Hereditary Neuropathy with Liability to Pressure Palsies: A Clinical and Genetic Study of A Taiwanese Family

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Hereditary neuropathy with liability to pressure palsies (HNPP), an autosomal dominant disorder, is characterized by recurrent isolated nerve palsies, which are precipitated by trivial compression or trauma. In this report, we present the clinical features, electrophysiological studies, nerve biopsy results, and molecular analyses of a Taiwanese family. Among the 7 members evaluated, one latent and three symptomatic patients were found who showed a heterogeneous presentation from asymptomatic to characteristically recurrent peripheral neuropathy. Electrophysiological studies revealed a general decrease in nerve conduction velocities in all four patients with focal conduction slowing, especially at the compression sites. A sural nerve biopsy with a teased fiber preparation in the index patient demonstrated a typical tomaculous appearance. Molecular genetic studies exhibited a deletion of the PMP22 gene in chromosome 17p11.2-12 in all 4 patients. In conclusion, the diagnosis of HNPP might be overlooked if based on clinical presentation only. Family survey and electrophysiological and genetic tests should be done to investigate this disorder. *(Chang Gung Med J 2005;28:56-63)*

Key words: hereditary neuropathy, HNPP, nerve conduction, tomaculous neuropathy, molecular genetic study.

Hereditary neuropathy with liability to pressure palsies (HNPP), also called tomaculous neuropathy, is an autosomal dominant disorder with recurrent isolated neuropathies. This disorder usually occurs in adolescence or adulthood, and is precipitated by minor trauma such as traction or compression, which leads to peripheral nerve damage at the compression sites.[1] The clinical manifestations include decreased sensory perception and weakness of the muscles that are innervated by the entrapped nerves. The disorder may occur acutely and resolve within weeks or months. Electrophysiological studies reveal a general slowing of nerve conduction velocity (NCV) with a segmental slowing of NCV at the nerve entrapment sites, a reduction of action potentials, and prolonged distal latencies.[2-4] Nerve biopsies show a characteristic sausage-like focal thickenings of the myelin sheath, called tomacula.[1, 2] Molecular genetic analysis has shown a deletion of the chromosome 17p11.2-12 region containing a dosage-sensitive gene, peripheral myelin protein (PMP22), in patients with HNPP.[5] Affected patients carry only one copy of PMP22, and a gene dosage effect leads to under-expression of the protein.[6]

To our knowledge, there is only one report on this condition among Taiwanese, but no pathological or genetic studies were done in that study.[7] Recently, we encountered a young man with HNPP who had

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Received: Jan. 4, 2004; Accepted: May 4, 2004
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recurrent entrapment neuropathy. In this report, we studied the clinical manifestations, electrophysiology, sural nerve pathology, and genetic analyses of the index patient and his family members with HNPP.

CASE REPORT

Index patient

The patient (III-4), a 20 year-old man, visited our neurology outpatient clinic with complaints of 4 episodes of right upper limb weakness since he was 17 years old. This condition was precipitated by compression of the arms. During the first episode at age 17, he experienced weakness in both arms, with predominance in the right arm, when he woke up in the morning. He had difficulty raising his arms and was unable to carry heavy subjects. The condition resolved itself within one week. The second episode occurred 1 year later. Although he could raise his right arm, the weakness persisted for 3 weeks. At 19, he experienced another episode of muscle weakness and numbness in the right arm. He could raise his right arm, but he was unable to extend his right hand. The numbness persisted for one week, while the weakness lasted for more than one month. Three months prior to this admission, he had another episode of weakness and numbness in the right arm when he woke up in the early morning. The numbness disappeared two weeks later, but the muscle weakness persisted, and he was unable to elevate his right arm. Despite the proximal arm weakness, he could write with his right hand.

On evaluation three months after the last episode, neurological examination showed mild weakness and a relative reduction of muscle bulk in the right arm, particularly the deltoid, biceps, and triceps muscles, and generalized hyporeflexia indicating an involvement of multiple nerves. Otherwise, the findings were unremarkable. The results of sensory examination were essentially normal.

