman V, Nelis E, De Jonghe P, Hoogendijk JE, Baas F, Barker DF, Martin JJ, De Visser M, Bolhuis PA (1991) Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT 1a). The HMSN Collaborative Research Group. *Neuromuscul Disord* 1:93-97.

Said G, Bigo A, Améri A, Gayno JP, Elgrably F, Chanson P, Slama G (1998) Uncommon early-onset neuropathy in diabetic patients. *J Neurol* 245:61-68.

Schreiber O, Schneiderat P, Kress W, Rautenstrauss B, Senderek J, Schoser B, Walter MC (2013) Facioscapulohumeral muscular dystrophy and Charcot-Marie-Tooth neuropathy 1A-evidence for "double trouble" overlapping syndromes. *BMC Med Genet* 14:92.

Sheth S, Francies K, Siskind CE, Feely SME, Lewis RA, Shy ME (2008) Diabetes mellitus exacerbates motor and sensory impairment in CMT1A. *J Peripher Nerv Syst* 13:299-304.

Sima AA (2006) Pathological mechanisms involved in diabetic neuropathy: can we slow the process? *Curr Opin Investig Drugs* 7:324-337.

Thomas PK, Marques W, Davis MB, Sweeney MG, King RH, Bradley JL, Muddle JR, Tyson J, Malcolm S, Harding AE (1997) The phenotypic manifestations of chromosome 17p11.2 duplication. *Brain* 120:465-478.

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