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Tibial neuropathy, a rare manifestation of hereditary neuropathy with liability to pressure palsy: A case report

Geke Zhu [a,1,2], Xiangtao Nie [a,1,2], Wenjing Qi [a], Yongbo Ma [a], Lei Hao [a,**], Xiuming Guo [a,*]

[a] Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China

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ABSTRACT

Hereditary neuropathy with liability to pressure palsy (HNPP) is characterized by acute, painless and recurrent mononeuropathies. Genetic testing shows PMP22 gene deletion of chromosome 17p11.2 can provide evidence for the diagnosis of HNPP. Reports on tibial neuropathy as the main manifestation of HNPP are very rare. We report a 14-year-old girl who was admitted to our hospital due to plantar foot numbness and plantar flexion weakness of her left foot. The patient had a history of lateral dorsal numbness and right foot drop when she was 3 years old. Clinical symptoms, and neurological examination demonstrated tibial neuropathy. Electromyography showed extensive peripheral nerve, including median nerve, ulnar nerve, tibial nerve and peroneal nerve, were involved. The diagnosis of HNPP was confirmed by genetic testing which disclosed a deletion of PMP22 gene. She was completely asymptomatic in one month after neurotrophic drug treatments.

1. Introduction

Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant disorder associated with the deletion on chromosome 17p11.2 which bears the peripheral myelin protein 22 (PMP22) gene [1,2]. The pathological feature of HNPP is focal thickenings of the myelin sheath, also called tomacula [3]. Recently, it has been found that as an important factor in the differentiation, proliferation and apoptosis of Schwann cells, PMP22 dosage affects nonmyelinating as well as myelinating Schwann cells [4]. HNPP is estimated to affect 1–16 people per 100,000, but it might be underestimated due to the inexistence of epidemiological study and the mild symptoms of HNPP [5]. This neuropathy is characterized by acute, painless and recurrent sensory and motor mononeuropathies those are secondary to minor trauma or compression, which are most likely to occur at sites subjected to compression, such as wrist, knee, elbow and shoulder. The peroneal nerve and ulnar nerve are most commonly affected [6,7]. The disease is easily misdiagnosed or missed when the damage occurs in other nerves or when the patient has no family history. While existing literature has reported some HNPP cases of peripheral nerve damage, no previous reports have documented HNPP with tibial neuropathy as the main manifestation. Here we report a case of a 14-year-old girl with HNPP whose clinical manifestation was mainly tibial nerve damage, and her

* Corresponding author. Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China
** Corresponding author. Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China
E-mail addresses: haolei1102@163.com (L. Hao), xmguo813@163.com (X. Guo).
[1] These authors contributed equally to this work.
[2] **Present address**: The First Affiliated Hospital of Chongqing Medical University, 1 Yixue Yuan Road, Chongqing, P. R. China.

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family members were asymptomatic.

2. Case report

A 14-year-old girl complained of numbness of left plantar foot awaking in the morning, and exhibited partial loss of ankle active range of motion for plantar flexion. Neurological examination revealed motor abnormality in her left leg. Plantar flexion of the left foot was limited. On the Medical Research Council (MRC) Scale for grading muscle strength in her left leg, she scored foot plantar flexion 3/5 and foot dorsiflexion 5/5. The left ankle reflex was absent. She had hypoaesthesia in the left anterior part of the sole. There was no foot deformity. The remaining physical examinations were normal. An extensive laboratory testing was performed (white blood cells and platelets count, sedimentation velocity, C-reactive protein, liver and renal function, muscular enzymes, folic acid and vitamin B12, thyroid function, autoantibodies, Hepatitis B, HIV infection, syphilis, cerebrospinal fluid (CSF) routine and biochemistry) with normal results. Pelvic and chest CT scan was normal as well as magnetic resonance imaging of sacral plexus. Nerve conduction study (NCS) revealed decreased motor nerve conduction velocity (MNCV) of left tibial nerve and left peroneal nerve, slightly decreased MNCV of right median nerve and right ulnar nerve, and mild reduction in sensory nerve conduction velocity (SNCV) of left sural nerve, right median nerve and right ulnar nerve (Table 1). Unfortunately, due to her fear of pain, the needle EMG was not performed.

