

Case Report

Acute Intermittent Porphyria: A Report of 3 Cases with Neuropathy

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Keywords

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Abstract

The porphyrias are metabolic disorders due to a defect in the heme biosynthetic pathway. Patients have diverse clinical presentations with neuropathy being frequent in acute intermittent porphyria (AIP). Associated symptoms are abdominal pain and seizures. Three patients presenting with neuropathy were later diagnosed with AIP on the basis of clinical features, erythrocyte porphobilinogen deaminase activity, neuropathic patterns, and nerve conduction studies. Testing for the HMBS genetic mutation confirmed the diagnosis of AIP in 1 patient. The findings from this case series confirm that porphyric neuropathy in AIP is a predominantly motor neuropathy with differing neuropathic presentations ranging from focal motor neuropathy to quadriplegia and respiratory failure.

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Introduction

Porphyrin molecules are called the “pigments of life” for their contributions to heme, the responsible molecule for the color of red blood cells [1]. The porphyrias are a group of metabolic disorders representing a diverse range of clinical symptoms according to the specific subtype and underlying enzymatic defect in the heme biosynthetic pathway caused by genetic mutations with a consequent overproduction of porphyrins, the essential intermediates of this pathway [2, 3]. The acute porphyrias can be either autosomal dominant, such as acute intermittent porphyria (AIP), variegate porphyria, and hereditary coproporphyria, or autosomal recessive, such as delta aminolaevulinic acid (ALA) dehydratase deficiency [4].

The typical acute porphyria attacks manifest with severe and diffuse abdominal pain, constipation, nausea, and vomiting followed sometimes by a confusional state and psychiatric disturbances. Autonomic instability with tachycardia and hypertension may be present, and seizures commonly occur [4, 5]. It has also been reported that severe porphyric neuropathy can occur in isolation without other preceding symptoms [4] and that peripheral neuropathy occurs in up to 40% of patients during an acute attack of porphyria [3, 6, 7]. Of the porphyrias, neurological involvement is limited to 4, namely AIP, HCP, variegate porphyria, and ALA dehydratase deficiency porphyria [8–10]. Within these disorders, AIP is the form that is most commonly associated with neurological disease [3]. The clinical presentations of porphyric neuropathy range from mild focal neuropathy to more severe presentations with a Guillain-Barré-like picture [3, 6, 11]. Here, we report 3 cases of porphyria with differing neurological presentations.

Case Report

Case 1

A 42-year-old woman presented with an 8-month history of distal symmetric hand weakness affecting the extensor muscles that started during hospitalization following an episode of severe abdominal pain and electrolyte disturbance. Her medical history includes hypertension, generalized seizures, cardiac arrhythmia, and chronic neck pain. She had been hospitalized previously with episodes of abdominal pain and generalized seizures. On examination, she had bilateral grade 0/5 of extensor indicis, 3/5 extensor digitorum communis and interossei muscles with decreased brachioradialis reflexes. All sensory modalities were normal, and no gait or cerebellar abnormalities were observed. On electromyography (EMG), the patient had reduced radial compound muscle action potential (CMAP) amplitudes with normal conduction velocities and normal radial nerve sensory studies. The EMG studies showed scattered active fibrillation potentials in the radial and ulnar nerve supplied muscles with reduced recruitment of normal motor unit action potentials. The urinary porphobilinogen level was 188 $\mu\text{mol/L}$ (NI <9 $\mu\text{mol/L}$) and ALA 94 $\mu\text{mol/L}$ (NI <50 $\mu\text{mol/L}$). The genetic test showed the HMBS genetic mutation which is associated with autosomal dominant AIP (c.716delA in HMBS).

Case 2

A 33-year-old previously healthy woman presented with abdominal pain and behavioral symptoms. She developed hyponatremia, seizures, and rapidly progressive weakness leading to respiratory failure, quadriplegia, and autonomic instability. Cerebrospinal fluid was acellular with normal protein and glucose. Initial nerve conduction studies showed prolonged F

waves, and follow-up studies demonstrated absent sensory and motor responses with signs of profuse active denervation on needle examination (fibrillation potentials and reduced recruitment). Quantitative urine testing for porphyria was abnormal and in keeping with AIP. The patient had severe axonal porphyric neuropathy resulting in significant disability.

