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A case report of hereditary neuropathy with liability to pressure palsies accompanied by type 2 diabetes mellitus and psoriasis

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Abstract

Rationale: Hereditary neuropathy with liability to pressure palsy (HNPP) is an episodic, multifocal neuropathy, with a typical clinical presentation of recurrent transient pressure palsies, which is induced by a PMP22 deletion. Another neuropathy caused by a PMP22 duplication is Charcot-Marie-Tooth disease type 1A (CMT1A). PMP22 is a gene coding a protein called peripheral myelin protein 22 (PMP22), which plays an essential role in the formation and maintenance of compact myelin. Coexistence of type 2 diabetes mellitus (T2DM) and CMT1A has been reported in many work, however HNPP patients with T2DM are rare, and comorbidity of HNPP and psoriasis has not been reported previously. Electrophysiological features of HNPP has been found progressing with aging. Patient concerns: Here we present a 20-year-old man who exhibited lower extremity weakness and foot drop as the initial manifestation.

Diagnoses: HNPP was diagnosed on the basis of clinical features, positive sural nerve biopsy findings, and genetic testing results. Moreover, physical examination, blood/urine glucose test, and diabetes-related autoantibodies investigations demonstrated that he had psoriasis and T2DM. The electrophysiological manifestations revealed profound demyelinating injuries and axonal injuries in distal peripheral nerves and facial nerves, which were more severe than general HNPP cases.

Interventions: The young patient was treated with continuous subcutaneous insulin infusion and blood glucose monitoring, and then transferred to oral acarbose therapy. The psoriatic lesions were treated with calcipotriol ointment.

Outcomes: In the follow-up, the right leg weakness was alleviated, and his gait was improved.

Lessons: The findings indicate that diabetes mellitus may have an impact on the severity of HNPP. Physicians should consider that worsening of symptoms might result from newly diagnosed diabetes mellitus while treating patients with HNPP.

Abbreviations: CMT1A = Charcot–Marie–Tooth disease type 1A, HNPP = hereditary neuropathy with liability to pressure palsy, PMP22 = peripheral myelin protein 22, T2DM = type 2 diabetes mellitus.

Keywords: electrophysiological examination, hereditary neuropathy with liability to pressure palsies, psoriasis, sural nerve biopsy, type 2 diabetes mellitus

1. Introduction

Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant disorder characterized by recurrent transient nerve palsies associated with compression at the typical anatomic sites of potential nerve entrapment.[1,2] Tomacula, which represent focal thickening of the myelin sheath, characteristically are seen in both sensory and motor nerves in HNPP. This disorder is usually associated with a 1.5-Mb deletion of locus 17p11.2, which contains the gene for peripheral myelin protein 22 (*PMP22*).[3] In addition, a duplication on chromosome 17p11.2-p12 containing the *PMP22* gene can cause Charcot–Marie–Tooth (CMT) disease type 1A (CMT1A), which have a typical phenotype characterized by onset in childhood, distal weakness, sensory loss, foot deformities, and absent reflexes.[4,5] CMT1A is a common subtype of CMT disease. CMT is also known as hereditary motor and sensory neuropathy, which was named after Dr Charcot, Marie, and Tooth. It encompasses a clinically and genetically heterogeneous group of disorders characterized by predominantly distal muscle weakness and atrophy, and sensory loss.[6] Literature gives calculated prevalences of CMT1A in the range of 1:3800 to 1:12,500.[6] On the other hand, the prevalence of HNPP is not well known. Prevalences of 7.3 per 100,000 to 16 per 100,000 are reported.[7,8]

The age of onset of CMT1A is mainly in the first 2 decades and most frequently in the first 10 years of life, while age at onset of

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JL and BN have contributed equally to the article.

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first HNPP symptoms is mostly in the second or third decade, with a large range from birth to the eighth decade.[6] It is reported that there are factors that may influence CMT1A and HNPP, although the detailed factors and mechanisms are not clear. Certain medications such as vincristine have been shown to exacerbate the neuropathy in CMT and HNPP.[9,10] Hypothyroidism might be a risk factor for the worsening of neuropathies of HNPP.[11] Moreover, several studies showed that diabetes mellitus and obesity contributed to increasing the phenotype severity in patients with CMT1A.[12,13] Type 2 diabetes mellitus (T2DM) is a common metabolic disease that is characterized by hyperglycemia and/or chronic vascular complications. In most cases, onset occurs after the third or fourth decade.[14] Diabetic neuropathy is the most common and troublesome complication of diabetes with a prevalence of 50% to 60%.[15] Coexistence of CMT1A and diabetes mellitus has been reported previously in many work,[14–17] while comorbidity of HNPP and T2DM is rarely reported.[18,19] Although diabetes mellitus has shown a tendency of worsening CMT1A conditions, whether diabetes mellitus exacerbates HNPP remains unknown.