The girl was referred to outside hospital with numbness of the anterolateral aspect of the right calf and upper surface of the right foot and right foot drop after a cold when she was 3 years old. She had steppage gait and limitation of dorsiflexion of right foot. The remaining physical examinations were unremarkable. NCS revealed multifocal demyelinating anomalies with diminished sensory and motor conduction velocity in both upper and lower extremities (Table 2). MNCV of the right peroneal nerve decreased significantly, especially at 2.5 cm in the superior and inferior segment of the fibula head. The abnormality of the conduction of the peroneal nerve on the left was not as visible as that on the right. The distal motor latency (DML) of bilateral median nerves increased. In addition, the SNCV of bilateral median nerves decreased obviously and the sensory nerve conduction amplitude also showed a reduction. Needle EMG indicated neurogenic damage in bilateral tibialis anterior muscle and abductor digiti minimi. These symptoms were improved after symptomatic treatment in one month. She had no family history of neurological diseases. Her development was normal, and consciousness was clear.

Combined with clinical manifestations, past medical history and results of electrophysiological examinations, HNPP was considered, and the weakness of right lower limb after a cold at her age of 3 might be the first onset. Her genetic testing confirmed the diagnosis of HNPP showing PMP22 deletion of chromosome 17p11.2. Meanwhile, a gene detection was also performed on her parents, and the loss of heterozygosity was showed in her mother. Her parents are both asymptomatic. In addition, the DNA of her maternal uncle and male cousin also showed a 1.43mbDNA deletion of chromosome 17p12 and PMP22 gene was almost completely included. After admission, the girl was given vitamin B12 and mecobalamin to nourish the nerves, gabapentin capsules to relieve numbness and other symptomatic treatment. Four days later, she was discharged from the hospital. After one month, she completely recovered.

3. Discussion

HNPP, characterized by recurrent transient mononeuropathy, is an autosomal dominant disorder that affects the peripheral nerves

Table 1
Results of nerve conduction studies (2022.5).

Motor nerve conduction	Lat [ms]	Amp [mV]	CV [m/s]
Left Tibial			
Ankle-AHB	4.3 (< 4.8)	9.77 (> 6.0)	
Knee-Ankle	17.7	1.33 (> 6.0)	30.0 (> 45)
Left Peroneal			
Ankle-EDB	6.8 (< 5.6)	3.78 (> 2.4)	
Below Knee	16.9	2.8 (> 2.4)	31.2 (> 41.6)
Right Median			
Wrist-APB	3.6 (< 3.9)	6.94 (> 5.7)	
Elbow	9.2	4.89 (> 5.7)	40.7 (> 51)
Right Ulnar			
Wrist-ADM	3.0 (< 3.1)	6.97 (> 8.0)	
Elbow	7.9	5.03 (> 8.0)	45.5 (> 54)
Sensory nerve conduction	Lat [ms]	Amp [μV]	CV [m/s]
Left Sural			
Ankle-Foreleg	3.8 (< 4.2)	3.97 (> 1.2)	36.8 (> 46.7)
Right Median			
Digiti II-Wrist	3.4 (< 3.4)	13.77 (> 11.3)	38.2 (> 49.5)
Right Ulnar			
Digiti V-Wrist	2.2 (< 3.1)	22.08 (> 7.2)	44.6 (> 47.4)

Normal values refer to the reference values established by Peking Union Medical College Hospital.
Lat, latency; Amp, amplitude; CV, conduction velocity.
AHB, abductor hallucis brevis; EDB, extensor digitorum brevis.
APB, abductor pollicis brevis; ADM, abductor digiti minimi.

Table 2
Results of nerve conduction studies (2010.12).