Other members of the family

Detailed histories were obtained from the index patient and six other family members, and neurological examinations were performed. The pedigree of the seven members studied is shown in Figure 1. The index patient's grandmother (I-1) had neither muscle weakness nor distal numbness and her tendon reflexes were normal during the neurological examination. The index patient's grandfather died at the age of 56 years due to a hepatoma. His grandfather had one brother and two sisters who all died of strokes or heart disease at the ages of 69, 70 and 70 years. The clinical histories and manifestations of the index patient's mother were not available because she had moved away from the family after a divorce when the index patient was 2 years old. The index patient's father (II-2) had repeated episodes of numbness in both upper limbs after waking up in the morning, beginning at the age of 20 years. Neurological examination revealed mild weakness in the interosseous muscles of the left hand indicating an ulnar nerve lesion and hyporeflexia of the bilateral upper limbs. The index patient's aunt (II-5) had muscle weakness in the right thumb and index finger for two years, and carpal tunnel syndrome was diagnosed in another hospital. She also experienced left foot pain and numbness half a year ago which was diagnosed as a herniation of an intervertebral disc, and improved after several months. Neurological examination revealed generalized hyporeflexia. The index patient's sister (III-3) and his two aunts (II-6, II-7) had no symptoms or neurological signs of this condition including the tendon reflexes. The index patient and his sister were not married.

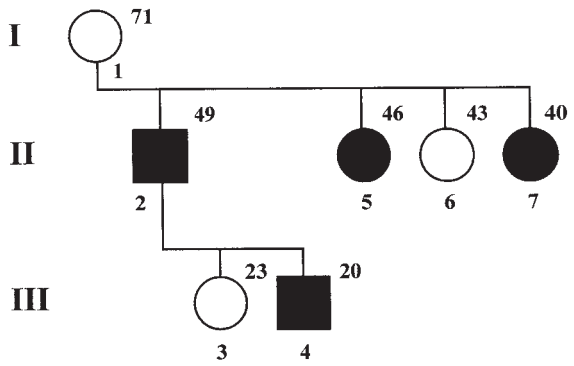


Fig. 1 A pedigree of 7 members of a Taiwanese family in which one latent and three symptomatic patients have the clinical features of HNPP. Solid squares and circles indicate patients. Numbers in the upper right indicate current ages.

Motor nerve conduction

The results of the motor NCV are shown in Table 1. In patient III-4, prolonged distal latency in the left median and peroneal nerves and a slowing of

Table 1. Motor Nerve Conduction Velocity Studies in 4 Patients with HNPP, One Healthy Family Subject and 20 Healthy Controls

Patients and family subjects		Median N			Ulnar N			Peroneal N			Tibial N		
		DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)
Patients													
III-4	L	4.7*	7.1	51.0	3.2	8.5	35.0*	6.2*	7.0	41.0*	5.4	14.0	47.0
	R	4.0	8.5	49.0*	3.3	12.1	45.0*(29.0+)*	5.3	10.5	37.0*	6.3	14.0	34.0*
II-2	L	6.1*	8.8	48.0*	4.4*	5.5	28.0*	5.4	2.0	30.0*	5.2	9.8	43.0
	R	5.2*	9.3	50.0	4.2*	5.2	36.0*	5.2	5.0	37.0*	4.2	3.5	42.0
II-5	L	4.4*	10.9	45.0*	3.0	7.9	44.0*	5.6*	1.6	31.0*	4.5	7.2	34.0*
	R	5.1*	8.4	46.0*	3.4	7.4	40.0*	5.5*	2.8	33.0*	5.7	9.1	36.0*
II-7	L	NA	NA	NA	NA	NA	NA	8.3*	0.1*	25.0*	NA	NA	NA
	R	5.2*	15.8	49.0*	3.0	9.5	43.0* (29.0+)*	11*	0.5*	33.0*	5.7	8.0	37.0*
Subject													
III-3	L	2.5	11.0	61.0	2.0	9.4	53.0	3.2	6.5	53.0	3.2	22.8	51.0
	R	2.6	10.9	61.0	2.4	8.9	58.0	3.0	8.3	52.0	2.8	20.5	51.0
Controls	Mean	3.0	10.9	60.5	2.4	9.1	60.5	4.2	5.9	51.1	5.3	9.8	49.1
(n=20)	SD	0.4	2.4	3.8	0.4	1.8	4.2	0.4	2.0	3.2	1.0	2.5	3.2

Abbreviations: HNPP: hereditary neuropathy with liability to pressure palsies; DL: distal latency; SD: standard deviation; Amp: amplitudes; NCV: nerve conduction velocity; L: left; R: right; NA: not available.