Psoriasis is a common chronic immune-mediated inflammatory disorder affecting the skin, nails, and joints in both children and adults.[20] The concomitant occurrence of peripheral neuropathy has been reported in several psoriatic patients with this possibly neuroimmunologic skin disorder; however, there is no sufficient evidence to demonstrate an association of psoriasis with peripheral large fiber neuropathy.[21]

Here we report a rare case of HNPP with T2DM and psoriasis, whose electrophysiological symptoms were more significant than general HNPP patients.

2. Patient information

A 20-year-old male patient was admitted to our neurology department in February 2015 with intermittent numbness and weakness of the limbs that had lasted for more than 10 years, and right leg weakness over 6 months.

Ten years ago, he developed right lower extremity weakness and foot drop while walking. The patient was given treatment of traditional Chinese medicine at a local hospital which had no obvious effect, and then the symptoms were slowly alleviated without further treatment. And later, he noticed many instances of numbness in his both upper extremities while holding his arms long time on the table or head on his arms, which could last for several days. Numbness could also occur in the both lower extremities while lying on the side. In August 2014, right leg weakness and numbness occurred again without apparent cause. The right leg weakness aggravated in the next months, which caused him to fall down the stairs once in December 2014. He was diagnosed with peripheral neuropathy in his local hospital and was given therapy of Vitamin B1, cobamamide, and traditional Chinese medicine. His symptoms were slightly improved but not completely alleviated, and then he was referred to our department.

2.1. Clinical findings

In neurological examination, there was weakness (2/5) in his foot back muscle groups of right lower extremity. The other muscle groups were normal (5/5). Tendon reflexes were decreased in all the extremities. Hypalgesia in his right lateral leg and 1.5 left ulnaral fingers were noted. Bilateral finger-to-nose test and heel–knee–shin test were normal. The Babinski sign and meningeal irritation sign were negative.

Family history investigation revealed that the patient's 47-year-old father had a medical history of recurrent pressure induced numbness in the extremities. Decreased tendon reflexes were noted in the father's extremities.

2.2. Diagnostic assessment

In laboratory investigations, the complete blood count, stool routine examination, blood biochemical test, liver function test, blood lipid test, erythrocyte sedimentation rate, and coagulation function were normal. Immunologic laboratory tests found antinuclear antibodies and antiganglioside antibodies were negative, as well as serum immunofixation test and Bence–Jones protein urine test.

Medical history investigation found that the polyuria polydipsia symptoms had occurred since 2 years ago, and the patient had lost 15-kg weight. Further investigation showed that his fasting blood glucose level was 14.59 mmol/L. Postprandial blood glucose level was 38.74 mmol/L. Glycosylated hemoglobin level was 14.0% (normal range: 4.5%–6.0%). Glucose urine test was ++++. Diabetes-related autoantibodies test found that insulinoma-associated antigen-2, glutamic acid decarboxylase autoantibodies, islet cell cytoplasmic autoantibodies, and insulin autoantibodies were all negative.

Physical examination revealed red papules covered with scales on his scalp, bilateral anterior legs, and right foot back. Auspitz sign was positive.

The patient and his father were examined with electrophysiological examinations, and the findings are shown in Table 1. Motor and sensory conduction studies of nerves of the upper and lower extremities disclosed slowing of motor and sensory conduction velocities (CVs) and prolonged distal motor latencies in all nerves, markedly reduced compound muscle action potential (CMAP) amplitudes, and reduced F-wave CV in the young patient, which were much more serious than in his father. Electromyography revealed profound demyelinating injuries and secondary axonal injuries in distal peripheral nerves and parts that were easy to be compressed, involving the facial and extremity nerves, especially in the right lower extremity.

Histopathological examination of a biopsy from the patient's sural nerve showed sausage-like enlargements of the myelin sheath (tomaculae) and thinly remyelinated internodes (Fig. 1A). Transverse Epon sections demonstrated marked variation in myelin thickness and several large hypermyelinated axons (Fig. 1B and C). Electron microscopy confirmed that fiber enlargement was due to a markedly thickened myelin sheath (Fig. 1D).

