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Case Report

Peripheral neuropathy in diabetes: it's not always what it looks like

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What's new?

- For the first time a case of Type 1 diabetes and Hereditary Neuropathy with liability to Pressure Palsies (HNPP) is described.
- Longstanding motor and sensory symptoms were previously attributed to golfer's elbow, diabetic neuropathy and spinal degenerative disease.
- Many cases of HNPP are thought to remain undiagnosed.
- This case suggests that the differential diagnosis of peripheral neuropathy in people with diabetes and other co-morbidities may be challenging and requires a careful and comprehensive approach.

Abstract

Background Hereditary Neuropathy with liability to Pressure Palsies (HNPP) is an autosomal dominant neuropathy, associated with deletion of the Peripheral Myelin Protein-22 (PMP-22) gene, causing recurrent painless palsies with age of onset between 10 and 30 years old. Only a few cases of Type 2 Diabetes and HNPP have been described and the coexistence of HNPP and Type 1 diabetes has never been reported.

Case report A 54-year old man with a history of Type 1 diabetes, managed with continuous subcutaneous insulin infusion (CSII), presented with deterioration of long-standing motor and sensory symptoms, previously attributed to golfer's elbow, diabetic neuropathy and spinal degenerative disease. He had multilevel severe spine degenerative changes and L4/L5 and L5/S1 root impingements with a L4/L5 discectomy performed when he was 25 years old. On physical examination he had normal power and distal hypoaesthesia of the digits and plantar aspect of the feet. Investigations revealed normal full blood count, liver and renal function, electrolytes, vitamin B12 and serum folate. He suffered from primary hypothyroidism and thyroid function tests indicated adequate levothyroxine replacement. Nerve conduction studies revealed a generalized demyelinating

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sensorimotor neuropathy, with more severe involvement of nerves over entrapment sites. Further history that his father suffered from episodes of weakness and numbness was elicited. Genetic analysis revealed one copy of the PMP22 gene at 17p11.2 confirming the diagnosis of HNPP.

Conclusion In people with diabetes the evaluation of peripheral neuropathy should include a careful history, a comprehensive physical examination, blood tests and in some cases nerve conduction studies and genetic testing.

<H1>Background

Hereditary Neuropathy with liability to Pressure Palsies (HNPP) is an autosomal dominant neuropathy associated with deletion of the Peripheral Myelin Protein-22 (PMP-22) gene causing recurrent painless palsies with age of onset between 10 and 30 years old (1,2). PMP-22 is a gene encoding the peripheral myelin protein which plays a crucial role in the formation of myelin. The prevalence of HNPP is estimated between 7.3 to 16 cases per 100,000, although many cases are thought to remain undiagnosed (3,4). While the coexistence of HNPP and Type 2 diabetes has previously been described (5), this is the first report of a person with Type 1 diabetes, HNPP and diabetic peripheral neuropathy.

<H1>Case report

A 54-year old man with a 14-year history of Type 1 diabetes, managed with continuous subcutaneous insulin infusion (CSII), was seen at the authors' clinic. He presented with deterioration of longstanding motor and sensory symptoms which had previously been attributed to golfer's elbow and spinal degenerative disease. He reported recent worsening of an intermittent right leg numbness after prolonged sitting and episodes of parasthesia of his right arm after nocturnal sleep. He was known to have multilevel vertebral degenerative changes with L4/L5 and L5/S1 root impingements. At the age of 25 years old he had a L4/L5 discectomy for low back pain and right leg numbness