* abnormal (if the data are above mean ±3SD and/or the amplitudes < 1.0 mV in the peroneal nerve.

+ across the elbow segment.

motor NCV in the right median and tibial nerves, and bilateral ulnar and peroneal nerves, were noted in the motor NCV study. In addition, focal slowing in the right ulnar nerve was noted across the elbow segment, indicating an entrapment neuropathy. Patient II-2 showed prolonged distal latency of the bilateral median and ulnar nerves. Motor NCV was slow in the left median and bilateral ulnar and peroneal nerves. Patient II-5 also had prolonged distal latency in the bilateral median and peroneal nerves, and slow motor NCV in all nerves tested, including the bilateral median, ulnar, peroneal, and tibial nerves. Patient II-7 had prolonged distal latency in the right median and bilateral peroneal nerves, as well as slow motor NCV in the right median, ulnar, tibial, and bilateral peroneal nerves. Reduced amplitude of compound muscle action potentials was also noted in the bilateral peroneal nerves. Nerve conduction velocities calculated in short segments across the elbow of patient II-7 showed marked focal slowing. In the non-symptomatic family subject III-3, the motor NCV data were essentially normal.

Sensory nerve conduction

Table 2 shows the results of the sensory NCV studies. There was a prolongation of distal latency in the bilateral median, ulnar, and sural nerves of patient III-4. The amplitudes of sensory nerve action potentials were decreased in the right median and bilateral ulnar nerves. Slowing of sensory NCV was also observed in the right median and ulnar nerves. In addition, no response was noted on proximal stimulation above the elbow segment of the left ulnar nerve. The above data indicated a polyneuropathy. In studies of patient II-2, most of the parameters were abnormal except for the sensory nerve action potential in the bilateral median and right ulnar nerves. There was no pick-up of sensory nerve action potentials from right proximal sural nerve stimulation. In studies of patient II-5, a prolongation of distal latency in the bilateral median and sural nerves, and a slowing of sensory NCV in the left median and bilateral ulnar nerves were found. In sensory NCV studies of the subclinical patient II-7, only a slowing of the sensory NCV in the right median and ulnar nerves was noted. In the non-symptomatic family subject III-3, the sensory NCV findings were within normal limits.

Sural nerve biopsy

A sural nerve biopsy from patient III-4 was done. Light microscopic examination of the nerve biopsy showed a variable degree of thickness of the myelin sheaths, with marked enlargement of some

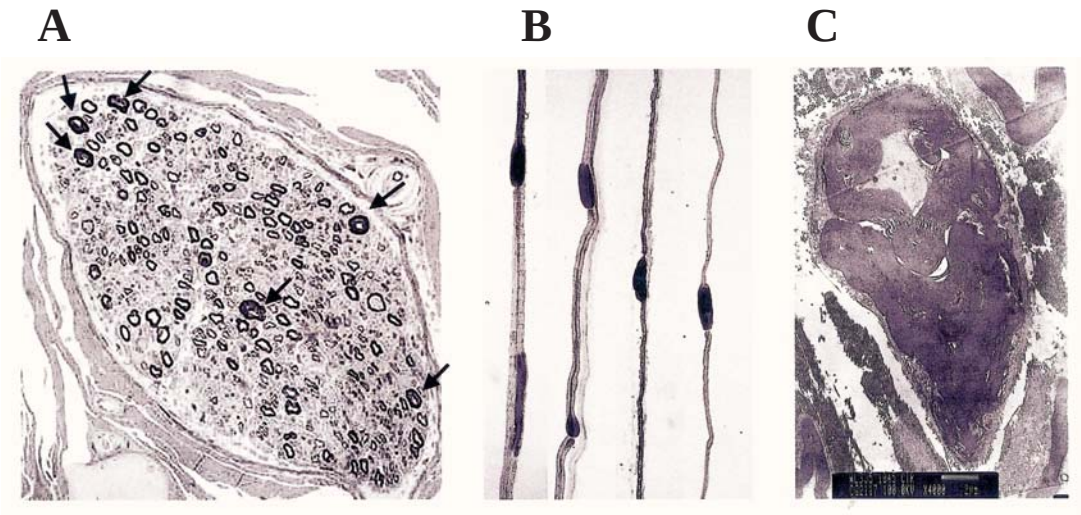
Table 2. Sensory Nerve Conduction Velocity Studies in 4 Patients with HNPP, One Healthy Family Subject, and 20 Healthy Controls