Genetic testing by multiplex ligation-dependent probe amplification demonstrated PMP22 heterozygous deletions in the patient and his father.

The patient was diagnosed as HNPP, with T2DM and psoriasis.

2.3. Therapeutic intervention and outcome

The young patient was treated with continuous subcutaneous insulin infusion and blood glucose monitoring and then transferred to oral acarbose therapy. The psoriatic lesions were treated with calcipotriol ointment. He was discharged on oral therapy of 200 mg/d acarbose, 30 mg/d dibazol, 30 mg/d coenzyme Q10, 30 mg/d vitamin B6, 30 mg/d vitamin B1, and 1500 μg/d mecobalamine. Blood glucose monitoring was recommended. In the follow-up, the right leg weakness was alleviated, and his gait was improved.

Table 1

Results of the nerve conduction study.

Nerve	Normal values	Patient		Patient's father	
		Left	Right	Left	Right
Motor neurography					
Facial nerve					
Distal motor latency	3.0 ± 0.6 ms	4.1*	4.0*	2.5	2.5
Median nerve					
Distal motor latency (wrist)	3.63 ± 0.56 ms	8.5*	8.7*	9.0*	8.8*
CMAP (wrist)	>6 mV	8.9	8.0	10.5	10.9
CMAP (antecubital fossa)	>6 mV	8.8	7.9	9.0	10.3
MNCV (wrist-antecubital fossa)	>50 m/s	45.5*	43.7*	59.3	59.7
F-wave CV	>55 m/s	50.9*		55.6	
Ulnar nerve					
Distal motor latency (wrist)	3.07 ± 0.6 ms	5.3*	5.5*	3.5	3.3
CMAP (wrist)	>7 mV	6.1*	6.3*	12.9	11.8
CMAP (below the elbow)	>7 mV	6.1*	6.2*	10.0	10.2
CMAP (above the elbow)	>6 mV	5.6*	5.6*	10.1	10.3
MNCV (wrist-below the elbow)	>50 m/s	40.0*	44.2*	48.0*	48.3*
MNCV (across the elbow)	>50 m/s	16.7*	24.3*	28.6*	29.5*
Peroneal nerve					
Distal motor latency (ankle)	4.5 ± 0.7 ms	14.4*	9.2*	7.4*	6.8*
CMAP (below the fibular head)	>3 mV	8.2	2.3*	4.8	5
CMAP (above the fibular head)	>3 mV	7.6	0.9*	4.6	5.2
CMAP (acrotarsium)	>6 mV	8.1	4.2*	6.0	5.9
MNCV (ankle-fibular head)	>40 m/s	30.7*	27.0*	36.2*	35.0*
MNCV (across fibular)	>40 m/s	29.2*	25.0*	34.2*	33.3*
Tibial nerve					
Distal motor latency (ankle)	4.82 ± 0.95 ms	11.9*	12.0*	6.7*	6.5*
CMAP (popliteal fossa)	>6 mV	10.2	2.2*	8.9	9.3
CMAP (medial malleolus)	>6 mV	14.4	2.3*	10.3	11.2
MNCV (popliteal fossa-medial malleolus)	>40 m/s	32.5*	29.0*	44.2	43.9
Sensory neurography					
SNCV					
Median nerve	>50 m/s	NR*	29.2*	20.6*	25.6*
Ulnar nerve	>50 m/s	NR*	NR*	37.8*	36.9*
Peroneal nerve	>43 m/s	NR*	NR*	25.8*	27.6*
Sural nerve	>43 m/s	NR*	NR*	34.2*	35.3*
Tibial nerve	>43 m/s	NR*	NR*	36.8*	37.6*

CMAP = compound muscle action potential, CV = conduction velocity, MNCV = motor nerve conduction velocity, SNCV = sensory nerve conduction velocity, NR = no response.
* Abnormal values.

3. Discussion

This patient, with pathological and genetic confirmation of HNPP, presented with numbness and weakness secondary to compression. Further clinical and electrophysiological investigations revealed widespread neuropathic dysfunction, including bilateral motor and sensory nerves. Immunological, infectious, and neurotoxic investigations were unrevealing. Other diagnostic consideration, such as spontaneous or hereditary neuralgic amyotrophy, was eliminated by the widespread clinical distribution, sensory loss, and genetic findings.

