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CASE REPORT

A case report of type 1 diabetes mellitus coexistent with Charcot–Marie–Tooth type 1A and a literature review

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Abstract

Introduction Charcot–Marie–Tooth disease (CMTD) is a common group of single-gene hereditary neuropathy characterized by chronic progressive exacerbation of distal limb weakness, sensory abnormalities, and nerve conduction dysfunction. It can be grouped into various subtypes based on the median nerve motor conduction velocity (MNCV) and gene mapping. CMTD1A is the most common subtype, accounting for > 50% of all subtypes, caused by the duplication of the peripheral myelin protein 22 (PMP22) gene on chromosome 17. Diabetes mellitus is a common metabolic disorder that frequently causes predominant sensory neuropathy. Diabetes with CMTD is not commonly reported. Especially diabetes type 1 (T1D) with CMTD1A has not been reported so far. This study reports a case of T1D with CMTD1A diagnosed by a gene test.

Results Upon the clinical manifestations, physical examination, EMG and genetic testing results, we diagnosed the patient as T1D with CMTD1A, and the related literatures were reviewed.

Conclusion It is not yet clear whether there is a genetic association between the CMTD and diabetes, the genes causing CMTD are perhaps related to T1D and T2D genes. When CMTD and diabetes coexist, the resulting neuropathy is more severe than that observed with either condition alone. We recommend that such patients should strictly control their blood-glucose level to slow down the progression of the disease.

Keywords Charcot–Marie–Tooth disease · Diabetes · PMP22 gene · Diabetes type 1

Introduction

Charcot–Marie–Tooth disease (CMTD), also known as hereditary motor sensory neuropathy, is a common group of single-gene hereditary neuropathy characterized by chronic progressive exacerbation of distal limb weakness, sensory abnormalities, and nerve conduction dysfunction. It has an incidence rate of approximately 1 in 2500. The majority of CMTD cases are autosomal dominant inheritance, although a few instances of autosomal recessive and linkage inheritance have been reported. To date, more than 80 related disease-causing genes responsible for CMTD have been identified [1]. Based on the median nerve motor conduction velocity (MNCV), it can be divided into CMTD1 (demyelinating type; MNCV < 38 m/s), CMTD2 (axonal type; MNCV ≥ 38 m/s), and intermediate type. According to gene mapping, it can be further divided into individual subtypes: CMTD1 (1A, 1B, 1C, 1D, and 1E), CMTD2, CMTD3\CMTDX, and CMTD4. The clinical phenotypes of different subtypes of CMTD are highly heterogeneous. Diabetes can frequently cause predominantly sensory neuropathy. When CMTD and diabetes coexist, the resulting neuropathy is more severe than that observed with either condition alone. Here, we report a case of T1D with CMTD1A diagnosed by a gene test to improve our understanding of this disease.

Case report

A 27-year-old male patient was admitted to our hospital on September 22, 2021. Three years before admission, the patient was hospitalized because of diabetic ketoacidosis

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(DKA) and T1D (the fasting C-peptide and 2-h C-peptide levels at that time were below the detection limit, and the anti-islet cell antibody and anti-glutamate decarboxylase antibody were negative). After discharge, the patient was given long-term subcutaneous injections of insulin lispro and insulin glargine to control the blood glucose. Three months prior to admission, the patient had no obvious cause of numbness and pain in both lower extremities. More than 1 month ago, however, numbness of the distal ends of the upper limbs and weakness of both lower limbs began to gradually develop, accompanied by symmetrical atrophy of the distal muscles of the lower limbs and difficulty walking, which affected his daily life activities and eventually made him unable to stand and walk alone. The patient had a negative family history of diabetes and a negative family history of a similar disease.

The patient with clear consciousness and normal intelligence was found to exhibit a cross-threshold gait, unstable walking, thin body, normal gonadal development, and no deafness. He had typical arched feet, drooping feet, symmetrical muscle atrophy of both lower extremities (Fig. 1). The distal muscle strength of both upper limbs was grade 4, while that of both lower extremities was grade 1. The proximal muscle strength of both lower extremities was grade 4. His deep tendon reflexes were weakened. The perception of pain, touch, pressure, and position were diminished in both the hands and below the knee joints. Babinski sign and Gonda sign were negative.

Further evaluation was performed; the cranial MRI and cardiac ultrasound were normal; and pancreatic and kidney ultrasound were normal (Table 1). Electromyography demonstrated the peripheral neurogenic damage of the limbs and the involvement of motor and sensory nerves. The latent period of bilateral median, bilateral ulnar, and bilateral radial motor nerves was prolonged; the wave amplitude was severely reduced; and the conduction velocity significantly slowed down (the conduction velocities of the right median, left median, right ulnar, left ulnar, right radial, and left radial nerves were 11.6, 12.2, 14.5, 14.5, 10.7, and 16.7 m/s, respectively).