Motor nerve conduction	Lat [ms]	Amp [mV]	CV [m/s]
Right Tibial			
Ankle-AHB	3.2 (< 4.8)	12.0 (> 6.0)	
Knee-Ankle	8.8	10.0 (> 6.0)	39.6 (> 45)
Left Tibial			
Ankle-AHB	2.8 (< 4.8)	12.0 (> 6.0)	
Knee-Ankle	8.8	11.0 (> 6.0)	38.3 (> 45)
Right Peroneal			
Ankle-EDB	4 (< 5.6)	4.2 (> 2.4)	
Below Knee	8.8	2.0 (> 2.4)	32.5 (> 41.6)
Above Knee	12.8	1.9 (> 2.4)	12.5 (> 41.6)
Left Peroneal			
Ankle-EDB	4.2 (< 5.6)	4.3 (> 2.4)	
Below Knee	8.8	4.2 (> 2.4)	35 (> 41.6)
Above Knee	10.0	4.2 (> 2.4)	38.5 (> 41.6)
Right Median			
Wrist-APB	4.2 (< 3.9)	6.3 (> 5.7)	
Elbow	7.4	6.5 (> 5.7)	46.9 (> 51)
Left Median			
Wrist-APB	5.1 (< 3.9)	4.9 (> 5.7)	
Elbow	7.9	4.9 (> 5.7)	52.5 (> 51)
Right Ulnar			
Wrist-ADM	1.83 (< 3.1)	10.2 (> 8.0)	
Elbow	5.6	8.4 (> 8.0)	45.1 (> 54)
Left Ulnar			
Wrist-ADM	2.4 (< 3.1)	8.0 (> 8.0)	
Elbow	6.2	7.2 (> 8.0)	41.8 (> 54)
Sensory nerve conduction	Lat [ms]	Amp [μV]	CV [m/s]
Right Sural			
Ankle-Foreleg	2.4 (< 4.2)	15.0 (> 1.2)	36.6 (> 46.7)
Left Sural			
Ankle-Foreleg	2.1 (< 4.2)	15.0 (> 1.2)	42.9 (> 46.7)
Right Median			
Digiti II-Wrist	3.4 (< 3.4)	4.8 (> 11.3)	26.7 (> 49.5)
Left Median			
Digiti II -Wrist	4.4 (< 3.4)	5.7 (> 11.3)	24.1 (> 49.5)
Right Ulnar			
Digiti V-Wrist	1.94 (< 3.1)	12.0 (> 7.2)	46.7 (> 47.4)
Left Ulnar			
Digiti V-Wrist	2.5 (< 3.1)	11.0 (> 7.2)	42.4 (> 47.4)

Normal values refer to the reference values established by Peking Union Medical College Hospital.
Lat, latency; Amp, amplitude; CV, conduction velocity.
AHB, abductor hallucis brevis; EDB, extensor digitorum brevis.
APB, abductor pollicis brevis; ADM, abductor digiti minimi.

usually provoked by minor trauma [8]. In our case, because the patient was an adolescent female with acute onset, characterized by persistent limb weakness and paresthesia, GBS was initially suspected, but her two episodes and the result of CSF analysis did not indicate the albuminocytologic dissociation reminded us of HNPP. In general, the symptoms of HNPP occur in the second or third decade of life and rarely present in childhood [9]. The age of onset in this case was less than 20 years, which may be associated with different PMP22 gene expression in different ethnic populations [10]. At that time, she experienced acute mononeuropathy mainly involving right peroneal nerve, and NCS indicated significant injury of right peroneal nerve and varying degrees of damage of other peripheral nerves. Common clinical features, coupled with a wider range of electrophysiological abnormalities than manifestations, gave us a reason to interpret the onset at age three as the first episode. After the improvement of clinical symptoms, the later course of the disease was uneventful until the age of 14.

HNPP symptoms usually incorporate episodes of numbness, paresthesia, muscle weakness, and atrophy. Peripheral nerves including the median, ulnar, radial, and peroneal nerves, and the brachial plexus are most frequently affected, which was possibly related to these sites commonly exposed to trauma or entrapment due to their anatomical locations. Notably, tibial nerve is not usually involved due to its anatomical location. The tibial nerve originates from the tibial portion of the sciatic nerve and ultimately from the lower lumbosacral plexus. It travels through the popliteal fossa and passes between the two heads of the gastrocnemius muscle [11]. Therefore, most part of the tibial nerve is located in the deep layer of the muscle and is difficult to be oppressed. In this case, the manifestations of this patient at the age of 14 were numbness mainly at the bottom of the left foot, weakness of the left lower limb with limitation of plantar flexion in the left foot, and the left ankle reflex was not elicited, which tend to be the symptoms of tibial nerve involvement. The cause of her onset was not clear, and actually the event caused the nerve involvement is unknown in a large number of reported cases [12]. In the existing case reports of HNPP in children, the pathogenic factors are varied in children of different ages. For example, the onset of HNPP in infants and very young children may be related to intrauterine or intrapartum trauma [13], while in

