



EMG Case No. 78, February 2006

Presenting Symptom(s):

Numbness, tingling and weakness in all extremities

This case is no longer available for CME Credit.

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Disclosures: Y. Li, None; M. Al-Lozi, None.

Appropriate Audience: Residents and practicing physicians.

Learning Objectives: After completing this educational activity, participants will be able to: (1) Formulate a differential diagnosis for chronic peripheral neuropathy with superimposed entrapment syndromes; (2) Recognize clinical and electrophysiologic features of HNPP; (3) Be familiar with the etiology and diagnosis of common hereditary neuropathies

Level of Difficulty: Advanced.

History

The patient is a 45-years-old woman who presents with a long history of numbness, tingling and weakness in all extremities. Her symptoms started 10 years prior to presentation with a foot drop on the left, followed by numbness and tingling in her hands and feet. The symptoms resolved in a few months. Several months later, she noted intermittent paresthesia and numbness in her hands, and weakness in her hands and legs.

- Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.
- Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?

Commentary I

This patient presents with a chronic, recurrent weakness and paresthesia. These symptoms are non-specific and may be produced by a lesion in many places along the neuro-axis. The sensory symptoms suggest involvement of the nervous system and argue against myopathy, neuromuscular junction disorder or anterior horn cell disease where pathology at these sites produce pure motor deficit. The differential diagnosis is broad at this point. A foot drop may be produced by a mononeuropathy like peroneal entrapment, sciatic neuropathy, lumbosacral plexopathy, L5 radiculopathy, asymmetric polyneuropathy, a localized brain lesion involving the leg area or even a myelopathy. Occasionally, foot drop may be an isolated presentation of a brain lesion. Myelopathy may be associated with sphincteric disturbances and sensory symptoms that may extend up to the trunk, depending on the level of the lesion. The lack of shooting or radiating pain down the limbs may argue against radiculopathy. Involvement of all extremities may suggest peripheral



polyneuropathy; however, cervical myelopathy may produce symptoms in all extremities. At this point, the constellation of symptoms suggests peripheral polyneuropathy or cervical radiculopathy. Differential diagnosis of peripheral polyneuropathy is extensive, however. Causes include but are not limited to diabetes mellitus, nutritional deficiencies, immune and inflammatory conditions, toxins (including alcohol, heavy metals and medications), paraneoplastic syndrome, paraproteinemia, and systemic disorders like connective tissue disease, hypothyroidism and uremia. As the symptoms were recurrent, immune peripheral neuropathy like chronic inflammatory demyelinating neuropathy (CIDP), toxic neuropathies with repeated toxic exposure, vasculitic neuropathy, porphyria, and hereditary neuropathy with pressure palsies are included in the differential diagnosis. Cervical myelopathy may produce numbness and weakness in all extremities and may mimic peripheral polyneuropathy. Getting a more detailed history is the first step to further localize the process and narrow down the list of possible causes. We should inquire about the past medical and surgical history, family history, social history including the detailed employment status, exposure to toxins, and past and present medications.

History, continued

Her hand weakness is aggravated by writing and typing for even a few minutes. The symptoms are intermittent, but are more frequent as time progressed. The patient appeared to be debilitated by her progressive symptoms to the point that she could not perform housework and was unable to maintain her office job. She complains of burning sensation and weakness in her hands. She is unsteady on her feet and her balance has gotten worse over the last year. Her past medical history includes gastric esophageal reflux disease (GERD), depression, and migraine headache. She has no history of diabetes mellitus, thyroid disease or other infectious diseases. She denied tobacco smoking and alcohol or drug abuse. She reported an accidental one time exposure to organic phosphate at her work prior to the onset of her symptoms. There is no family history of neuropathy. She had bilateral carpal tunnel release 5 years ago. She was diagnosed with peripheral polyneuropathy and was given a steroid trial and treated with analgesics, atropine, Mestion, and muscle relaxants without relief. She is currently on Effexor for depression. The etiology for her peripheral neuropathy remained unclear for many years and she was referred to our institution for further evaluation.