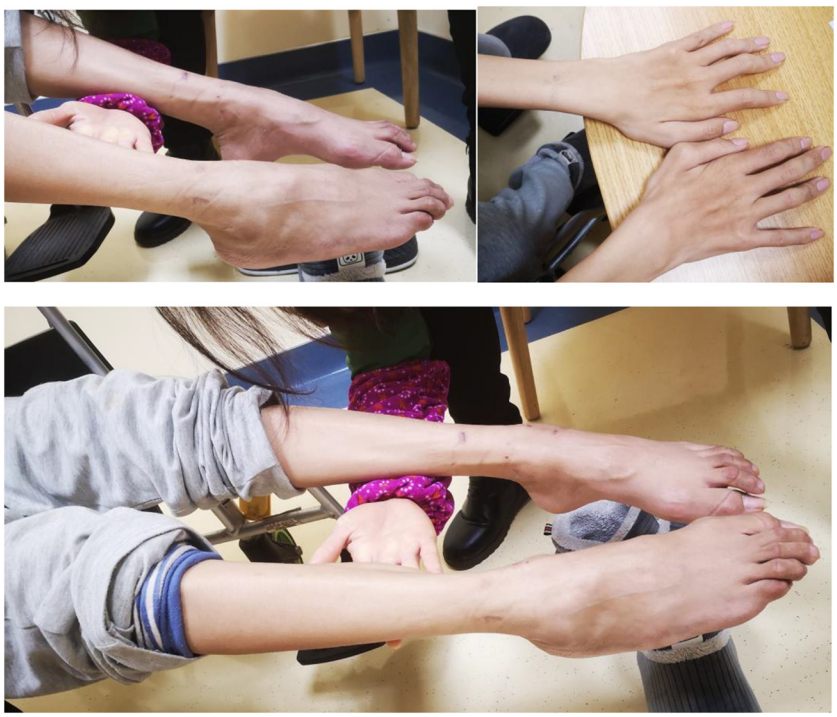

Fig. 1 The patient had typical arched feet, drooping feet, symmetrical muscle atrophy of both lower extremities, and atrophy of the thenar and palmar muscles in both hands

Table 1 Laboratory results of the patient

HbA1c	Fasting C-peptide (0.1–1.24 nmol/L)	Fasting blood-glucose (mmol/L)	Insulin autoantibody	Tyrosine phosphatase antibody	Zinc transporter 8 antibody
8.7%	< 0.01	4.75	Negative	Negative	Negative
Anti-glutamate decarboxylase antibody	Anti-islet cell antibody	Serum potassium	Creatine kinase	Vitamin B12	Thyroid function
Negative	Negative	Normal	Normal	Normal	Normal

The patient was young at the onset of the disease syndrome, with typical bilateral arched feet; the distal portions of both lower and upper limbs significantly atrophied; these were inconsistent with diabetic peripheral neuropathy (DPN). Next, whole-exon testing was performed by using the next-generation gene detection method. The currently known single-gene diabetes-related pathogenic genes were not detected in the patient; however, a 339.25-kb haploid repeat mutation was detected at chr17: 15,133,095–15,472,344 (Fig. 2). This region contains the *PMP22* gene; one haploid repeat variation of the *PMP22* gene was considered. The *PMP22* gene haploduplication had also been found in his father (Fig. 3). The copy number of the *PMP22* gene in the mother and sister of the patient was normal. The *GJB1* and *MPZ* genes were simultaneously tested. The copy numbers of these two genes were normal in the patient, as well as those of his parents and sister.

Discussion

The patient was a young man with a 3-year history of diabetes. He was diagnosed with diabetes at the age of 24, with DKA onset, without any family history of diabetes. The C-peptide level at the first visit was below the detection limit, with poor islet function. Combined with the results of genetic testing, the currently known monogenic diabetes can be ruled out. The patient tested negative for islet autoantibodies, which could be considered as T1D with negative islet autoantibodies.

