RESIDENT & FELLOW SECTION

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Clinical Reasoning: A 20-year-old woman with rapidly progressive weakness

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SECTION 1

A 20-year-old healthy woman developed abdominal pain accompanied by mild frontal headaches, labile mood, vomiting, and dark urine. She underwent an extensive workup including endoscopy, abdominal CT scan, and eventually exploratory laparotomy. No abdominal cause of her symptoms was detected and she was discharged. Approximately 1 week after surgery, she developed low back pain and numbness in the buttocks and upper thighs. Within several days, her sensation was reduced in her hands and she developed generalized weakness. Her only medication was an oral contraceptive, which was started 1 month before onset of abdominal symptoms. She presented to our institution 3 weeks after symptom onset and reported diffuse weakness, most prominent in the proximal arms. She still had mild pain and numbness in the abdominal area, low back, and buttocks, but the numbness in the arms and legs had subsided. Neurologic examination revealed profound symmetric weakness in the proximal arms and moderate weakness in the proximal legs. Sensory examination demonstrated a band-like area of decreased sensation to pinprick in the lower abdomen and low back. Deep tendon reflexes were 2+ at the biceps and triceps and 3+ at the knees. Hoffmann sign was present on both sides. There were 1 to 2 beats of unsustained ankle clonus bilaterally. Plantar responses were flexor. Cranial nerve examination was normal.

Question for consideration:

1. What is your differential diagnosis at this stage?

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SECTION 2

This patient presented with rapidly progressive symmetric weakness preceded by several days of abdominal pain of unclear etiology. Associated symptoms included headaches, labile mood, and dark urine. The initial clinical presentation included sensory disturbances with low back pain and numbness in the buttocks and upper thighs. At the time of our evaluation, 3 weeks after onset, there was still mild pain and numbness in the trunk area, but the clinical picture was clearly dominated by a motor rather than a sensory deficit. Weakness was more pronounced proximally and was worse in the arms than the legs.

A pure CNS process affecting only strength appeared unlikely given the pattern of weakness and reflex examination. Peripheral causes of rapidly progressive, diffuse weakness include polyradiculopathy, motor neuropathy or neuronopathy, acute polyneuropathy with motor predominance, disorders of neuromuscular junction transmission, and myopathy. Polyradiculopathy was less likely given the absence of arm or leg pain. The presence of numbness argued against motor neuropathy or neuronopathy, neuromuscular junction disorder, or myopathy. Therefore, the most likely diagnosis was acute polyneuropathy with motor predominance.

The differential diagnosis for acute motor-predominant polyneuropathy includes immune-mediated or inflammatory causes such as Guillain-Barré syndrome (GBS) or acute onset of chronic inflammatory demyelinating neuropathy (which may be associated with an underlying gammopathy), infections (e.g., Lyme disease, HIV, tick paralysis, West Nile virus, and other polio-like–causing viruses), vasculitis, sarcoidosis, toxic exposure (lead), and metabolic causes (e.g., porphyria, thyrotoxicosis, or diabetes mellitus). GBS, the most common consideration in this scenario, usually presents as ascending paralysis and areflexia. Lower extremity reflexes were brisk in our patient.

Question for consideration:

1. What testing would you perform to clarify the diagnosis?

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SECTION 3

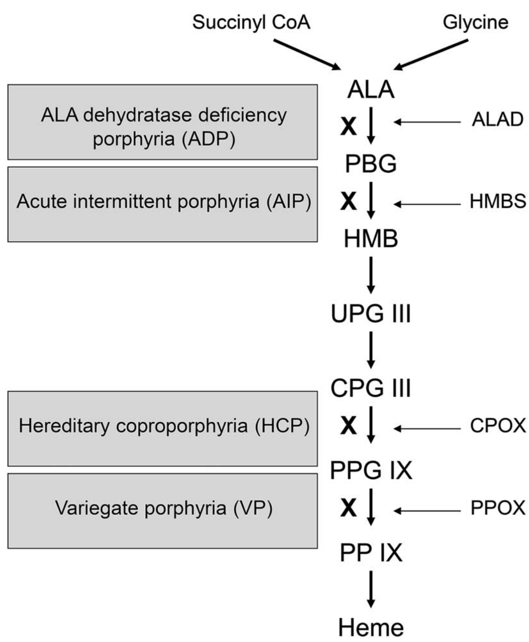
Pertinent laboratory evaluations include complete blood count, complete metabolic panel, thyroid studies, creatine kinase level, erythrocyte sedimentation rate, C-reactive protein, HbA1C, GM-1 antibodies, serum protein electrophoresis with immunofixation, serology for Lyme, HIV, cytomegalovirus, and West Nile virus, and a blood lead level. CSF examination can be considered and should include cell count, glucose, protein, and cytology.