- If necessary, revise your differential diagnosis based on the additional clinical history.
- On which details of the physical examination should you focus at this point?

Commentary II

Neurological conditions that may be aggravated by writing include median nerve entrapment and dystonia. The history of paresthesia argues for nerve entrapment and against dystonia. The loss of balance suggests involvement of proprioceptive fibers in the peripheral nerve or posterior column. There are no underlying systemic diseases. The lack of similar disease in the family argues against but does not exclude inherited neuropathy. The history of exposure to organic phosphate may be associated with neuropathy; however, the recurrence of symptoms over the years was not associated with further exposure to the toxin. None of the medications used are associated with increased incidence of peripheral polyneuropathy. The possibility of chronic heavy metal poisoning has to be considered. Carpal tunnel syndrome, which the patient had surgery for five years prior, may be



increasingly seen with neuropathies associated with diabetes mellitus, hypothyroidism, amyloidosis or hereditary neuropathy with pressure palsy (HNPP).

The neurological physical examination is the next step that may shed more light on the cause of the neuropathy. The examination should further characterize the neuropathy and evaluate for skeletal deformities like pes cavus and hammer toes, thickened nerves, the extent and distribution of sensory and motor involvement, and status of tendon reflexes.

Physical Examination

The patient is a well-nourished, well-developed, middle-aged female in no acute distress. Her mental status was normal. Cranial nerves were intact. Motor examination showed normal muscle tone, but mild distal muscle weakness. Deltoids, biceps, triceps, wrist extensors and wrist flexors were 5/5 (Medical Research Council protocol), intrinsic hand muscles were 4+/5 bilaterally. Hip flexors and knee extensors 5/5, ankle dorsal flexors and plantar flexors 5-/5 bilaterally, toes flexors and extensor 4/5. There was no side-to-side asymmetry. Sensory examination was significantly decreased in a stocking and glove distribution for pinprick and light touch. She had moderately decreased vibration in her hands and feet. She had decreased sensation to temperature that was greater in both feet. Her deep tendon reflexes were 2+ and symmetric and plantar response was flexor bilaterally. She had positive Phalens's sign at both wrists and positive Tinel's sign across the elbows and fibular heads

- At this point, review your differential diagnosis and revise as appropriate.
- Are there additional observations on physical examination that might be helpful in narrowing your differential list?

Commentary III

The lesion appears to localize to the peripheral nerves with no upper motor neuron signs. The decreased sensation in glove and stocking distribution and the mild distal muscle weakness further lend support to peripheral neuropathy, which, based on the clinical examination, appears symmetric and length dependent. The multiple nerve entrapments, as suggested by the history and physical examination, may help in narrowing down the differential diagnosis.

Physical Examination, continued

Further physical exam revealed a non-specific Gait with normal coordination. No involuntary movements were noted. There is no limb deformity such as pes cavus (fore-shortened foot with high arch and hammer toes). Magnetic resonance imaging (MRI) of brain and spinal cord were unremarkable

- If necessary, revise your differential diagnosis based on the additional physical findings.
- Design your approach to the electrophysiologic examination based on the existing data.

Commentary IV



From the information given so far, the lesion localizes to the peripheral nerves and is consistent with peripheral polyneuropathy. In evaluating neuropathy, we need to address the following questions: 1) Type of functional deficit, motor, sensory, sensorimotor, autonomic or mixed; 2) the anatomic distribution of the deficit: symmetric or asymmetric, distal, proximal or distal and proximal; 3) the time course of the neuropathy, i.e., acute, subacute, chronic, constant or fluctuating; and 4) historical information of associated systemic diseases or exposure to toxins; 5) family history of peripheral neuropathy; and 6) the electrophysiological changes, demyelinating, axonal or mixed.