Patients and family subjects		Median N			Ulnar N			Sural N		
		DL (ms)	Amp (μV)	NCV (m/s)	DL (ms)	Amp (μV)	NCV (m/s)	DL (ms)	Amp (μV)	NCV (m/s)
Patients										
III-4	L	4.1*	27.8	53.0	3.2*	3.0*	—*	4.5*	14.8	38.8
	R	5.2*	5.8*	40.0*	4.0*	5.5*	43.0*	5.0*	11.0	36.8
II-2	L	5.0*	11.4	48.0*	4.1*	3.6*	31.0*	12.8*	3.0*	—*
	R	4.5*	18.2	45.0*	4.2*	12.4	46.0*	13.7*	3.8*	—*
II-5	L	4.7*	20.3	53.0*	2.9	33.8	50.0*	5.0*	9.8	46.7
	R	4.2*	16.7	54.0	3.0	34.0	40.0*	5.1*	9.5	41.2
II-7	R	2.9	12.0	53.0*	2.5	14.5	45.0*	NA	NA	NA
Subject										
III-3	L	2.6	58.4	69.0	2.2	72.6	61.0	2.9	35.6	63.0
	R	2.8	56.3	64.0	2.4	58.5	67.0	2.9	35.6	46.0
Controls Mean		2.5	42.0	66.0	2.1	41.0	66.0	3.0	29.0	49.4
(n = 20)	SD	0.4	18.0	4.0	0.3	14.4	5.1	0.3	15.1	4.2

Abbreviations: DL: distal latency; Amp: amplitudes; NCV: nerve conduction velocity; NA: not available; L: left; R: right; —: no response.

* abnormal (if the data are above mean ±3SD, and/or the amplitudes < 8 mV in the median, ulnar and sural nerves).

hyper-myelinated nerve fibers (Fig. 2A). There were also some regenerating clusters with thin myelinated fibers. A teased fiber preparation of the sural nerve biopsy revealed a typical sausage-like or tomaculous appearance (Fig. 2B). Under an electron microscope, the thickened myelin sheaths were produced by folded and redundant myelin loops (Fig. 2C). The fiber size of each myelinated nerve fiber was measured in a morphometric analyzer *(LEICA Q500MC image processing and analysis system). Morphometric study showed a decrease in fiber density in the myelinated nerves with a fiber density of 4031/mm2 (fiber density was 6743/mm2 in a reference control). The histogram was unimodal with a loss of large



Figs. 2 Sural nerve biopsy specimens from patient III-4. (A) Focal myelin thickening (arrows) in cross-sectional views under a light microscope, toluidine blue stain x 40 before reduction. (B) A teased fiber preparation showing tomaculous formations, x 100 before reduction. (C) Thickened myelin sheaths with folded and redundant myelin loops under electron microscopy, x 4000 before reduction.

myelinated fibers in the patient (Fig. 3A) compared with the bimodal pattern in the reference control (Fig. 3B).