This patient's manifestations of HNPP are unique in coexistence of T2DM and psoriasis. Moreover, his electrophysiological symptoms were much more serious than his father. The electrophysiological manifestations of this young patient showed diffuse and extensive abnormalities of peripheral nerves. Both motor and sensory nerves were involved, especially the sensory nerves, as sensory nerve conduction velocitys were not able to be detected except the median nerve. The motor nerve manifestations were mainly increased distal conduction latencies and decreased ulnar nerve CVs through the carpal tunnel. His facial nerve was also involved, and the CMAPs of the right peroneal and tibial nerves decreased significantly suggesting that secondary axonal damage occurred in his right lower extremity leading to his clinical symptoms.

A previous work reported that irreversible axonal damage of motor nerves in HNPP patients was progressing with aging.[3] A reduction in CMAP with increasing age at examination was observed in the median, ulnar, and peroneal nerves. However, in our case the damage of motor nerves of the young patient was more severe than his father and general HNPP cases. Moreover, the clinical features of HNPP are usually mild, and a previous report found that 40% of cases with the PMP22 deletion were unaware of their illness.[22] A possible explanation may be that his disease severity worsened due to diabetes mellitus. There have been reports of HNPP worsened by some neurotoxic factors and diseases. The anticancer drug, vincristine, which is known to potentially cause polyneuropathy as a side effect, caused severe neuropathy presenting as tetraparesis in a patient with HNPP.[10] There is also a rare case of HNPP emerging after hypothyroidism, indicating hypothyroidism might increase the risk of developing peripheral neuropathy in HNPP patients.[11] As comorbidity of HNPP and diabetes mellitus is rare, there has been no evidence that diabetes mellitus exacerbates nerve injury in HNPP. Nevertheless, previous studies in patients with CMT1A and

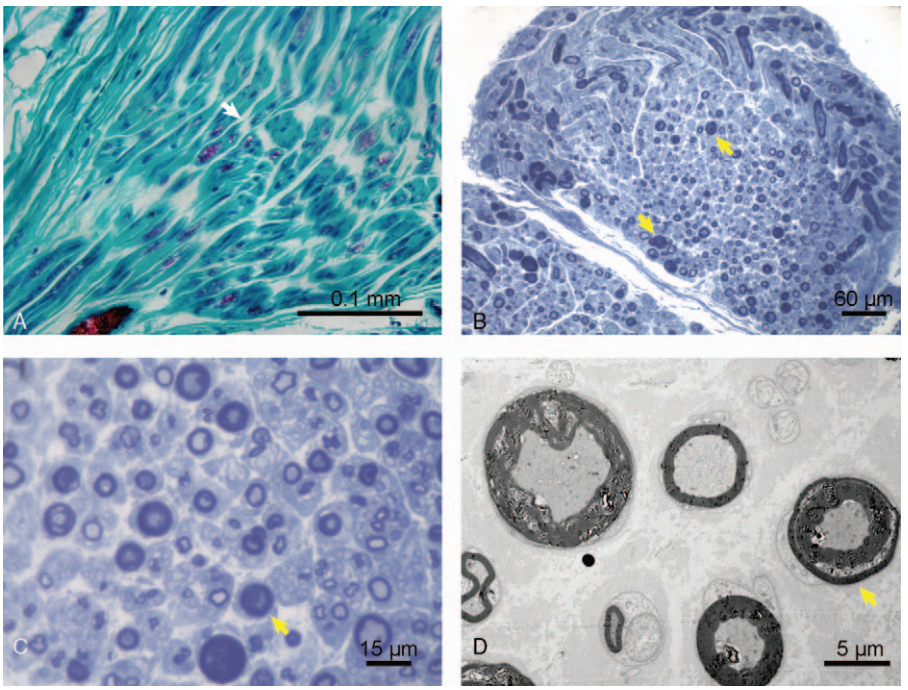

Figure 1. Sural nerve biopsy revealed myelin-related neuropathy. (A) Gomori trichrome stain showing focal sausage-shaped enlargements of the myelin sheath (tomaculae) and thinly remyelinated internodes, indicated by a white arrow. (B) and (C) Epon section of sural nerve demonstrating marked variation in myelin thickness and several large hypermyelinated axons, indicated by yellow arrows. (B) Low magnification, (C) high magnification). (D) Electron microscopy showing markedly thickened myelin sheathes, indicated by the yellow arrow.