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associated with weakness. Previous lumbar MRI scans had shown degenerative changes with foraminal impingement at various levels, with no significant progression over time. Nerve conduction studies performed in other hospitals had documented findings suggestive of a superimposed diabetic peripheral neuropathy. His medical history also included primary hypothyroidism, adequately replaced with levothyroxine. On examination, he had bilateral pes cavus, hammer toes and mild muscle wasting in the lower limbs. Power was normal in all four limbs. Deep tendon reflexes were reduced but symmetrical. There was hypoaesthesia of the toes and soles. The plantar responses were downgoing. A panel of blood tests including full blood count, renal and liver function, ESR, vitamin B_{12}, methylmalonic acid and serum protein electrophoresis was unremarkable. His HbA1c was 71 mmol/mol (8.6%). Repeat nerve conduction studies revealed a generalized demyelinating sensorimotor neuropathy with more severe involvement of nerves over entrapment sites (median neuropathy at the wrist, ulnar at the elbow and peroneal at the knee) (Table 1). The findings, although compatible with a diabetic neuropathy, showed rather slower velocities than were typical. Further questioning revealed history of recurrent right foot drop at the age of 18–20 years old, particularly after sitting with the right leg crossed over the left. The weakness recovered over several weeks. He had also experienced recurrent painless weakness of right shoulder abduction or elbow flexion following gym sessions with a weight over his shoulders. He recalled that his father had had similar symptoms of recurrent numbness and weakness. His history raised the suspicion of a demyelinating hereditary neuropathy. A subsequent multiplex ligation-dependent probe amplification analysis revealed one copy of the PMP22 gene at 17p11.2, confirming the diagnosis of HNPP.

<H1>Discussion

HNPP leads to episodic, painless, focal motor and sensory peripheral neuropathy and causes attacks of numbness and weakness (6). It is known that the most vulnerable nerves are the peroneal and the ulnar nerves (30–48% and 21–28%, respectively), followed by the brachial plexus, radial nerve and median nerve (2,7). In this case, the neurological symptoms had been attributed to a spinal

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degenerative process, recurrent tendinitis of the right elbow, and a superimposed diabetic neuropathy. HNPP and diabetic neuropathy may have similar neurophysiological features and, although sensory nerve conduction velocity slowing and distal motor latency prolongation is said to be more marked in HNPP (8), the distinction is not absolute. The main clue to the correct diagnosis came from the history of typical recurrent pressure palsies and his detailed family history. Some unusual associations of HNPP with other pathologies such as hypothyroidism have been described and are believed to aggravate HNPP neurological symptoms (9). As the concurrence of HNPP and diabetes is rare, it is not known if diabetes exacerbates the nerve injury in this genetic condition. This case confirms that the differential diagnosis of peripheral neuropathy in a person with diabetes can be challenging and warrants specialist consultation in the presence of atypical features (Table 2) (10-12). Nerve conduction studies represent an easy and accurate method for determining which patients may have HNPP but genetic testing is the most reliable tool for the diagnosis. In the present case, the correct diagnosis allowed the adoption of strategies (activity modification and protective padding) to prevent further progression in nerve injury and facilitated appropriate genetic counselling and management (4). Furthermore, beyond the uncommon concomitancy of Type 1 diabetes, HNPP and peripheral diabetic neuropathy and the misleading presence of spine disease, this report provides the reader with an important key clinical message. In people with diabetes and nerve damage the diagnostic process is not always straightforward and should include meticulous history taking, a comprehensive physical examination and consideration of nerve conduction studies.

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Competing interests

The authors confirm that there are no conflicts of interest.

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<H1>References

1. Spagnoli C, Iodice A, Salerno GG, Frattini D, Bertani G, Fusco C. Hereditary neuropathy with liability to pressure palsies in childhood: Case series and literature update. *Neuromuscul Disord.* 2016; 26: 394.

2. Mouton P, Tardieu S, Gouider R, Birouk N, Maisonobe T, Dubourg O, *et al*. Spectrum of clinical and electrophysiologic features in HNPP patients with the 17p11.2 deletion. *Neurology*. 1999; 52: 1440-1446.

3. Meretoja P, Silander K, Kalimo H, Aula P, Meretoja A, Savontaus ML. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. *Neuromuscul Disord*. 1997; 7: 529-532.

4. Foley C, Schofield I, Eglon G, Bailey G, Chinnery PF, Horvath R. Charcot-Marie-Tooth disease in Northern England. *J Neurol Neurosurg Psychiatry*. 2012; 83: 572-573.

5. Li J, Niu B, Wang X, Hu H, Cao B. A case report of hereditary neuropathy with liability to pressure palsies accompanied by type 2 diabetes mellitus and psoriasis. *Medicine (Baltimore)*. 2017; 96: e6922.

