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Clinical short communication

Porphyria: A rare differential diagnosis of polyradiculoneuropathy

Farwa Ali*, Neeraj Kumar, Peter J.B. Dyck, Sarah Berini, James Klaas

Department of Neurology, Mayo Clinic, Rochester, MN, USA

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Dear Editors,

A 37-year-old right-handed man presented after two episodes of weakness. During the first episode, he developed painful paresthesias followed by quadriparesis. A presumptive diagnosis of an immune mediated polyradiculoneuropathy, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or multifocal mononeuropathy (MMN) was made. Details of diagnostic tests from this evaluation were unavailable. He was treated with intravenous immunoglobulins with which muscle strength partly improved. Several months later he developed nausea, vomiting, and abdominal pain for which no cause could be determined.

Concurrently, he developed severe quadriparesis associated with dysautonomia; hypertension (systolic blood pressure > 200mmHg), tachycardia (heart rate over 150 bpm) and encephalopathy. During both episodes, cranial and respiratory muscles were spared. He was treated with intravenous immunoglobulins with partial recovery of muscle strength, but he remained severely weak. Encephalopathy, dysautonomia, and hallucinations completely resolved. At the time of this evaluation, his systemic and skin examination was normal. Neurologic exam revealed severe flaccid, areflexic, bilateral, distal predominant, upper greater than lower extremity weakness, and reduction of small and large fiber sensory modalities. He was unable to ambulate unassisted and suffered from severe neuropathic pain in the limbs. He worked as a carpenter and did not have a history of toxic exposure or travel.

The patient reported a motor vehicle accident at age 10. At age 21, he developed a seizure disorder which was attributed to traumatic head injury. He had recurrent episodes of abdominal pain, nausea and vomiting but an etiology was never discovered despite repeated evaluations. His grandfather suffered from an unknown psychiatric illness, and his father suffered from neuropathy.

Magnetic resonance imaging of the brain, cervical and thoracic spinal cord was normal. Flouro- deoxy-glucose positron emission tomography (FDG-PET) scan of the body was negative for hypermetabolic lesions suggestive of malignancy or inflammation. Bone survey did not reveal myelomatous osteolytic or osteoblastic bony lesions. Bone marrow pathology was normal.

Complete blood count was normal except mild lymphopenia $2.9 \times 10^{(9)}$/L (reference range $3.5–10.5 \times 10^{(9)}$/L). In the presence of normal bone marrow histology, lack of other cytopenia or infections, this was attributed to intravenous immunoglobulin use. Electrolytes (sodium, potassium, calcium, magnesium and phosphate), thyroid stimulating hormone, vitamin B12, E, B6, folate, Hgb A1c, ceruloplasmin, copper, serum/urine monoclonal proteins, cryoglobulins, testosterone, luteinizing hormone, follicle stimulating hormone, cortisol, rheumatoid factor, anti- cyclic citrullinated peptide antibody, anti-neutrophil cytoplasmic antibodies, extractable nuclear antigen antibody, human immunodeficiency virus, Lyme serology and anti-ganglioside antibodies, were negative or within normal limits. Antinuclear antibody (ANA) titer was 1.4 (negative < 1.0), but in the absence of extractable nuclear antigen antibody this was considered non-specific. Cerebrospinal fluid was normal with 3 nucleated cells, 30 mg/dL protein, and negative oligoclonal bands, Lyme, West Nile virus and cytomegalovirus serology. Paraneoplastic panel in both serum and CSF was negative. Electromyography (EMG) and nerve conduction studies (NCS) revealed a non-length dependent, axonal large fiber neuropathy where mild slowing of conduction velocity did not meet criteria for CIDP (Table 1).

Sural nerve biopsy showed significant axonal degeneration with myelin loss, but the findings were not diagnostic (Fig. 1A–D).

Quantitative urine porphyrin analysis was performed with High-Performance Liquid Chromatography (HPLC), and tandem mass spectrometry. Urine porphobilinogen was markedly elevated at 749.7

* Corresponding author at: Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA.
E-mail address: ali.farwa@mayo.edu (F. Ali).

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Table 1
Nerve conduction and needle electromyography.