The muscle weakness, ataxia with proprioceptive sensory loss, and the decreased pinprick sensation suggest a mixed sensory motor peripheral polyneuropathy; there is no involvement of the autonomic nervous system. Although the physical examination showed distal symmetric polyneuropathy, significant asymmetry was suggested by the onset of symptoms in the left leg. Asymmetry is commonly seen with vasculitic neuropathy but may be seen in diabetes mellitus, neuropathy with multiple entrapments like in amyloidosis, diabetes mellitus or rheumatoid arthritis. The neuropathy has a chronic and a fluctuating course over a ten years period. Fluctuating course may occur with immune neuropathies like chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), vasculitic neuropathy, hereditary neuropathy with pressure palsy (HNPP), porphyria, or repeated toxic exposure. A brief toxic exposure to organic phosphate was reported by the patient at the beginning of the disease course. However, the lack of subsequent exposures argues against this being the only cause of the neuropathy. Note that CIDP and toxic exposures tend to be symmetric, and vasculitic neuropathy and HNPP may be asymmetric. The history of bilateral carpal tunnel syndrome at young age may favor the latter. For further characterization of the neuropathy, nerve conduction studies and electromyography (EMG) are very valuable tests.

Electrophysiologic Data

NR = no response

| SENSORY NERVE CONDUCTION STUDIES | | | | | | | |
|----------------------------------|------|-----------|--------------|----|-------|------------|----------|
| NERVE | SIDE | STIM SITE | RECORD | cm | AMPL | LAT (peak) | CV (m/s) |
| Radial | R | forearm | Snuff box | 10 | 13 µV | 3.3ms | 45 |
| Median | L | wrist | Index finger | 14 | 10 µV | 5.1ms | 35 |
| Median | R | wrist | Index | 14 | 12 µV | 4.6ms | 40 |
| Ulnar | L | wrist | Digit-V | 14 | 17 µV | 3.8ms | 37 |
| Ulnar | R | wrist | Digit-V | 14 | 10 µV | 3.7ms | 38 |
| Sural | L | lower leg | Ankle | 14 | NR | NR | |
| Sural | R | lower leg | Ankle | 14 | NR | NR | |



| MOTOR NERVE CONDUCTION STUDIES | | | | | | | |
|---------------------------------------|-------------|------------------|---------------|-----------|------------------|-------------------------|-----------------|
| NERVE | SIDE | STIM SITE | RECORD | cm | AMPL (mV) | LAT (<4.4 ms) | CV (m/s) |
| Median | L | wrist | APB | 7 | 5.9 (>4) | 5.3 | |
| | | elbow | APB | 22.5 | 5.8 | 10.0 | 47 (>49) |
| Median | R | wrist | APB | 7 | 9.1 (>4) | 4.8 | |
| | | elbow | APB | 22.5 | 8.8 (>6) | 9.5 | 48 (>49) |
| Ulnar | L | wrist | ADM | 7 | 10.5 (>6) | 3.6 | |
| | | Below elbow | ADM | 20 | 8.6 | 7.2 | 56 |
| | | Above elbow | ADM | 10 | 7.4 | 10.3 | 32 |
| | | axilla | ADM | 10 | 7.0 | 12 | 59 |
| Ulnar | R | wrist | ADM | 7 | 10.1 (>6) | 3.1 | |
| | | Below elbow | ADM | 21 | 8.7 | 6.8 | 57 (>49) |
| | | Above elbow | ADM | 10 | 7.8 | 9.7 | 34 |
| | | axilla | ADM | 10 | 8.0 | 11.3 | 63 |
| Peroneal | R | ankle | EDB | 10 | 3.6 (>2) | 8.8 | |
| | | Fibular head | EDB | 29.5 | 2.6 (>2) | 17.4 | 34 (>41) |
| | | Popliteal fossa | EDB | 10 | 2.6 (>2) | 20.2 | 36 |
| Peroneal | L | ankle | EDB | 10 | 3.5 | 8.1 | |
| | | Fibular head | EDB | 29 | 2.4 | 16.9 | 33 |
| Peroneal | L | Popliteal fossa | EDB | 10 | 2.7 | 19.7 | 36 |
| Tibial | R | ankle | AH | 10 | 4.3 | 5.8 | |
| | | Popliteal fossa | AH | 39 | 3.0 | 17.7 | 33 |
| Tibial | L | ankle | AH | 10 | 4.5 | 5.6 | |
| | | Popliteal fossa | AH | 39 | 3.3 | 17.0 | 34 |