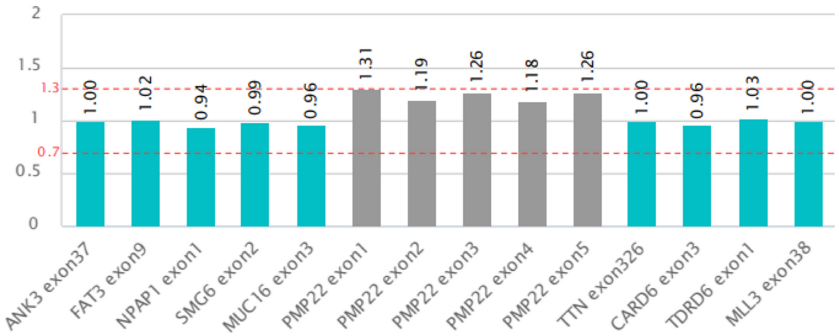

Fig. 2 Test results of the patient.PMP22 EXON: 1–5 haplotypes

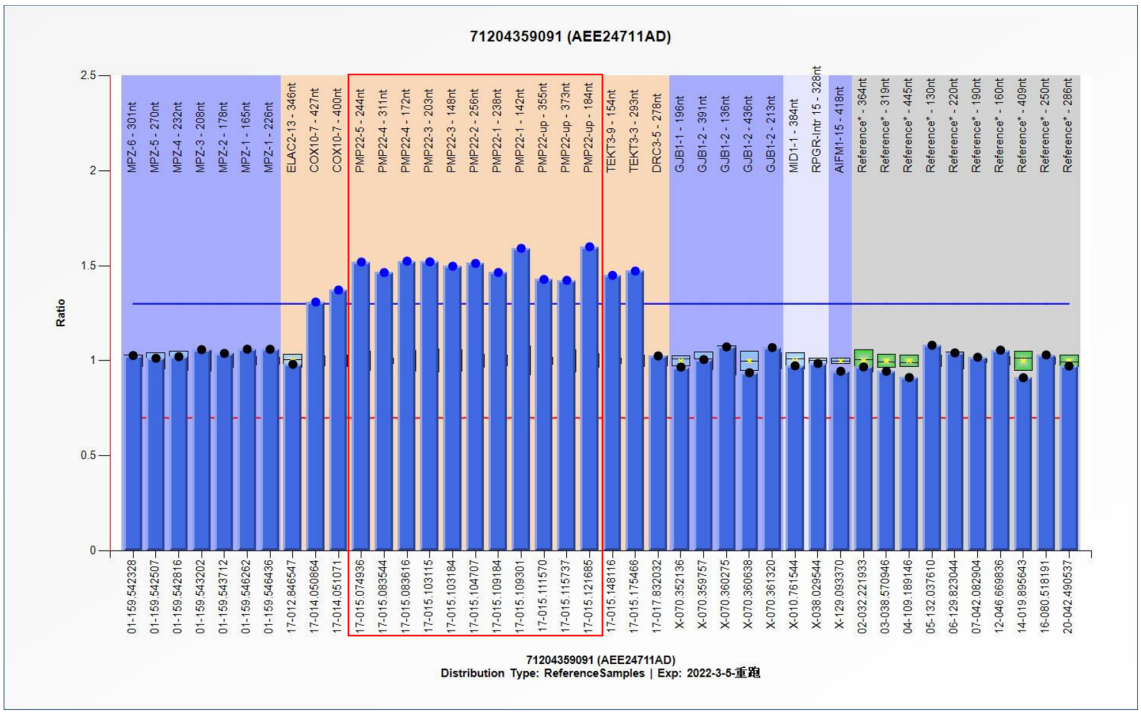

Fig. 3 Test results of the patient's father

The patient visited our hospital mainly due to chronic progressive and symmetrical distal muscle weakness and atrophy since the past 3 months. His lower extremities were heavier than his upper extremities. Bipedal drooping and arched feet were also noted. His EMG showed peripheral neurogenic damage and the involvement of motor and sensory nerves in the extremities. The conduction velocity of the bilateral median, bilateral ulnar, and bilateral radial motor nerves became significantly low, with the most significant changes being observed in demyelination. While DPN often has a long course, and the electrophysiological changes observed in the EMG conform to the characteristics of length-dependent axonal peripheral neuropathy [2], that is, the amplitude of the sensory nerve action potential reduced; the conduction velocity was relatively normal. Based on the clinical manifestations, physical examination, EMG results, and genetic testing results, the neuropathy of the patient was diagnosed as CMTD1A.

CMTD is also known as hereditary motor sensory neuropathy; it often develops in children or adolescents (before the age of 20). CMTD1A is the most common subtype, accounting for > 50% of all subtypes [3], characterized by MNCV < 38 m/s. It is caused by *PMP22* gene duplication mutations. Approximately 55–70% of the patients with CMT1A experience pain, which is mainly confined to the foot [4]. CMTD1A is an autosomal dominant genetic disorder. The earliest pedigree studies conducted on the condition showed that 89% of this gene originated from the paternal line [5]. In the father of this patient also, *PMP22* gene haploduplication was detected, which is consistent with previous studies on the topic. The *PMP22* gene is located on chromosome 17p11.2 and encodes peripheral myelin sheath protein 22 (PMP22). The PMP22 protein is mainly expressed in Schwann cells and only appears in the peripheral nervous system [6].