6. Chance PF. Inherited focal, episodic neuropathies: hereditary neuropathy with liability to pressure palsies and hereditary neuralgic amyotrophy. *Neuromolecular Med*. 2006; 8: 159-174.

7. Gouider R, LeGuern E, Gugenheim M, Tardieu S, Maisonobe T, Leger JM, *et al*. Clinical, electrophysiologic, and molecular correlations in 13 families with hereditary neuropathy with liability to pressure palsies and a chromosome 17p11.2 deletion. *Neurology*. 1995; 45: 2018-2023.

8. Andersson PB, Yuen E, Parko K, So YT. Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. *Neurology*. 2000; 54: 40-44.

9. Kaneko K, Sugeno N, Tateyama M. Hereditary neuropathy with liability to pressure palsy emerging after hypothyroidism. *Neurol Clin Neurosci*. 2013; 1: 160–161.

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10. Watson JC, Dyck PJ. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. *Mayo Clin Proc*. 2015; 90: 940-951.

11. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, *et al*. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care*. 2017; 40: 136-154.

12. Rajabally YA, Stettner M, Kieseier BC, Hartung HP, Malik RA. CIDP and other inflammatory neuropathies in diabetes - diagnosis and management. *Nat Rev Neurol*. 2017; 13: 599-611.

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Table 1 Neurophysiology results ǂ

Sensory studies	Amplitude (uV)	Norm (uV)	CV (m/s)	Norm (m/s)
Median				
Digit II (index finger)	absent	> 8		
Digit III (long finger)	absent	> 8		
Mid palm	absent			
Ulnar				
Digit V (little finger)	3	> 6	35	> 50
Mid palm	6		39	> 50
Radial				
Forearm	4	> 13	34	> 50
Superficial peroneal				
Lower leg	absent			
Sural				
Lower leg	absent			

Motor studies	DML (ms)	CMAP (mV)	Segment	MCV* (m/s)
Median				
Wrist	9.9 TLI 0.22	2.3	Abductor pollicis brevis-Wrist	
Elbow	16.6	1.4	Wrist-Elbow	38
Ulnar				
Wrist	4.4	10.2	Abductor DM-Wrist	
Below elbow	9.3	7.8	Wrist-Below elbow	49
Above elbow	13.5	5.5	Below elbow-Above elbow	29

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Peroneal				
Ankle	6.5	0.1	Extensor Digitorum Brevis-Ankle	
Fibula (head)	22.4	0.1	Ankle-Fibula (head)	25
Peroneal				
Fibula (head)	4.9	2.0	Tibialis anterior-Fibula (head)	
Popliteal fossa	7.8	2.3	Fibula (head)-Popliteal fossa	29
Tibial				
Ankle	5.3	1.2	Abductor Hallucis-Ankle	
Median-Ulnar comparison				
Median				**DML difference:**
Wrist	6.4	1.6	Wrist-2nd Lumbrical	
Ulnar				3.6 ms
Wrist	2.8	2.9	Wrist-2nd Interosseous	

F-Wave Studies

Nerve	**Minimum F-Latency**
Median	40.8
Ulnar	35.7

ǂAll results shown were from the right side.

*Normal values for upper limbs > 50 m/s, lower limbs > 40 m/s.

CV, conduction velocity; Norm, normative data; DML, distal motor latency; CMAP, compound muscle action potential; MCV, maximum conduction velocity to onset of CMAP; TLI, terminal latency index (normal > 0.34).

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Table 2 Features suggesting further investigation of peripheral neuropathy in diabetes
▪ Acute or subacute onset of symptoms
▪ Rapidly progressive symptoms
▪ Family history of sensory and motor symptoms
▪ Asymmetry of signs or symptoms
▪ Motor greater than sensory neuropathy
▪ Multifocal symptoms
▪ Sensory neuropathies causing gait ataxia and proprioceptive dysfunction
▪ Symptoms associated with severe dysautonomia
▪ Severe symptoms, functionally limiting

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