| NEEDLE ELECTROMYOGRAPHY | | | | | | | | | |
|---|---------------------------------|-------|-----|-----|-----|-----|-----|-----|-------|
| INSERTional activity: N, sust, unsust FIBrillation: 0, 1+, 2+, 3+, 4+ OTHer: 0 or fascic, myotonia, myokymia EFFort: N, decr RECRuitment: N, inc or dec 1+, 2+, 3+, 4+ AMPLitude: N, inc or dec 1+, 2+, 3+, 4+ DURation: N, inc or dec 1+, 2+, 3+, 4+ POLyphasia: N, inc or dec 1+, 2+, 3+, 4+ | | | | | | | | | |
| R/L | MUSCLE | INSER | FIB | PSW | EFF | REC | AMP | DUR | POL |
| L | Abductor pollicis brevis (APB) | inc | 0 | 0 | N | N | N | N | N |
| L | First dorsal interosseous (FDI) | N | 0 | 0 | N | N | N | N | N |
| L | Tibialis anterior | N | 0 | 0 | N | dec | N | inc | inc2+ |
| L | Gastrocemijs (median head) | N | 0 | 0 | N | N | N | inc | inc2+ |
| L | Vastus medialis | N | 0 | 0 | N | N | N | N | N |
| L | APB | N | 0 | 0 | N | N | N | N | N |
| L | FDI | N | 0 | 0 | N | N | N | N | N |

- On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.
- Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)

Electrophysiologic Data, continued

The sensory nerve conduction studies demonstrate prolonged median and ulnar distal onset latencies and slowed conduction velocities bilaterally with normal SNAP amplitudes. The right radial SNAP amplitude and sensory conduction velocity were within normal limits. The sural sensory response was absent bilaterally. The motor nerve conduction studies revealed prolonged median distal onset latencies and slowed conduction velocities across the wrists bilaterally. The ulnar motor conduction velocity across the elbow was slowed bilaterally. The ulnar distal motor latency was normal on the right and prolonged on the left. The peroneal distal onset latencies were prolonged and conduction velocities across the fibular head were slowed bilaterally. Bilateral tibial distal onset latencies were normal, but conduction velocities were slowed. The CMAP amplitudes of bilateral median, ulnar, peroneal and tibial nerves were within normal limits. There was no evidence of conduction block or temporal dispersion in this study. EMG of left abductor pollicis brevis showed increased insertional activity without spontaneous activity. Many polyphasic MUAPs were noted in the left tibialis



anterior and medial gastrocnemius. Decreased recruitment patterns were also noted in the left tibialis anterior muscle. The rest of needle electromyography was normal.

- Make the final revisions of your diagnostic impression(s).

Diagnostic Impression

The above study showed two main abnormalities. First, there is electrodiagnostic evidence of a primarily axonal peripheral polyneuropathy based on the absent sural sensory nerve action potentials (SNAPs) and slowed motor conduction velocities in the lower limbs. Additionally there are electrodiagnostic features of demyelination with multiple areas of slowing in typical compression regions and mild slowing in locations without compression. Second, there are findings suggestive of multiple nerve entrapments, bilateral ulnar and median. The markedly prolonged peroneal distal motor latency to the extensor digitorum brevis with the normal ipsilateral tibial distal motor latency to the abductor hallucis may support another entrapment of the peroneal at the ankle, anterior tarsal tunnel syndrome. Peripheral polyneuropathy with multiple entrapments has a narrow differential diagnosis including diabetes mellitus, hypothyroidism, rheumatoid arthritis, acromegaly, amyloidosis, and HNPP. Most of these conditions are easily ruled out by careful history and blood tests. However, the latter two conditions need further diagnostic tests. The time course of neuropathy, the history of exacerbations and remission, and the lack of autonomic involvement point against amyloidosis. Further work up that may include nerve biopsy or alternatively genetic testing is the essential next step to reach a diagnosis.