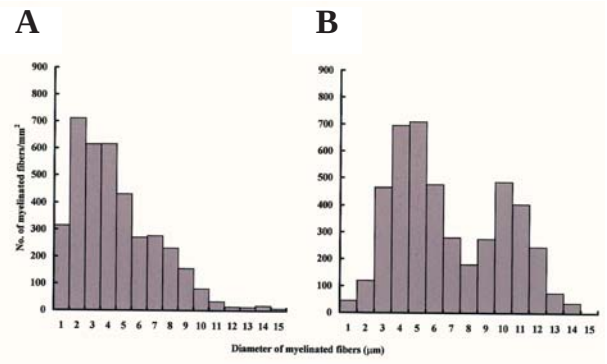
Molecular genetic studies

DNA extracted from blood samples of one latent and three symptomatic patients with HNPP and 3 asymptomatic family members was analyzed. The following allele-specific primers Hot-PF 5´-TTGGATTCAAAGATATTAGTGTTAT-3´, Hot-DR 5´-TAGTAGAGTGAGTACAGTGGAC-3´ were designed according to published proximal and distal CMT1A-REP sequences.[9, 10] Amplification was carried out in 30 μL with 1.5 mmol/L $MgCl_2$, 50 pmol of each primer, 250 μmol of each dNTP, 50 ng template DNA, and 2.5 unit *Taq* DNA polymerase (Takara Bio Inc., Japan). The PCR buffer (10X) was composed of 100 mmol/L Tris-HCl (pH8.3), 500 mmol/L KCl and 15 mmol/L $MgCl_2$. Amplification was done by initial denaturation at 94°C for 5 min, followed by 25 cycles of 30 sec at 94°C, 1 min at 56°C, and 3 min at 72°C, including 1 sec autoextension function on the extension time with a final extension of 5 min at 72°C using a PTC-200 Peltier thermal cycler (MJ Research, Watertown, MS, USA). About 5 μL of amplified products were digested with 0.4 μL EcoRI (10U/ μL), and 0.4 μL NsiI (10U/ μL) (New England Biolabs, City? and State? USA) and 2 μL buffer H. In addition, 12.2 μL of distilled water was added to reach a total volume of 20 μL. The mixtures were incubated overnight at 37°C and electrophoresed on 1% agarose gels. Gels were stained in ethidium bromide (0.1 mg/L) and visualized under UV light.

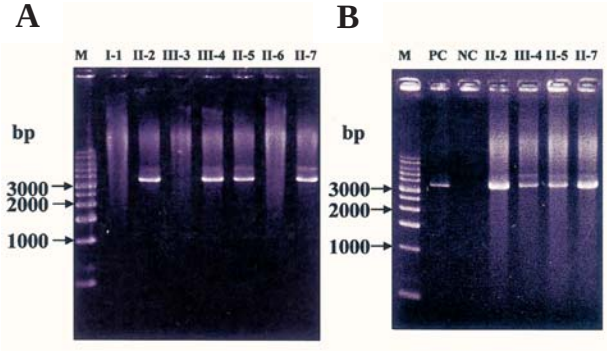
With the primers Hot-PF and Hot-DR, a 3.6 kb product was observed in the one latent and three symptomatic patients (III-4, II-2, II-5, and II-7). In the other family subjects (I-1, II-6, III-3), no 3.6 kb product was found (Fig. 4A). With the digested enzymes Nsi I and EcoRI, the PCR products (3.6 kb) could not be cleaved into two segments (1.5 kb and 1.7 kb) because there were no restriction sites (Fig. 4B). The molecular genetic study indicated a deletion of 1.5 Mb in the short arm of chromosome 17p11.2-12 in patients III-4, II-2, II-5, and II-7.

DISCUSSION

The present study shows a typical presentation of recurrent episodic monoparesis with sensory impairments, characteristic nerve conduction studies, and the tomaculous neuropathy of HNPP in one sural nerve biopsy in a Taiwanese family. Molecular genetic analysis also confirmed a 1.5 Mb deletion of the PMP22 gene at chromosome 17p11.2-12 in one latent and three symptomatic patients in this HNPP family. Interestingly, the electrophysiological studies were well correlated with the molecular genetic studies, particularly in one subclinical patient who had no clinical symptoms but had abnormal NCV studies



Figs. 3 Histogram of the sural nerve biopsy findings showing (A) a decrease in myelinated fiber density of 4031/mm^3 and a unimodal pattern with relative loss of large myelinated fibers in the index patient III-4, and (B) a fiber density of 6743/mm^3 and a bimodal pattern in a reference control.



Figs. 4 Restriction analysis of polymerase chain reaction (PCR) (A) With the primers of Hot-PF and Hot-DR, only 4 patients (II-2, II-5, II-7 and III-4) show 3.6 kb products; the other 3 family subjects do not have the 3.6 kb products. (B) With the digested enzymes of *Nsi* I and *Eco* RI, the PCR products (3.6 kb) can not be cleaved because there are no restriction sites. (NC = negative control, PC = positive control, M = markers, bp = base pair)

and a deletion of the PMP22 gene.