Case 3

A 27-year-old woman developed abdominal pain, nausea, and vomiting attributable to hyperemesis gravidarum as she was 7 weeks pregnant. She developed persistent hyponatremia, seizures, and behavioral symptoms and then, after a few weeks, progressive weakness and autonomic instability. She also had significant neuralgia. CSF studies were normal. Magnetic resonance imaging of the brain showed changes in keeping with reversible posterior leukoencephalopathy. Consecutive nerve conduction studies were normal, but needle assessment showed marked increased insertional activity and fibrillation potentials in the paraspinal, proximal, and distal muscles. Electrodiagnostic findings were in keeping with multilevel axonal polyradiculopathy. Expedited urine quantitative testing confirmed the diagnosis of AIP. She received heme and supportive therapy with resolution of weakness and seizures but had a spontaneous abortion.

Discussion

We present 3 patients with AIP with varying degrees and patterns of motor weakness. In the first patient, motor symptoms were limited to the radial and ulnar nerve innervated muscles. In the second patient, the clinical presentation mimicked Guillain-Barré syndrome (GBS) with progressive weakness leading to respiratory failure and quadriplegia. The electrodiagnostic studies demonstrated absence of both sensory and motor responses with profuse fibrillation potentials and loss of recruitment on needle examination. In the third patient, progressive weakness was associated with marked fibrillation potential activity in the paraspinal, proximal, and distal muscles on EMG in keeping with multilevel axonal polyradiculopathy. All 3 patients had abdominal symptoms and seizures. The second and third cases also had hyponatremia and behavioral changes during the acute phase of the illness. In summary, the presentation of porphyric neuropathy in our patients ranged from focal motor neuropathy to quadriplegia and respiratory failure.

During an acute attack, heme precursors accumulate due to the deficient enzyme, and the excess porphyrin metabolites are then excreted in the urine and feces. In AIP, urinary ALA and porphobilinogen are markedly elevated, leading to the diagnosis as found in these cases [4]. Drugs can provoke an acute porphyric attack, especially those that induce cytochrome P450 proteins (CYP) and those that cause transcription of the rate-limiting enzyme of the heme biosynthetic pathway [12]. The mechanism contributing to the development of nerve dysfunction remains unclear, but recent studies suggest that axonal dysfunction relates to Na⁺/K⁺ pump energy dysfunction resulting from the lack of heme availability and a direct neurotoxic effect of porphyrin precursors [13]. Previous reports have demonstrated that hyponatremia has been observed in up to 30% of the patients, due to either primary salt wasting or the syndrome of inappropriate antidiuretic hormone secretion [3].

Motor symptoms are prominent and, as apparent in our first patient, have a predilection for the upper extremities and particularly the radial nerve innervated muscles for unknown reasons [14]. More recent studies have demonstrated that focal weakness, manifesting as isolated wrist drop or foot drop, is an increasingly common finding [3, 11]. Reports of nerve

conduction studies in patients with porphyric neuropathy have demonstrated decreases in compound action potential amplitudes, particularly in radial and fibular nerves with varying sensory involvement [6, 11, 14].

The electrophysiologic picture in porphyric neuropathy is consistent with axonal damage similar to changes observed in lead intoxication and other neuropathies [6, 11]. Interestingly, a coasting phenomenon is also reported, in which the CMAP amplitude reductions continued to worsen for up to 3–5 months after the initial diagnosis. This phenomenon is also described in some toxic neuropathies, including vitamin B₆, thalidomide, chemotherapy, and acrylamide [15].

In contrast to motor nerve conduction study findings, sensory nerve conduction findings are scant or show only subtle changes in the patients with AIP [6, 7, 15]. This predominantly motor pattern in porphyric neuropathy may help in the differentiation from other common metabolic neuropathies, such as those related to diabetes mellitus or kidney impairment, in which sensory involvement is typically more prominent. Cranial nerve involvement has also been described in AIP, most commonly affecting the facial and vagus nerves and leading to facial weakness, dysphagia, and dysarthria [7]. In addition, needle EMG typically shows evidence of widespread active fibrillation potentials and loss of recruitment, particularly in proximal muscles [5, 15].

Information on the prognosis of porphyric neuropathy is limited, although the degree of axonal damage probably predicts the ultimate prognosis. Recovery often takes many months with some patients with the GBS variant remaining permanently quadriparetic [4, 5]. Treatment for AIP includes both supportive and specific therapies. Once a porphyric attack is diagnosed, precipitating factors or provoking agents should be withdrawn. In addition, glucose supplements or parenteral administration of hematin are suggested [12, 14].

Conclusion

Porphyric neuropathy is a predominantly motor neuropathy with differing clinical presentations that may mimic various neuropathies, such as GBS, with diffuse axonal involvement or lead neuropathy with specific nerve involvement, such as bilateral radial neuropathy. A diagnosis of porphyria should be considered particularly in those patients with abdominal complaints and seizures.

Statement of Ethics

The patients have given their written informed consent to publish their case.

Disclosure Statement

The authors have no conflicts of interest to declare.

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