Electrodiagnostic studies were obtained 3 weeks after the onset of weakness. Sensory and motor nerve conduction results, including F waves, were normal. Needle EMG demonstrated fibrillation potentials and positive sharp waves in the proximal muscles of the arms and legs and reduced recruitment of remodeled motor units in several muscles (table). Based on the presentation of acute proximal weakness preceded by unexplained abdominal pain, dark urine, and mood changes, the urine porphyrin precursor PBG (porphobilinogen) was evaluated and found to be elevated. Diagnosis of acute intermittent porphyria (AIP) was confirmed by molecular analysis, which revealed a pathogenic mutation in the *HMBS* (hydroxymethylbilane synthase) gene (also known as *PBGD* gene).

DISCUSSION The patient's presentation, examination, and clinical testing results are classic for an attack of acute porphyria.

The porphyrias are a group of inherited diseases caused by deficiency of enzymes of the heme synthetic pathway (figure), resulting in accumulation of porphyrins and their precursors.[1] The porphyrias are divided into the acute hepatic porphyrias and the erythropoietic porphyrias. The acute hepatic porphyrias are most relevant for neurologists because of their neurologic manifestations, whereas the erythropoietic porphyrias do not cause neurologic symptoms.[1] The acute hepatic porphyrias include ADP (ALA dehydratase deficiency porphyria), AIP, HCP (hereditary coproporphyria), and VP (variegate porphyria) (figure).[1] The most common acute porphyria is AIP, an autosomal dominant disorder with low penetrance (estimated between 10% and 50%).[2,3] Individuals who do manifest symptoms typically do so after a "second hit," such as an environmental trigger (certain medications, stress, hormonal changes, and starvation) or other unknown factors.[1,2] Our patient had started using oral contraception about a month before onset of abdominal symptoms, a possible trigger for the attack.

Figure **Enzymatic steps and intermediates of the heme synthetic pathway**



The first step in heme synthesis is the synthesis of δ-aminolevulinic acid (ALA) from succinyl coenzyme A and glycine. ALA is then metabolized to porphobilinogen (PBG) by ALA dehydratase (ALAD). Mutations in ALAD cause ALA dehydratase deficiency porphyria (ADP), an exceptionally rare condition. PBG is then converted to hydroxymethylbilane (HMB) by HMB synthase (HMBS). Mutations in *HMBS* cause acute intermittent porphyria (AIP), the most common acute hepatic porphyria. Note that *HMBS* is also known as PBG deaminase. ALA and PBG accumulate during acute attacks of AIP. The other acute hepatic porphyrias are hereditary coproporphyria (HCP), which is caused by mutations in CPOX (CPG oxidase, the enzyme that catalyzes the formation of PPG IX from CPG III), and variegate porphyria (VP), which is caused by mutations in PPOX (PPG oxidase, the enzyme that catalyzes the formation of PP IX from PPG IX). Mutations in the other enzymes that are part of the heme synthetic pathway cause erythropoietic porphyrias and are not represented here. Note that heme acts as a direct negative feedback on the formation of ALA. CPG = coproporphyrinogen; PP = protoporphyrin; PPG = protoporphyrinogen; UPG = uroporphyrinogen.

Table **Needle EMG results**

	Fibs/PSWs	MUAP amplitude	MUAP duration	Recruitment
R deltoid	3+	No units	No units	No units
L biceps	3+	Normal	Long	Severely reduced
R biceps	3+	Normal	Long	Severely reduced
R triceps	1+	Normal	Long	Severely reduced
R pronator teres	0	Normal	Normal	Normal
R FDI	0	Normal	Normal	Normal
R iliopsoas	1+	Normal	Normal	Normal
R vastus lateralis	2+	Normal	Normal	Mildly reduced
R tibialis anterior	0	Normal	Normal	Normal

Abbreviations: FDI = first dorsal interosseous; Fibs = fibrillations; MUAP = motor unit action potential; PSWs = positive sharp waves.
MUAP amplitude, duration, and recruitment were normal unless otherwise indicated. Sensory and motor nerve conduction studies (including F waves) were normal in the bilateral arms and legs. There was no evidence of slowed conduction in any of the nerve conduction studies.