In NCV studies, these four patients had a more prominent prolongation of distal latencies and slowing of NCV than reduction of amplitude in compound muscle action potentials and sensory nerve action potentials. The hallmark features of the electrophysiological studies were an entrapment neuropathy of the right ulnar nerve across the elbow area of patients III-4 and II-7, compatible with other studies.[2, 4, 9-12] In our research, the electrophysiological study was a reliable screening tool in detecting HNPP, because the correlation between the electrophysiological and molecular studies was rather good. In addition, the electrophysiological studies showed a slowing of NCV in both affected and non-affected limbs, and particularly entrapped nerves, compatible with a previous study.[9] In one report, symptomatic and asymptomatic genetically confirmed HNPP patients showed electrophysiological abnormalities.[4] In addition, up to 50% of these patients were asymptomatic but had abnormalities in electrophysiological studies, indicating the importance of these studies.[13] However, in some sporadic cases with a de novo deletion, electrophysiologic studies were only suggestive and the definite diagnosis required molecular analysis.[13]

The sural nerve biopsy of our patient III-4 showed typical tomacula due to the redundancy or overfolding of variable thicknesses of the myelin sheath. The presence of tomacula is the most characteristic nerve pathology in HNPP patients, but these formations do not appear in all patients. In addition, tomacula have also been reported in Charcot-Marie-Tooth types 1 and 8, neurogenic scapuloperoneal syndrome, multiple sclerosis, entrapment neuropathy, IgM kappa paraproteinemia and autosomal recessive demyelinating neuropathy with focally folded myelin.[14-18]

Molecular genetic studies have shown a deletion of the PMP22 gene in chromosome 17p11.2-12 in HNPP patients. Our one latent and three symptomatic patients also had a deletion of the same gene. Therefore, this deletion has become a standard in the diagnosis of HNPP. However, in a recent study, only 84% of HNPP patients had 17p11.2-12 deletions.[19] Patients with a PMP22 frame shift mutation also had other neuropathic features mimicking hereditary motor sensory neuropathy type 1 in addition to common HNPP characteristics.[20]

In Taiwan, there has been only one report dealing with HNPP.[7] In that report, the symptoms of most of the family members were very mild and the index patient was not diagnosed until the age of 80 years. However, important pathological studies and genetic analysis were not performed. Recurrent and episodic peripheral neuropathies with a positive family history, and detailed sensory and motor examinations for family members with subtle signs of neuropathy may help to establish the diagnosis of HNPP. The early diagnosis of HNPP patients is important to avoid unnecessary surgery and management of conditions such as carpal tunnel and lumbar disc compression syndromes. Since the disease may present with very mild symptoms or even no symptoms, HNPP may be underestimated. We conclude that detailed histories, electrophysiological studies, and sural nerve biopsies as well as molecular genetic studies are important in the early diagnosis of HNPP.

Acknowledgements

We express our appreciation to Dr. Tong Wu for technical assistance in the pathological study and to Dr. Chin-Song Lu for referring the index patient. The authors are grateful to Ms. Y-C Hsieh for preparing the manuscript.

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易壓迫性麻痺之遺傳性神經病變：一台灣家族之臨床和基因研究

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易壓迫性麻痺之遺傳性神經病變是體顯性遺傳的疾病，特徵是輕微的神經壓迫或傷害後，會造成某些部位的麻痺。本文中，我們仔細分析了一個台灣家族的臨床特徵，電生理學檢查，神經切片及分子生物學上的檢查結果。檢查的7人當中，我們發現了3位有症狀及1位潛在的病患，從無症狀到反覆的神經麻痺的各種表現都有。神經電生理學檢查發現這3位有症狀及1位潛在的病患的神經傳導速度整體來說皆較慢，且在易壓迫處局部的傳導速度慢得特別明顯。在指標病人的腓腸神經挑取纖維中，看到了臘腸狀的神經纖維外觀。在這3位有症狀及1位潛在的病患中，分子生物基因學檢查皆發現在17p11.2-12的染色體上有PMP22基因的缺失。結論若只從臨床上來診斷，易壓迫性麻痺之遺傳性神經病變很有可能被忽視。在本疾病中，我們必須多放心力在家族調查，電生理學檢查及基因分析上。(長庚醫誌 2005;28:56-63)

關鍵字：遺傳性神經病變，易壓迫性麻痺之遺傳性神經病變，神經傳導檢查，臘腸狀神經病變，分子基因研究。

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受文日期：民國 93年1月4日；接受刊載：民國 93年5月4 日。
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