diabetes mellitus revealed more severe disabilities, more pronounced motor impairment, and more remarkable depletion of myelinated fibers than CMT1A controls, suggesting that diabetes mellitus could exacerbate axonal loss.[23] A retrospective analysis found that the neuropathy is more severe in diabetic patients with CMT1A than in those without diabetes and also suggested that more severe diabetes, requiring insulin, caused the most severe neuropathy. However, the CMT neuropathy score was also higher in most of the well controlled noninsulin-dependent diabetic patients compared with patients without diabetes. It is surprising that pronounced motor symptoms and signs were found in patients with both diabetes and CMT1A because diabetes causes primarily a sensory neuropathy.[12] A study of a large Chinese family with CMT1 and concurrent T2DM found that the onset age of patients with CMT and concurrent T2DM was later, which is different from most patients with simple CMT1, which implies that the incidence of the concurrent symptom may have its own intrinsic reasons. Furthermore, the fact that only some of the CMT patients in the family experienced concurrent T2DM indicates that T2DM is associated with CMT, not vice versa.[24] Sural nerve biopsies of CMT1A with diabetes mellitus found a very severe neuronal type of neuropathy: nearly all nerve fibers are lost, no axonal regeneration is seen, and no signs of demyelination or remyelination are found.[25] A retrospective study evaluated a large population of patients having CMT1A with different comorbidities reported that the presence of comorbidities in CMT1A patients can exacerbate their phenotype, including diabetes mellitus, obesity, hypothyroidism, and exposure to toxic substances. All comorbidity groups show a worse CMT neuropathy score compared to control group, though disability is significantly higher only in diabetic patients. And this study reported a tendency toward worsening of the clinical and neurophysiological manifestations in patients with CMT1A and diabetes mellitus.[13]

The underlying mechanisms of diabetes mellitus affecting CMT1A remain unknown, as well as HNPP. There are hypotheses that diabetes exacerbates neuromuscular junction transmission defects, aggravates impairments of axonal transport and function of mitochondria, and reduces mitofusin 2 level that is a pathogenic gene of CMT1A.[12] Studies have shown that the serum insulin-like growth factor level and its binding protein 2 are elevated in patients with CMT1A.[24] Previous studies demonstrated that diabetes mellitus compromised peripheral nerve regeneration. Several possible mechanisms of regenerative failure were considered, including microangiopathy at the peripheral nerve injury site, defective inflammatory repair, abnormalities in the retrograde cell body reaction to injury, impairments in the reparative activities of Schwann cells, and failure of growth factor support.[23] These hypotheses need evidence in future studies.

Although cases of HNPP patients with T2DM are rarely reported,[18,19] coexistence of CMT1A and diabetes mellitus is relatively common.[14–17] Considering that the genetic pathogenesis of HNPP and CMT1A are deletion and duplication of *PMP22* respectively, *PMP22* may play a role in the pathogenesis of diabetes mellitus, which needs evidence of molecular biology. As genome-wide association studies (GWAS) have identified scores of common variants associated with type 2 diabetes,[26] we retrieved *PMP22* and genetic association studies at GWAS Central (www.gwascentral.org)[27] but found no significant relevance of single nucleotide polymorphisms (SNPs) of *PMP22* to glycemic traits included in the database (Supplemental table 1, http://links.lww.com/MD/B700). The

GWAS results of *PMP22* and psoriasis were the same. On the other hand, considering that GWAS bases on SNPs, while HNPP/CMT1A is deletion/duplication of *PMP22*, there may still be some kind of association between *PMP22* and T2DM.

Up to now, there has been no evidence to demonstrate an association of psoriasis with peripheral large fiber neuropathy and HNPP. However, a twin study reported that psoriasis, T2DM, and obesity are strongly associated in adults after taking key confounding factors, indicating a common genetic etiology for psoriasis and obesity.[28] And cohort studies and meta-analyses support the association between psoriasis and T2DM.[29–32] Most of the genetic studies related to T2DM show that diabetes mellitus does not result from unique major gene variations but conversely develops in multiple gene loci like a polygenetic disorder.[14] Perhaps psoriasis and T2DM have some pathogenic genes in common or linkage disequilibrium.

4. Conclusion

In this report, we present a rare case of comorbidity of HNPP, T2DM, and psoriasis. The concurrent presence of these 3 diseases in the patient makes him vulnerable to peripheral nerve injuries. This case indicates that diabetes mellitus has an impact on the severity of HNPP. Our report suggests that physicians should consider that worsening of symptoms might result from newly diagnosed diabetes mellitus while treating patients with HNPP. There may be genetic association between HNPP, diabetes mellitus, and psoriasis, which needs further investigations.

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