

Pearls & Oy-sters: Guillain-Barré syndrome

An unusual presentation of acute intermittent porphyria

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Pearls

- Porphyria is a rare disorder of heme metabolism and clinical manifestations are determined by the accumulation of porphyrin precursors.
- The best management is through prevention, mainly by avoidance of precipitating factors, such as alcohol intake, cytochrome P450-inducing agents, hormone treatments, and starvation.
- The mainstay of treatment is IV hematin but IV glucose should also be considered in the context of an acute attack.

Oy-sters

- Acute intermittent porphyria is an essential differential diagnosis in patients with rapidly progressive weakness.
- Acute intermittent porphyria should be suspected in patients with a combination of abdominal pain, psychiatric disturbance, and peripheral neuropathy with prominent proximal weakness; dysautonomia and limb pain are frequently present.
- Porphyric neuropathy differs from Guillain-Barré syndrome (GBS) as it affects mostly the proximal muscles and upper limbs and nerve conduction study typically shows axonal motor neuropathy. The classic cytoalbuminologic dissociation is not present in acute porphyria attack.

A 61-year-old man presented to the hospital with a 1-week onset of progressive abdominal pain, constipation, and vomiting. Ten days before this presentation, he had been diagnosed with cystitis by his general physician and treated with levofloxacin 500 mg daily for 7 days. On admission, he described recurrent severe paroxysmal abdominal pain. His medical history was notable for heavy alcohol use (149 g daily). No illicit drug use or chemical exposure was reported. For 2 years, he had repeatedly attended his general practitioner with recurrent abdominal pain, but with no cause found. There was no known family history of neurologic disease.

On assessment in the emergency department, the patient had mild hypertension and tachycardia with a heart rate of 115 beats per minute. He presented with acute urinary retention and with intermittent agitation but no focal motor weakness while on observation.

Laboratory workup revealed acute kidney failure with creatinine of 3.8 mg/dL and blood urea nitrogen 28.1 mmol/L, hyponatremia of 122 mmol/L, sedimentation rate 40 mm, and C-reactive protein 168.2 mg/L. After urinary catheterization and IV hydration, his renal function resolved (creatinine 1 mg/dL). His serum creatinine kinase concentration was normal. Abdominal radiograph showed generalized, uniform, gaseous distension of the large and small bowel. Intestinal occlusion was excluded by the surgical team and the patient was diagnosed with adynamic ileus due to cystitis.

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The patient's progress in the ward was eventful as he was noted to have fluctuating agitation and confusion. He was persistently hypertensive and became progressively agitated and remained constipated. The patient also presented with dysphonia and hoarseness. Two days later, he developed proximal muscle pain and weakness; examination showed moderate bilateral hip flexion weakness. Over the next few days, he developed profound weakness in all 4 limbs, and was transferred to the neurology unit with a probable diagnosis of GBS.

On admission to the neurology unit, the patient was alert with preserved orientation, memory, and language. His pupils were normal and there was no evidence of ptosis or ophthalmoplegia. His speech was normal and there was no tongue atrophy or fasciculations. Swallow test revealed severe dysphagia. He had marked bilateral weakness, predominantly proximal (Medical Research Council [MRC] grades in lower limbs, proximal 2/5 and distal 4/5). Upper limb examination revealed distal weakness (MRC 1/5) and neck flexion MRC 2/5. Vibration and proprioception were normal. Gag reflex was absent and there was aquiline, patellar, and brachioradialis areflexia. CSF examination showed a normal cell count but an elevated protein level of 870 mg/dL (normal range 100–400 g/L). CSF glucose, white cell count, Gram stain, and culture were unremarkable.

Considering the postinfectious nature of the disease, associated with progressive ascending and symmetric weakness and areflexia, a diagnosis of GBS was suspected and a 5-day course of IV immunoglobulin was started. Worsening neuropathy led to hypoxic respiratory failure due to aspiration pneumonia requiring noninvasive ventilation and antibiotics.

The persistent abdominal pain and mental status changes and the pure motor involvement with proximal distribution were not in keeping with GBS and several tests were performed.

EMG was performed 1 week after symptom onset and revealed low compound muscle action potential amplitudes more pronounced in the lower limbs as well as reduced sensory nerve action potentials. Sensory responses were relatively preserved. These findings would be supportive of acute axonal motor neuropathy (table).

Further workup including autoimmune panel and vasculitis screen were negative as well as infectious diseases screening for Lyme disease, HIV, hepatitis B and C, campylobacter, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. Paraneoplastic antibodies panel was also negative, as well as anti-voltage-gated calcium channel antibody, antiganglioside antibodies, and anti-acetylcholine receptor antibody. Tests for heavy metals including lead, mercury, and copper were also normal. Brain CT and MRI of the brain and spine were unremarkable.

The combination of abdominal and behavioral symptoms with axonal neuropathy raised the suspicion of porphyria,

which was confirmed by high levels of urinary porphyrins. Total urinary porphobilinogen of 482 $\mu\text{g}/24$ hours (reference <150 $\mu\text{g}/24$ hours), urinary coproporphyrin I 33 $\mu\text{g}/24$ hours (reference <25 $\mu\text{g}/24$ hours), urinary coproporphyrin III 55 $\mu\text{g}/24$ hours (reference <75 $\mu\text{g}/24$ hours), and urinary δ -aminolaevulinic acid 0.8 mg/dL (reference <0.60 $\mu\text{g}/24$ hours) were noted. These findings support a diagnosis of acute intermittent porphyria.

IV dextrose (40% dextrose, 1 L over 12 hours) was started and there was no need for specific treatment with daily human hemin (Normosang; Orphan Europe) as the patient started to improve and was discharged home well. Two months later, the patient had recovered completely and remains healthy.

