Hereditary Neuropathy with Liability to Pressure Palsies:  
A Report of Two Cases

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Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal-dominant disorder 
characterized by self-limited, recurrent compressive mononeuropathies at common entrapment sites 
precipitated by trivial injuries. This disorder typically develops in early adulthood. Electrodiagnostic 
studies revealed diffuse mild demyelinating neuropathies with entrapment over common entrapment 
sites. Nerve biopsies frequently show segmental demyelination and thickening of the myelin sheath 
which is mostly caused by 1.5 Mb deletion of the 17p11.2 site containing the peripheral myelin protein 22 
(PMP22) gene on the 17th chromosome. This report describes the clinical features, electrodiagnostic 
studies, and genetic studies of a Taiwanese family. Among the 5 members evaluated, 1 latent and 2 
symptomatic cases had generally decreased nerve conduction velocities with further focally decreased 
conduction velocities or conduction blocks at common entrapment sites. Genetic studies demonstrated 
deletion of the Charcot-Marie-Tooth type IA sequences in 17p11.2 in all 3 patients. Our case studies 
suggested that diagnosis of HNPP can be based on clinical suspicion, positive family history, and elec-
trodiagnostic tests; however final confirmation should be based on genetic study. ( Tw J Phys Med Re-
habil 2007; 35(1): 41 - 47 )

Key words: nerve compression syndrome, hereditary neuropathy, nerve conduction study, 
peripheral myelin protein (PMP22), tomaculous neuropathy

INTRODUCTION

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant hereditary 
disorder with high penetration and variable expression.[1] The typical manifestation of HNPP is recurrent compres-
sion mononeuropathy, due to either minor traction or compression, repetitive minor trauma, or no obvious 
reason. The patient may have acute muscle weakness, painless sensory deficit, or numbness. In most cases, 
neurological deficits achieve complete recovery within a few months. [2]

The first case of HNPP was reported by De Jong in
1947 in the Dutch literature. The prevalence of HNPP is roughly 160-400 per million. The male/female ratio is approximately 1.23/1.00. No significant differences exist for clinical manifestation between male and female subjects. The higher prevalence in males than females is probably due to the fact that males are more likely to experience nerve compression when performing certain jobs. Since symptoms of HNPP are usually very mild and 10–15% patients are asymptomatic, they may not be diagnosed in the whole life. Consequently, the prevalence rate may be underestimated.

Onset of initial neurological symptoms is commonly when subjects are aged around 20–30 years (mean, 25.8 years). However, the age range of subjects with HNPP varies from newborns to the age of 60. The youngest patient reported had HNPP presented with transient Erb’s palsy. The duration of neurological symptoms also varies. The shortest duration was 1 day, and the longest was 6 months (mean duration, 7 weeks). The most commonly involved nerve is the peroneal nerve, followed by ulnar nerve (at the elbow), radial nerve, median nerve, digital nerve, sciatic nerve, and cranial nerve. Superficial nerves are more vulnerable to trauma than deep nerves.

To our knowledge, only two reports exist for HNPP in Taiwan. This report describes 2 patients in a family; other family members were prospectively investigated using electrodiagnostic and genetic studies.

### CASE REPORT

**Case 1**

A 15-year-old boy had been diagnosed with glucose-6-phosphodehydrogenase deficiency and had no other significant medical history. Early in the morning in August 2005, the patient noted numbness and weakness in his right ring and little fingers when he awakened. He stated he had lain on his right side. The symptoms lasted for a few days. The patient visited the rehabilitation clinic 4 days after symptom onset.

On examination, the patient had hyperextension at the metacarpophalangeal joints and flexion at the interphalangeal joints in ring and small fingers on the right hand and was unable to extend them completely. A manual muscle test demonstrated weakness in the abductors and adductors of all fingers and the adductors in the thumb of the right hand with a positive Froment’s sign. He also had sensory deficit to pinprick over ulnar side of right hand ring finger and little finger. Initial diagnosis was right ulnar nerve entrapment neuropathy. An electrodiagnostic test was arranged, and the patient was sent home to wait for the electrodiagnostic test.

Two days later, he had another episode of mild weakness in the whole left upper limb and numbness in the left ring and small fingers. Several days later, he received an electrodiagnostic test. Test results demonstrated that he had diffuse demyelinating neuropathy in all 4 limbs with superimposed bilateral subclinical carpal tunnel syndrome and ulnar nerve entrapment at the elbow (Tables 1,2). Further investigation of family history revealed that the patient’s elderly brother also experienced a similar episode of weakness and recovered almost completely within a few months. Under an impression of hereditary peripheral neuropathy, the patient was referred to the neurology clinic for genetic study and other assessments.

