**CLINICAL VIGNETTE**

# Acute Intermittent Porphyria

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***Case Presentation***

A 33-year-old female presented with lethargy and one day of altered mental status. She had been feeling poorly for five days and complained of abdominal pain and persistent nausea and vomiting. Past medical history includes fluctional abdominal pain with multiple ED visits for generalized abdominal pain, with unremarkable labs and imaging. No etiology was ever established.

Vital signs in the emergency room showed she was afebrile, tachycardic to 107, with BP 170/113, RR of 18/min with 95% O2sat on room air. The patient was confused and altered from baseline. Exam was otherwise unremarkable. Initial labs revealed severe hyponatremia to 110. Urine was orange to brown colored. She was admitted and started on hypertonic saline with initial improvement in her sodium levels. Her hyponatremia was attributed to hypovolemia from nausea and vomiting. She was continued on maintenance IV fluids. After initial improvement of sodium to the low 120s, it began to drop, leading to consideration of inappropriate secretion of anti-diuretic hormone. Her mental status improved somewhat but did not return completely to her normal baseline. She repeatedly complained of severe abdominal pain and was significantly agitated and exercised constantly. She was closely monitored and did not sleep for multiple days. She remained persistently tachycardic to 110s-120s and hypertensive to 150s/100s. Labs included markedly elevated urine porphobilinogen establishing diagnosis of acute intermittent porphyria. She received intravenous hemin with improvement and was discharged with close hematology outpatient follow-up.

***Discussion***

Porphyrias includes a range of conditions resulting from disorders in the biosynthesis of heme. The heme biosynthesis pathway involves eight different enzymes, and abnormal enzyme activity of any of these leads to different types of porphyria. Acute intermittent porphyria (AIP), the second most common of the porphyrias (after porphyria cutanea tarda), is caused by a mutation in the gene encoding porphobilinogen deaminase (PBG), which converts porphobilinogen to hydroxymethylbilane. AIP is inherited in an autosomal dominant fashion, but there is significant variability in penetrance, indicating other genetic or environmental factors also impact clinical symptoms.[1]

The overall prevalence of AIP is about 50 in a million. While men and women have an equal chance of inheriting a mutation causing AIP, clinical symptomatic disease is much more common in women. Symptoms typically start after puberty.[2] AIP presents classically with intermittent, acute attacks. These attacks usually involve severe abdominal pain, which also have associated nausea and vomiting, constipation, or ileus. Patients often present with neurologic and psychiatric symptoms such as anxiety, confusion, insomnia, hallucinations, or seizures. On exam, patients will often be tachycardic and hypertensive, with dark urine. Initial laboratory evaluation, AIP patients include frequent hyponatremia, either from inappropriately high secretion of antidiuretic hormone, or from gastrointestinal or renal losses. Abdominal imaging is usually normal, and thus diagnosis may be delayed by weeks or even years.

AIP attacks are thought to be triggered by several different factors, although in many cases no specific trigger can be identified. AIP is categorized as a hepatic porphyria because the porphyrin precursors that build up are related to hepatic heme synthesis, and attacks result from increased heme production in the liver. One common reason is from drugs metabolized through cytochrome P450, as heme is used in the synthesis of cytochrome P450 enzymes.[3] Attacks are also associated with dieting and decreased carbohydrate intake. Attacks also occur regularly with menstrual cycles, suggesting that hormones (particularly progesterone) may contribute to precipitating symptoms.

AIP diagnosis can be made by urine testing for porphyrin precursors. ALA (delta-aminolevulinic acid) and PBG (porphobilinogen) are both usually significantly elevated, over 5-fold the upper limit of normal. Serum porphyrin precursors are also often elevated, but not usually as high as in the urine. If these biochemical tests are suggestive of AIP, genetic testing can solidify the diagnosis.[4]

Treatment of AIP involves suppressing the heme synthesis pathway to decreased buildup of ALA and PBG. The mainstay of treatment is to mitigate potential modifiable triggers for example, stopping drugs that may induce CYP450, and intravenous hemin administration. Studies suggest early administration of hemin is associated with shorter hospitalizations.[5] Historically, carbohydrate loading may help suppress heme biosynthesis. However, this has been significantly less effective than hemin, and should be reserved for very mild attacks.

Supportive care is also important management of an acute AIP attack. Patients should receive pain control and antiemetics as needed, and tachycardia and hypertension should be managed with medications as tolerated. Hyponatremia should also be monitored closely and corrected appropriately.

Early identification and diagnosis of AIP is extremely important. Without adequate treatment, recurrent acute attacks of AIP can result in significant long-term consequences. Patients may develop chronic neuropathies that severely impact their overall quality of life. Repeated attacks associated with hypertension can lead to kidney damage and chronic renal disease.[4] Patients with gene mutations associated with hepatic porphyrias are also at significantly higher risk of hepatocellular carcinoma.[6] The diagnosis of porphyria should be considered in all patients with recurrent and unexplained abdominal pain, especially in menstruating women, to minimalize risk for irreversible long-term sequelae.

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