Discussion

Porphyria is a disorder caused by a defect in an enzyme responsible for the synthesis of heme.¹ The clinical manifestations of the porphyrias are determined by the accumulation of porphyrins and porphyrin precursors.

According to their clinical manifestations, they can be divided further into hepatic and erythropoietic porphyrias.² There are 5 hepatic porphyrias, with 4 typically presenting with episodic, acute neurovisceral manifestations, of which acute intermittent porphyria is the most prevalent.³

The classic triad of abdominal pain, mental status changes, and neuropathy occurs in approximately half of cases.⁴ Over 90% of autonomic neuropathy cases related to porphyria are associated with abdominal pain with or without constipation, diarrhea, nausea, and vomiting. This is thought to be caused by gastroparesis and pseudo-obstruction related to splanchnic autonomic neuropathy. Tachycardia occurs in most acute episodes and hypertension or less commonly postural hypotension may also occur.

Peripheral neuropathy is common during acute porphyria and complicates 10%–40% of episodes.⁵ The onset of neuropathic features is usually delayed and is typically an acute axonal motor neuropathy. Proximal muscles are predominantly affected, and respiratory muscle weakness is common. Respiratory failure with the need of assisted ventilation is a major source of morbidity and mortality.⁶

An acute attack is often preceded by irritability and subtle neuropsychiatric symptoms. Hyponatremia may also occur and may contribute to the neurologic manifestations.⁷ Acute porphyria may mimic a myriad of other conditions, particularly when abdominal symptoms are minor or absent. The classic presentation of GBS shares many features with acute porphyria.⁸ Autonomic dysfunction is associated with GBS and may follow an acute gastrointestinal infective illness, making the distinction from an acute attack of porphyria difficult. The pattern of involvement may help distinguish the 2 neuropathies,

Table Nerve conduction study results

Type of study	Side/nerve	Stimulation site	Recording site	Latency, ms	Duration, ms	Amplitude, μ V	Conduction velocity, m/s	F-wave, ms
Sensory	Right median	Index	Wrist	3	1.35	18.8	48.3	—
Sensory	Left	Leg	Ankle	2.23	1.94	16.6	41.3	—
	superficial peroneal							
Sensory	Left	Malleolus	Leg	2.77	2	12.4	41.9	—
	sural							
Sensory	Left	Digit V	Wrist	2.38	1.22	8.1	49.6	—
	ulnar							
Motor	Right median	Wrist	APB	3.25	—	9.7		36.8
		Elbow	Wrist	12.65		2.5	48.2	
Motor	Left fibular	Ankle	EDB	5.35	—	2.3		83.6
		Below knee	Ankle	14.4		1.09	33.1	
		Above knee	Below knee	17.5		1.05	32.2	
Motor	Left	Ankle	AB	4.61	—	8.5	29.7	76.9
	tibial	Knee	Ankle	19.3		1.4		
Motor	Right ulnar	Wrist	ADM	3.25	—	7.6		36.7
		Elbow	Wrist	8.6		3.2	44	

EMG

Spontaneous activity						Voluntary activity			
Muscle	Interpretation	Fibrillation potentials	Positive sharp waves	Fasciculations	Amplitude	Polyneuropathies	Stability	Interference pattern	Recruitment
Right biceps	Neurogenic	1+	0	1+	+	+	-	-	Reduced
Left biceps	Neurogenic	1+	0	1+	+	+	-	-	Reduced
Left extensor digitorum brevis	Neurogenic	1+	0	-	+	+	-	-	Reduced
Right dorsal interossei	Neurogenic	1+	0	1+	+	+	-	-	Reduced
Left tibialis anterior	Neurogenic	1+	0	1+	Normal	Normal	-	-	Reduced
Left vastus medialis	Normal	0	0	-	Normal	Normal	Normal	Normal	-

Abbreviations: AB = abductor hallucis; ADM = abductor digiti minimi; APB = abductor pollicis brevis; EDB = extensor digitorum brevis.

with acute porphyria characteristically involving the upper limbs and proximal muscles initially. CSF examination may also be helpful with typical protein elevation in GBS.

Nerve conduction studies also suggested GBS, showing predominantly acute motor axonal neuropathy out of proportion to sensory involvement. Because of the patient's medical history, alcohol-related peripheral neuropathy was ascribed as a probable cause for the subtle sensory findings. Chronic alcoholism-related neuropathy generally presents an insidious onset and is slowly progressive, length-dependent, and associated with lifetime alcohol consumption.⁹

High index of suspicion for porphyria is warranted in acute motor axonal neuropathy as it may not always present with the classic triad of abdominal pain, neuropsychiatric manifestations, and neuropathy at the same time. The porphyrias can be diagnosed by determining increased urine porphobilinogen on a random urine sample protected from light. Measurement of urinary porphyrin by itself may be misleading as it may be increased in other conditions such as hepatobiliary disease, alcohol abuse, or infections. All positive tests should be confirmed by quantitative method, usually by anion exchange chromatography and preferably on the same urine sample.¹⁰

The mainstay of treatment is avoidance of porphyrinogenic agents, supportive therapy, and reduction of the activity of the heme synthetic pathway. IV heme is used in severe attacks.⁹ In mild attacks, with no vomiting, weakness, or hyponatremia, high doses of IV glucose can inhibit heme synthesis and are useful for treatment, and preferable to heme preparations as the treatment of choice for an acute attack of porphyria, owing to fewer side effects.^{4,8,10}

Early diagnosis and prompt treatment ensure reduced morbidity and mortality.

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