The above symptoms have been gradually improved and completely recovered within 2 months although he has another episode of left arm weakness and numbness in January 2006 for about 6 weeks.

**Case 2**

This 17-year-old patient is the older brother of case 1. Since birth, he had claw foot on the left side. At age of 15, he fell and developed a contusion on his left hip. Three days later, he experienced weakness in his left ankle extension and had difficulty walking. He visited the neurosurgical clinic at Chiayi Chang Gung Memorial hospital (CGMH). The examination revealed that he had weakness in left ankle dorsiflexion (muscle power: 3/5), foot eversion (2/5) and big toe extension (0/5). However, no evidence of sensory deficit existed. He was diagnosed at that time with peroneal neuropathy. He was then referred to the rehabilitation service for an ankle foot orthosis to improve ambulation. This patient was also treated with electrical muscle stimulation on the involved muscles. A muscle strengthening program was prescribed. He attained significant improvement 1 week later and complete recovery in about 3 months.

At age of 16, the patient had another attack of
intermittent numbness in the ulnar aspect of his left hand. He visited the rehabilitation clinic at Chiayi CGMH. Initial diagnosis was ulnar entrapment neuropathy at the elbow. Since the symptom was mild, he was treated with antiepileptic medication, including carbamezepine and clonazepam, and a physical therapy program with a low power laser, transcutaneous nerve stimulation, and hand positioning. However, as he did not achieve significant improvement for 2 weeks, he underwent an electrodiagnostic test. Test results showed that he had diffuse demyelinating neuropathy in all limbs—a finding similar to that for case 1 (his brother) (Tables 1-3). The initial impression was Charcot-Marie-Tooth disease type I (CMT type I). He was then referred to the neurological clinic. The patient was treated with a muscle relaxant and vitamin B (Alinamin-F50). The symptoms were off and on gradually subsided over a period of several weeks. However, he still experienced episodic numbness up to the time of follow-up electrodiagnostic tests and genetic studies in August 2005.

**Case Studies (including the other family members)**

To obtain a definite diagnosis, all family members, including the father, mother, and sister, underwent electrodiagnostic tests and genetic studies.

**Electrodiagnostic studies:**

**Cases 1 and 2:** Both patients had evidence of obviously slow conduction in the bilateral median, ulnar, peroneal, and tibial motor nerves, and bilateral median, ulnar, superficial peroneal and sural sensory nerves. Mild amplitude reduction of sensory nerve action potentials and compound muscle action potentials were also noted but much less apparent than the slowing of conduction velocities. The F-wave latencies were prolonged in the bilateral median, ulnar, tibial and peroneal nerves. The H-reflex latencies were also slow in the bilateral tibial components. Both patients also had evidence of entrapment in bilateral ulnar nerve at the elbow (with conduction block and focal slowing at the elbow), and bilateral median nerve at the wrist (with prolonged distal latencies) over both symptomatic and asymptomatic limbs (Tables 1-3).

**Other family members:**

The mother had diffuse demyelinating neuropathy; the father and sister had normal findings. (Tables 1-3).

**Genetic studies:**

Blood was sampled from each family member except for the sister. Genomic DNA was isolated from -20°C frozen samples of EDTA anticoagulated whole blood using standard DNA extraction. A working dilution of 25 ng/µL was then prepared from each DNA sample. According to the method described by Latour et al. (2001),[11] three short tandem repeats (STRs), 4A, 9A, and 9B, which cover 0.55 Mb in the center of the Charcot-Marie-Tooth 1A duplication, were utilized for genotyping each DNA sample. Polymerase chain reaction (PCR) amplification was conducted for each marker using 50-ng genomic DNA. The PCR amplification products were denatured and then separated using electrophoresis on 8% polyacrylamide gels. The PCR product bands were visualized by silver staining.