The neurologic manifestations of the acute hepatic porphyrias are due to acute increases in the concentration of the heme precursors ALA (δ-aminolevulinic acid) and PBG (porphobilinogen) (figure). The typical neuropathy is an acute or subacute motor axonopathy predominantly affecting proximal muscles and generally worse in the arms than the legs.[1] Maximum involvement is usually reached within 4 weeks of symptom onset. Cranial nerves are involved in approximately 75% of cases. Ventilatory muscle weakness is common. Sensory symptoms are reported in about 60% of patients in either a proximal "bathing-trunk" or a "stocking and glove" pattern. Symptoms of weakness are usually preceded by episodes of abdominal pain secondary to autonomic neuropathy.[1] Nausea, vomiting, constipation, and diarrhea may be caused by gastroparesis and pseudo-obstruction secondary to splanchnic autonomic neuropathy. Other symptoms of autonomic dysfunction include tachycardia, hypertension or postural hypotension, urinary retention, and diaphoresis. CNS involvement manifests as a wide spectrum of psychiatric symptoms, which include irritability, depression, hallucinations, and delirium. When psychiatric symptoms dominate an acute presentation, misdiagnosis is common.[4] Seizures are also possible.[5] HCP and VP manifestations may also include photosensitive dermatologic lesions, which are not present in ADP and AIP. Discoloration of urine on exposure to light is common and is due to increased urinary porphyrins.

Porphyric neuropathy can mimic other acute neuropathies, particularly when abdominal symptoms are minor or absent.[5] Clinical clues to the presence of acute porphyria include the distribution of the weakness (with predilection of proximal arm muscles initially, rather than ascending weakness as in GBS), the history of recurrent attacks, and the presence of associated psychiatric symptoms and discolored urine. CSF examination can be normal or demonstrate elevated protein without pleocytosis. Deep tendon reflexes can be normal or depressed. Nerve conduction studies can be normal or show a pattern of motor predominant axonal neuropathy without demyelinating features.[6] EMG shows patchy denervation and chronic reinnervation changes.[6]

The porphyrias can be diagnosed by measurement of urinary ALA and PBG levels, which are increased during an acute attack.[7] A qualitative assay can be performed first but must be followed by quantitative measurements performed after a 24-hour urine collection. The urine collection for quantitative analysis should be protected from light, refrigerated, and sent to a laboratory with special expertise in porphyria diagnosis. Genetic testing should be performed to confirm the diagnosis.[7] The phenotype of acute porphyrias varies even within families and penetrance is low.[2,3] Nonetheless, knowledge about the mutation allows screening of asymptomatic family members at risk, an important management issue because early diagnosis and knowledge about precipitating factors can help diminish the morbidity of the disease.[7]

Management of an acute episode includes stopping attack triggers, supportive therapy, and downregulation of the heme synthetic pathway.[8] The list of medications that may induce a porphyric attack is extensive and can be found on a few dedicated Web sites.[9–12] Supportive therapy includes management of complications such as hyponatremia, hypertension, tachycardia, pain, and seizures.[8] Downregulation of the heme synthetic pathway is accomplished by carbohydrate loading (because glucose inhibits ALA synthesis) and/or administration of hematin.[8] Hematin replenishes the depleted heme pool and provides negative feedback on the heme synthetic pathway, thus reducing the production of the porphyrin precursors. The use of a medical alert bracelet should be considered to prevent future administration of potentially toxic medications. With prompt diagnosis and treatment, most patients recover from the acute neuropathy, with a small percentage developing a chronic neuropathy, but serious complications can occur with delayed management.[2,13] Our patient was transferred to an acute rehabilitation hospital and underwent multidisciplinary rehabilitation over a 3-week period. At discharge, she was able to walk independently but still required help with activities of daily living secondary to bilateral proximal upper extremity weakness. The patient then moved out of state and long-term follow-up is not available.

AUTHOR CONTRIBUTIONS

Sabrina Paganoni and Colin Quinn: study concept/design, analysis/interpretation of data, drafting/revising the manuscript. Mohamamd Kian Salajegheh: analysis/interpretation of data, drafting/revising the manuscript.

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