children of this age in our case, the causes are more variable which are often mechanical factors, such as excessive traction and overexercise. Our girl suffered from the symptoms of tibial nerve injury after waking up, since there are few similar reports, we can only make a preliminary speculation that this episode might be related to the placement of her lower limbs during sleep. Except for the compression, obstruction of blood circulation may be a potential factor.

Electrophysiological examinations are particularly important in the diagnosis of HNPP, which are useful adjuncts for determining the location and extent of damage. The results of electromyography often showed more extensive peripheral injury than clinical symptoms [14]. The electrophysiological pattern of HNPP is characterized by a nonuniform demyelinating polyneuropathy with accentuated distal slowing in some nerves, multifocal conduction slowing at sites of entrapment, and mildly reduced conduction velocities of other segments of motor nerves [15]. Recently, Robert-Varvat et al. proposed electrophysiological diagnostic criteria for HNPP patients under 30 years old [16]: at least one ulnar nerve showed MNCV slowing down in the elbow; at least one side of the common peroneal nerve showed distal motor latency (DML) prolongation; bilateral median nerve DML lengthened. The sensitivity of this standard to the diagnosis of HNPP was more than 90%. In our case, NCS results showed extensive peripheral nerve damage which almost meet the above criteria although the needle EMG was incomplete. HNPP is an autosomal dominant disorder. However, more than 21% of patients constitute sporadic cases with de novo onset and subclinical asymptomatic relatives [17], which is challenging for the diagnosis of HNPP, just like our patient. Genetic testing is the gold standard for diagnosis of HNPP. PMP22 located in 17p11.2 is the pathogenic gene, which encodes a myelin protein located on the surface of peripheral nerve [1,2]. Gene mutations of PMP22 are the most common cause of hereditary peripheral neuropathy, and different mutation types lead to different phenotypes [18,19]. Our patient's DNA had a 1.38MbDNA deletion of chromosome 17p12 which covered PMP22. Moreover, the heterozygosity loss of her mother, and the 1.43mbDNA deletion of chromosome 17p12 of her maternal uncle and male cousin, undoubtedly provided evidence for our diagnosis. Except for deletions, previous reports suggest that a small number of PMP22 gene mutations in HNPP are point mutations [20–22], and there are more than 20 small mutations have been found so far.

Unfortunately, there are no treatments to cure HNPP. It is currently managed mostly symptomatically [8]. It usually takes several months for patients to fully recover after they've been diagnosed and treated. Common anti-neuropathic pain agents and neurotrophic drugs should be offered to patients with positive sensory symptoms. Therefore, after HNPP was confirmed by gene detection, drug therapy dominated the treatment for our patient. Vitamin B12 and mecobalamin were used to nourish the nerves, and gabapentin capsules were used to relieve numbness. Furthermore, patient was advised to avoid cold, compression and other inducing factors. After a four-day admission, she was discharged, and she completely recover one month later, an outcome is indeed consistent with the course of HNPP.

4. Conclusion

The diagnosis of HNPP in cases without family history and atypical symptoms remains challenging, especially in young children. Involvement of the tibial nerve is quite rare in HNPP. After excluding other neurological diseases, HNPP should be considered combining with objective examinations. Electrophysiological examinations are imperative in determining the location and degree of neuropathy. Finding electrophysiological abnormalities are more extensive than clinical symptoms can provide clues for diagnosis. The final diagnosis of HNPP depends on genetic testing, which usually shows PMP22 deletion of chromosome 17p11.2. Currently, there is no effective therapy for HNPP, and the most helpful interventions are symptomatic and prophylactic treatment. However, the causes of rare nerve involvement in HNPP still need to be further explored.

Ethics statement

We have obtained written informed consent from the patient for publication of the data. The study was approved by the Research Ethics Board of the First affiliated hospital of Chongqing medical university.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article. </p>

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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