- What other diagnostic procedures (laboratory tests, etc.), if any, are needed?
- What treatment would you recommend?

Commentary V

A nerve biopsy was not done and a genetic test for HNPP was performed. A deletion of the PMP-22 gene was found, which is consistent with HNPP or hereditary neuropathy with susceptibility to pressure palsies. HNPP is a slowly progressive hereditary peripheral neuropathy, which makes an individual very susceptible to nerve injury from pressure, stretch or repetitive use. This disorder is inherited in an autosomal dominant manner and usually manifests in the second or third decade of life. The prevalence of HNPP is unknown but is estimated to be 2-5 cases per 100,000 [Neils et al 1996]. The actual prevalence may be much higher since about 90% of people with HNPP are undiagnosed. [Parry et al 1999]

Clinical Features: Compression of nerves across entrapment sites is common in HNPP. The commonly affected nerves are median nerve at the wrist (carpal tunnel syndrome), ulnar nerve at the elbow (cubital tunnel syndrome), radial nerve in the arm (spiral groove insult), and peroneal nerve at the fibular head. This most commonly occurs where nerves pass through restricted anatomic space, from direct pressure or from stretch. The pressure can be slight, causing symptoms of tingling, numbness and weakness. Normal individuals may have similar symptoms with nerve compression but the symptoms last less than five minutes. In persons with HNPP, symptoms occur with minimal pressure and may last longer, up to several weeks or months. Pain is uncommon. Recovery tends to be complete initially, but after many recurrences, permanent nerve damage may occur. Physical



examination initially is consistent with a focal mononeuropathy localized to the injured nerve's distribution. In patients with long standing disease, it is common to find symptoms and signs consistent with a generalized, primarily sensory peripheral neuropathy.

Histopathology: Biopsy of affected and unaffected nerves in patients with HNPP may reveal the characteristic finding of a globular thickening of the myelin sheath, which appears like a sausage, hence the name tomaculous neuropathy (Latin: sausage). The muscle biopsy may demonstrate a number of histological features consistent with a denervation/reinnervation.

NCS/EMG Findings: Because diagnosis of HNPP is frequently missed or delayed, we should look for electrodiagnostic features that raise suspicion of HNPP, which may include a generalized neuropathy, superimposed by usually multiple nerve entrapments. The slowing of sensory conduction in nearly all nerves and the distal accentuation of motor conduction abnormalities are the main electrodiagnostic features of HNPP. The distribution and severity of the background electrophysiologic abnormalities are closely related to the topography of common entrapment or compression sites. [Hong et al 2003]

Genetic Diagnosis: The hereditary neuropathies are a clinically and genetically heterogeneous group of disorders. To date, 30 loci and 14 genes have been identified. The diagnosis of HNPP is confirmed by a genetic test showing deletion of a segment of chromosome 17p11.2-12. This segment of the chromosome contains an important myelin gene, peripheral myelin protein-22 gene (PMP22); duplication of this gene is associated with CMT1A phenotype.

Differential Diagnosis: Pressure palsies most commonly result from environmentally acquired physical compression of peripheral nerves. The most common are carpal tunnel syndrome with compression of the median nerve at the wrist, peroneal pressure palsy with compression of the peroneal nerve at the fibular head, and ulnar nerve pressure palsy with compression at the elbow. Persons with an underlying polyneuropathy, such as those with diabetes mellitus, are at increased risk for compression neuropathies. The signs and symptoms of compression neuropathy in HNPP are the same as those of the acquired type. Thus, HNPP is part of the broad differential diagnosis of both compression neuropathies and general peripheral neuropathies, including hereditary neuropathies. [Bird 2003]

The two most common inherited peripheral neuropathies are CMT1A (CMT = Charcot-Marie-Tooth) and HNPP. CMT1A, an autosomal dominant/recessive neuropathy with an incidence of 1/ 2,500, is genetically a mirror image of HNPP, containing an extra copy of PMP22 at the same site that HNPP has a deletion. Characteristics of CMT1A include onset in late childhood-early adolescence, distal muscle weakness and atrophy, severely reduced motor and sensory nerve conduction velocities, absent or diminished deep tendon reflexes, and foot deformities (pes cavus). Nerve biopsy shows the formation of onion bulbs.