This patient had concurrent T1D, a very rare condition. A search of relevant literature showed some reports on diabetes with CMTD, including family reports and sporadic reports. We retrieved 5 articles of diabetes with CMTD based on pedigree reports [7–11]. Of these, 3 families were identified to have a history of T2D along with CMTD1A [8, 9, 11], caused by repeated mutations in the *PMP22* gene. In 2001, Çelik et al. reported 6 people with CMTD1A in a pedigree report, 5 of which had T2D. In 2006, Koç et al. reported that 6 out of 28 CMTD1A patients in a family from Turkey had concurrent T2D. Sun et al. reported that 7 individuals in a family had *PMP22* gene duplication mutations, of which 4 had clinical manifestations of polyneuropathy and were diagnosed with CMTD1A. These 4 patients also had T2D. In a pedigree reported by Yu et al. in Shanghai, China, 6 patients were diagnosed with CMTD1, 4 of which had T2D. Genetic testing of this family did not find *PMP22* gene mutation, because CMT has highly heterogeneous clinical phenotypes. They designated this type of demyelinating CMTD with diabetes as a new specific clinical subtype of CMTD, called "Yu–Xie syndrome (YXS)" [10]. In addition to pedigree reports, many single cases have also been reported. For example, Yan et al. in Sichuan, China, reported a CMTD1A patient with T2D and recurrent foot ulcer [12]. This case report is consistent with that by Win et al. [13]. Japanese scholars reported a 44-year-old woman, who had CMTD along with diabetes and severe bilateral phrenic nerve palsy [14].

CMTD with T2D is the most commonly reported condition in the literature, while CMTD with T1D is very rarely reported. The onset of CMTD with T2D mostly occurs after the age of 35–40 years. Three cases (a 41-year-old man, a 26-year-old man, and a 61-year-old woman) of insulin-dependent diabetes with CMTD1A had been reported in a retrospective study conducted by American scholars, but the author did not clarify the type of diabetes mellitus; it was not known whether it was type 1 diabetes. In these cases, the clinical manifestations of CMTD occurred after the diagnosis of diabetes [15]. In addition, in 2017, Argentinean scholars identified a 30-year-old woman with suspected T1D. The patient developed progressively worsening distal limb weakness and paraesthesia at the age of 29 and was eventually diagnosed with CMTD [16]; however, they did not classify this disease and did not perform any genetic testing.

Currently, it is not clear whether there is a genetic association between CMTD and diabetes. CMTD is a monogenic hereditary neuropathy, while T1D and T2D are polygenic diseases. Interestingly, there is no report on monogenic diabetes with CMTD, indicating that the gene mutation involved is not particularly continuous with the known cases of monogenic diabetes. Although it is unclear at present, the genes causing CMTD are perhaps related to T1D and T2D genes. Some American scholars have proposed the possibility of *Mfn2* gene mutations being associated with the onset of CMT2A along with T2D [15].

Whether diabetes can induce CMTD is still unclear. To date, it has been reported that diabetes can aggravate the pathological damage in CMTD1A patients, including increased myelin fiber loss, abnormal axonal–myelin sheath interaction, and damaged nerve regeneration [17]. High glucose levels in CMTD1A patients may change the severity of neuropathy, leading to heterogeneous phenotypes. CMTD patients with diabetes show a more severe damage of motor and sensory nerves; this nerve damage is more significant in insulin-dependent diabetes patients than it is in non-IDDM patients [15, 18]. In the present case, his sensory and motor nerves were severely damaged; he had pain in the skin of his lower extremities and was unable to stand and walk alone. Therefore, we recommend that such patients should strictly control their blood-glucose level to slow down the progression of the disease.

CMTD generally does not affect life expectancy. However, it severely affects the quality of life and may even cause disability. So far, this condition is mainly managed through physiotherapy, rehabilitation, and symptomatic treatment. Clarifying the genetic diagnosis and classification of CMT can provide a basis for disease prognosis and genetic counseling. When specific gene therapies and drugs for different genotypes are developed, relevant information and appropriate treatment guidance can be provided to patients in a timely manner for the corresponding CMTD condition. We believe that the development of a suitable molecular-level therapy and future gene modification will benefit CMTD patients.

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