Nerve conduction studies

Nerve	Type	Recording site	Amplitude(mV)	Normal amplitude	CV(m/s)	Normal CV	DL(m/s)	Normal DL
Peroneal	Motor	EDB	3.0	> 2.0	32	> 41	5.7	< 6.6
Sural	Sensory	Ankle	NR	> 6.0	NR	> 40	NR	< 4.5
Median	Motor	APB	2.5	> 4.0	40	> 48	4.6	< 4.5
Ulnar	Motor	ADM	4.2	> 6.0	42	> 51	3.0	< 3.6
Median	Sensory	2nd digit	15.0	> 15.0	51	> 56	3.6	< 3.6
Radial	Sensory	Dorsal hand	14.0	> 20.0	33	> 49	3.0	< 2.9
Ulnar	Sensory	Fifth digit	10.0	> 10.0	32	> 54	3.4	< 3.1

Electromyography

Muscle	Insertional activity	Fibrillations	Reduced recruitment	Long duration MUPs	High amplitude MUPs
Thoracic paraspinals	↑			+	+
APB	↑	+	+ + +	+ + +	+ + +
Triceps	↑	+ +	+ + +	+ +	+ +
FDI	↑	+ + +	+ + +	+ +	+ +
Deltoid	↑	+	+ +	+ +	+ +
MG	Normal		+ +	+ +	+ +
TFL	Normal		+ +	+ +	+ +
AT	Normal		+ +	+ +	+ +
VM	↑	+ +	+ + +	+ + + +	+ + + +

Nerve conduction and electromyography show a sensorimotor polyneuropathy with axonal loss. APB: abductor pollicis brevis, AT: anterior tibialis, CV: conduction velocity, DL: distal latency, FDI: first dorsal interosseous, mV: microvolt, m/sec: meter per second, MG: medial gastrocnemius, MUP: motor unit potential, NA: not available, NR: not recordable, TFL: tensor fasciae latae, VM: vastus medialis.

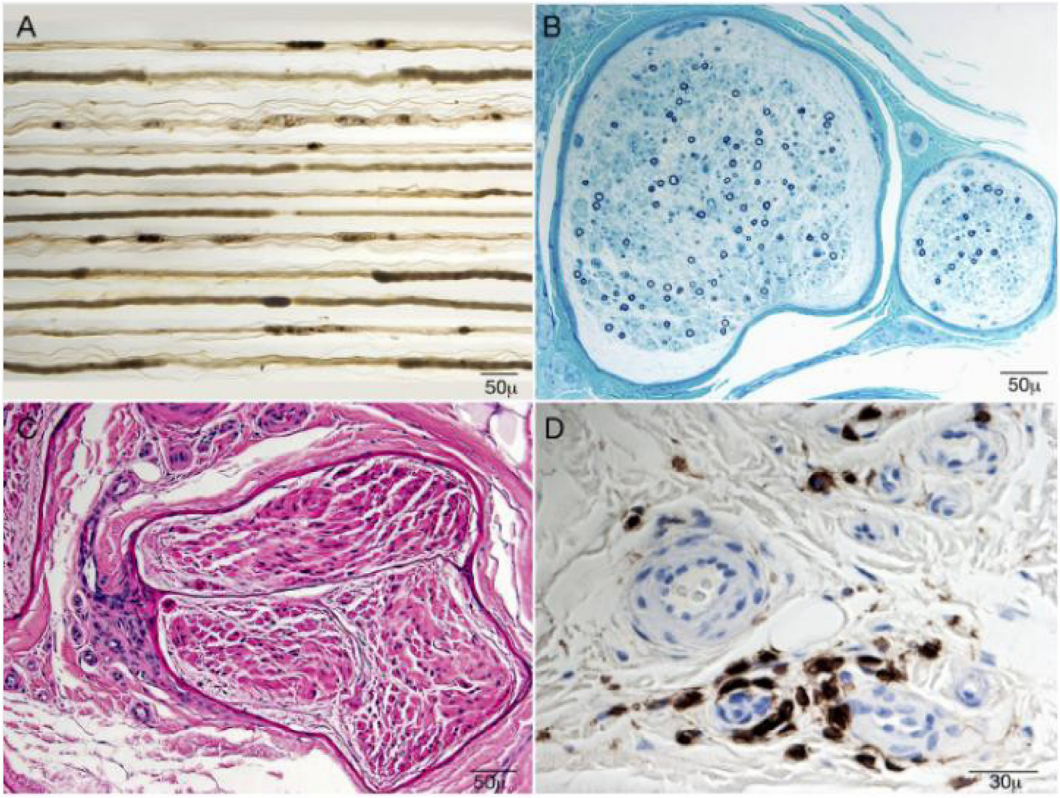

Fig. 1. Sural nerve biopsy.
A: Teased sural nerve fiber preparation shows axonal degeneration and segmental demyelination, B: Methylene blue epoxy stain shows an edematous nerve with reduced density of myelinated fibers, C: Hematoxylin and Eosin stain shows epineurial neovascularization, D: CD 45 staining shows some perivascular inflammatory cells.