**Table 1. Motor Nerve Conduction Studies of Right Side Limbs**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Median Nerves</th>
<th>Ulnar Nerves</th>
<th>Tibial Nerves</th>
<th>Peroneal Nerves</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL/FL Am CV</td>
<td>DL/FL Am BB AB CV</td>
<td>DL/FL Am CV</td>
<td>DL/FL Am CV</td>
</tr>
<tr>
<td>Father</td>
<td>3.0 7.7 62</td>
<td>2.2 10.4 10.2 67</td>
<td>3.8 17.7 47</td>
<td>3.1 7.1 49</td>
</tr>
<tr>
<td>Mother</td>
<td>6.1 7.4 48</td>
<td>3.5 7.0 7.7 48</td>
<td>6.0 4.0 41</td>
<td>5.8 2.1 42</td>
</tr>
<tr>
<td>Case 1</td>
<td>5.3/34.6 5.8 44</td>
<td>3.6/46.0 6.0 2.7 23</td>
<td>7.0/62.6 8.7 39</td>
<td>9.2/82.1 6.0 28</td>
</tr>
<tr>
<td>Case 2</td>
<td>5.6/37.8 7.3 48</td>
<td>4.2/42.7 4.3 3.5 24</td>
<td>5.0/69.6 8.9 35</td>
<td>6.8/70.0 7.2 31</td>
</tr>
<tr>
<td>Sister</td>
<td>2.7 10.6 58</td>
<td>2.6 11.5 11.1 65</td>
<td>4.3 19.9 50</td>
<td>3.5 4.5 52</td>
</tr>
</tbody>
</table>

DL = distal latency (msec); FL = F-wave latency (msec); Am = amplitude (µV); CV = conduction velocity (m/sec); BB = below elbow; AB = above elbow
Table 2. Sensory Nerve Conduction Studies and H-reflexes Latencies of Right Side Limbs

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Median Nerves</th>
<th>Ulnar Nerves</th>
<th>Sural Nerves</th>
<th>H-reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Am (µV)</td>
<td>CV (m/sec)</td>
<td>Am (µV)</td>
<td>CV (m/sec)</td>
</tr>
<tr>
<td></td>
<td>palm wrist</td>
<td>digit wrist</td>
<td>palm wrist</td>
<td>digit wrist</td>
</tr>
<tr>
<td>Father</td>
<td>19 14 58 50</td>
<td>12 52 8 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>44 33 52 24</td>
<td>22 36 7 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>12 9 31 64</td>
<td>5 34 12 37</td>
<td></td>
<td>39.6</td>
</tr>
<tr>
<td>Case 2</td>
<td>11 5 48 40</td>
<td>6 41 9 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td>24 41 53 49</td>
<td>28 50 9 48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Am = amplitude (mV); CV = conduction velocity (m/sec); NR = no response picked up

Figure 1. Genetic studies for the family revealed only one copy of the CMT1A sequences were identified in cases 1 and 2 and their mother. Their father had normal copy numbers of the CMT1A gene.

DISCUSSION

The electrodiagnostic test is an important procedure in diagnosing HNPP. Focal slowing of motor and sensory
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nerve conduction velocities or conduction blocks at common entrapment sites (i.e., the carpal and cubital tunnels, Guyon's canal and the fibular head) can be found in limbs with or without focal symptoms and signs. Furthermore, mild-to-moderate diffuse conduction slowing can be found in HNPP patients, even in asymptomatic cases. These findings indicate a generalized demyelinating processes. Distal latency of motor nerves may be prolonged.\[2,12-14\]

Nerve biopsy study may reveal focal and redundant myelin folding with periodic hypermyelination and demyelination which mimics a sausage.\[15\] Therefore, the term of tomaculous (Latin: sausage) neuropathy can also be used for in place of HNPP. However, Such change is not specific for HNPP, and can also be found in patients with CMT type I.\[16\]

Genetic study provides the most confirmatory diagnosis for HNPP\[2\] – the deletion of 1.5 Mb at the 17p11.2 site which contains CMT1A sequence of the 17th chromosome can be found in most HNPP cases; however, in very few cases, HNPP might be caused by small mutations within genetic materials.\[2\] This deletion can be a de novo mutation or inherited. This portion of genetic material contains genes for translation of peripheral myelin protein 22 (PMP22).\[17\] Conversely, duplication of this chromosome site is evident in CMT type IA. Namely, HNPP patients have only one copy of the PMP22 genes, whereas CMT 1A patients have 3 copies of the PMP22 gene. The clinical manifestations for each are assumed to be associated with gene dosage effect with overexpression of PMP22 in CMT1A and underexpression in HNPP.\[18,19\] Therefore, HNPP and CMT 1A are proposed to be reciprocal deletion/duplication syndromes caused by unequal meiotic crossover.\[11\] Consequently, the prevalence for these two diseases could be of similar magnitude.\[4,5,16\] However, the number of case reports of HNPP is much smaller than that of CMT 1A, possibly due to the fact that HNPP patients have relatively mild symptoms or even no symptom.