CMTX: X-linked inheritance, characterized by intermediately slowed nerve conduction velocities (NCVs) and nerve biopsies show demyelination with axonal loss. Connexin 32 is the mutated gene (*Cx32/GJB1*).

HMSN1: very slow NCVs. Peak age of onset in first decade.

HMSN2: normal or slightly reduced NCVs, peak age of onset in second decade.

HMSN3: also known as Dejerine-Sottas syndrome, characterized by severe neuropathy, childhood onset and markedly reduced NCVs (<10m/s). Gene involved is *PMP22*.



HNPP sometimes involves the brachial plexus, thus overlapping with hereditary neuralgic amyotrophy, a disorder that maps to chromosome 17q [Windebank et al 1995]. The clinical features of HNPP are contrasted with hereditary neuralgic amyotrophy [Stogbauer et al 2000]. In addition, HNPP and CIDP (chronic inflammatory demyelinating polyneuropathy) may be confused with each other as both may cause generalized demyelination. The two disorders can be distinguished by the electrodiagnostic studies, nerve biopsy, and genetic tests. As CIDP is treatable, it is important to differentiate between these conditions.

Management: No specific treatment for the underlying genetic or biochemical defect exists and no medication is known to alter the natural course of HNPP. However, HNPP is such a unique neuropathy in that activity plays a great role in the development of pressure palsies. The primary treatment is to prevent nerve injury by avoiding pressure or nerve stretch. The patients are advised to avoid certain activities such as crossing their legs, leaning on their elbows, repetitive movements of wrist, rapid weight loss, etc. Management of persistent paralysis is based on physiotherapy in order to avoid muscle retractions and debilities. Wrist splints and elbow pads can be worn at night and/or when palsy episodes are present. Some people with residual foot drop may use ankle-foot-orthosis. Controversy exists as to whether surgical decompression of nerves is of benefit. Because spontaneous recovery is common and no systematic controlled study of surgical intervention has been done, the decision should be made on an individual basis. [Bird 2003]

Genetic Counseling: Genetic counseling should be made available to patients with HNPP and their families. Clinical and electrodiagnostic examination of the parents may help in establishing the genetic nature of the neuropathy. Sometimes neither parent may show signs of the disorder; the family history is reported as negative due to undiagnosed mild symptoms in a parent who has mutated gene. About 80% of the patients with HNPP have inherited gene mutation from an affected parent. About 20% of the patients have a de novo mutation. Each child of an individual with HNPP has a 50% chance of inheriting the gene mutation. Testing of at-risk asymptomatic adults for HNPP is available, but it is not useful in predicting age of onset, severity, type of symptoms, or rate of disease progression. [Bird 2003]

Bibliography

1. Dumitru D. Electrodiagnostic medicine. Philadelphia: Hanley & Belfus; 2002
2. Preston D, Shapiro B. Electromyography and neuromuscular disorders: Butterworth-Heinemann; 1998
3. Hong YH, Kim M et al Clinical and electrophysiologic features of HNPP patients with 17p11.2 deletion. *Acta Neurol Scand.* 2003 Nov; 108(5):352-8 [PubMed]
4. Parry G, Horton M. The five major ways that HNPP can look and act or phenotype variability in HNPP simplified. [www.hnpp.org]
5. Bird TD. Hereditary neuropathy with liability to pressure palsies. Developed at the Uni. of Washington, updated August 2003 [www.geneclinics.org]
6. Andersson PB, Yuen E, Parko K, So YT. Electrodiagnostic features of hereditary neuropath with liability to pressure palsies. *Neurology* 2000; 1(54): 40-4
7. Multiple resources from Hereditary Neuropathy with liability to Pressure Palsies or HNPP website. [www.hnpp.org]