mcmol/24 h (reference < 2.2 mcmol/24 h). Porphobilinogen deaminase gene mutation was detected confirming acute intermittent porphyria (AIP). His weakness partially improved with physical therapy.

1. Discussion

Acute intermittent porphyria is a rare multisystem paroxysmal disorder of the heme biosynthesis. Patients present with attacks of

abdominal pain, psychiatric symptoms or episodic axonal neuropathy due to accumulation of toxic heme precursors. Triggers include stress, starvation, porphyrinogenic medications and hormonal fluctuations [1]. It is important for neurologists to recognize this disorder as recurrent attacks of axonal neuropathy can lead to disability. In our case, episodic abdominal pain was most likely representative of milder attacks of porphyria.

Patient's father suffered from neuropathy, and grandfather had episodes of psychosis; this may be representative of incomplete penetrance of this autosomal dominant disorder.

It is important to consider a broad differential diagnosis of recurrent acute to subacute onset axonal neuropathy. Immune mediated neuropathies such as CIDP, anti- MAG, anti-ganglioside associated neuropathy, multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), MMN, and paraproteinemic neuropathy can occasionally have a similar course. On neurophysiologic studies temporal dispersion is often present in CIDP; multifocal conduction block can be seen in vasculitic neuropathy, MMN and MADSAM [2].

Among paraproteinemic neuropathies, multiple myeloma is associated with axonal sensorimotor neuropathy. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome may cause CIDP like presentation. Waldenstrom's macroglobulinemia causes a sensory predominant neuropathy and light chain amyloidosis can cause neuropathy with prominent autonomic involvement [3].

Heavy metal neuropathy is a consideration when abdominal symptoms, neuropathy and encephalopathy coexist. Arsenic, lead and thallium are most likely to cause chronic sensorimotor neuropathy [4]. Infectious neuropathies including Lyme, West Nile virus, hepatitis and HIV, can cause asymmetric polyradiculoneuropathy [5]. In this case, infection was ruled out with CSF evaluation and negative serology. Vasculitic neuropathy, due to primary/sondary systemic or non-systemic vasculitis is an important differential of subacute neuropathy. In cases of systemic vasculitis skin abnormalities occur in 30% of the patients along with multisystem involvement [6]. Nerve pathology is usually diagnostic with perivascular inflammatory infiltrates.

Paraneoplastic involvement of the peripheral nervous system can result in isolated sensory/motor, mixed sensorimotor, autonomic neuropathy; these have been associated with ANNA-1, ANNA-2, CRMP-5 and PCA-1 antibodies [7]. In our case, negative serum and CSF paraneoplastic antibody titers effectively rule out this possibility.

Acute intermittent porphyria is a deficiency of porphobilinogen deaminase enzyme, inherited in an autosomal dominant manner. Accumulation of toxic metabolites porphobilinogen (PBG) and aminolevulinate (ALA) cause neurotoxicity. A mixed axonal and demyelinating neuropathy can occur with each attack. Recovery occurs without treatment however patients may be left with residual weakness due to axonal damage. Incomplete penetrance, carrier and latent states have been described where patients may not manifest the complete spectrum of disease. Treatment includes avoidance of triggers, dextrose and hematin infusions [1]. Our patient was not treated with acute treatment options as his symptoms related to chronic nerve injury from past AIP attacks as opposed to an acute AIP attack.

Porphyrinogenic medications include barbiturates, antiepileptics, alcohol and smoking. These should be avoided as they may trigger attacks.

Diagnosis is ascertained during the acute attack by demonstrating levels of urine porphyrins. Asymptomatic patient may also have elevated urine porphyrins such as our patient however this is much less common than during an acute attack. In these cases, diagnosis can be confirmed by porphobilinogen deaminase genetic tests and measuring enzyme activity.

Conflict of interests

None of the authors have any conflict of interest to disclose.

Ethical publication statement

“We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.”

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