This study found deletion of CMT1A sequences in 3 members of the family using the polymorphic short tandem repeats technique. This method uses three well-established combined short tandem repeat (STR) markers: 4A, 9A and 9B. The STR 4A is located inside the PMP22 gene and the other two are telomERICALLY positioned.\[11\]

The concordance of genetic and electrophysiological studies in both symptomatic and latent patients is compatible to those in literature, implying that electrophysiological studies can be used for diagnosing HNPP in suspet family members.\[12,13\]

Diagnosing a typical HNPP case using clinical manifestations, family histories, electrophysiological examinations, nerve biopsies and genetic studies is not difficult. However, differential diagnosis with other diseases such as CMT, other metabolic neuropathies vulnerable to compression should be considered.\[20\]

Notably, CMT is the most common hereditary polyneuropathy. Onset of symptoms is typically at when subjects are teenagers. Like HNPP, CMT typically presents as an autosomal-dominant inherited disease but manifested with diffuse, slowly progressive motor-sensory polyneuropathy. Distal limbs are first involved resulting in pes cavus, with atrophy of the intrinsic muscles in the calf and foot.\[16,20\] CMT type I is more easily confused with HNPP as it also presents with diffuse slowing motor and sensory conduction velocity (motor nerve conduction velocity < 38 m/sec) but rarely with conduction block by electrophysiological examination.\[16\] In nerve biopsies, focal hypertrophy of the myelin sheath can also be found. On the other hand, some literature reported that approximately 1/3 of HNPP cases have pes cavus\[16\] and a few HNPP cases presented with symmetrical distal neuropathy without symptoms of compression neuropathy.\[7\] Even with molecular study, mislead diagnosis can occur when a rare small mutation of PMP22 is present rather than the typical 1.5 Mb deletion of 17p11.2.\[17\] As in the case 2 in this report, CMT type I was initially impressed. Therefore, diagnosis of HNPP is based on careful histories assessments, adequate examinations and keeping HNPP in mind.

The typical feature of HNPP is the relatively rapid and complete recovery from symptoms over a period of a few months. Permanent lesions are extremely rare, consequently, early surgical intervention may not be beneficial.\[4,21\] Diagnosis of HNPP should be considered for patients with multiple episodes of nerves palsy, either occurring together or separately, and in patients with a family history of multiple episodes of nerve palsy. Awareness of this disease will reduce the incidence of unnecessary surgery, and enhance protection of peripheral
nerves in at-risk patients. Splinting in selective cases and patient education of avoiding repeated use, compression and trauma on common entrapment sites might be helpful.

**REFERENCES**


遺傳性壓迫易感性神經病變:兩病例報告

林衢序  羅榮昇1,2  許宏志  謝煒基  林智容  李建德3
嘉義長庚紀念醫院 運健科 神經內科
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遺傳性壓迫易感性神經病變(hereditary neuropathy with liability to pressure palsies,簡稱 HNPP)是一自體顯性遺傳的一種自限性、但易復發的壓迫性單一神經病變。患者常因為很輕微的傷害，便在常見的神經易生卡陷的部位(common entrapment sites)發生局部壓迫性神經病灶。這種疾病最常在青少年的階段開始出現症狀。藉由電學診斷可以發現患者有輕度廣泛性去髓鞘神經病變伴隨在常見的神經卡陷部位的發生局部壓迫性神經病變。神經活檢常可以發現有區段性去髓鞘與髓鞘肥厚的情形。此疾病大多是因爲人體第17對染色體17p11.2的部位發生了1.5Mb的缺失，這個部位的遺傳物質包含了周邊髓鞘蛋白22(peripheral myelin protein 22, 簡稱 PMP22)的基因。本文敘述了一個罹病的個案其家庭成員的臨床表徵、電學診斷與基因檢查的結果。在五位家庭成員中，其中1位為無症狀基因帶原者，2位為罹病的個案，他們的神經傳導速度皆有全面性降低的情形，並且在常見神經卡陷部位都發生了傳導速度局部減緩或是傳導阻滯(conduction block)的情形。並且3個人都經由基因檢查確定在第17對染色體17p11.2的部位發生Charcot-Marie-Tooth type IA序列的缺失。本個案研究的結果認爲經由臨床的症狀、家族史與電學診斷的發現可以幫助我們診斷HNPP。不過，最後的確診仍須仰賴基因檢查。（台灣復健醫誌 2007；35(1): 41 - 47）

關鍵詞: 神經壓迫症候(nerve compression syndrome)，遺傳性神經病變(hereditary neuropathy)，神經傳導檢查(nerve conduction study)，周邊髓鞘蛋白22(peripheral myelin protein 22, PMP22)，臘腸性神經病變(tomaculous neuropathy)