Effects of hemin and hemodialysis in a patient with acute intermittent porphyria and renal failure

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Key Points

• Hemin and hemodialysis had an additive effect in decreasing ALA and PBG in our patient with acute intermittent porphyria and renal failure.
• The time course of ALA and PBG reaccumulation after hemodialysis is not known.

Introduction

Acute intermittent porphyria (AIP) is the most common type of acute porphyria, with a prevalence of ~5 per 100 000 in the United States.1 It is caused by the partial deficiency of porphobilinogen (PBG) deaminase, also known as hydroxymethylbilane synthase (HMBS), which is the third enzyme in the heme synthesis pathway, resulting in hepatic overproduction of the porphyrin precursors 5-aminolevulinic acid (ALA) and PBG as well as porphyrins.2 The HMBS gene is a 10-kb gene located on11q23.3 and consists of 15 exons. To date, >400 HMBS gene mutations, predominantly point mutations, have been identified as responsible mutations for AIP.3

Most heterozygotes for HMBS mutations are asymptomatic (>80%). Factors such as certain medications, stress, dieting, and infections can provoke acute attacks, and unidentified modifying genes may increase attack susceptibility. Symptoms of an acute attack, which can be life threatening, may include abdominal pain, vomiting, constipation, dark or red urine, muscle weakness, paralysis, hypertension, hyponatremia, and seizures. Clinical manifestations are perhaps due to the neurotoxic effects of ALA on the sensory, motor, and autonomic nervous systems.4-6

Chronic kidney disease is a long-term complication in up to 59% of patients with symptomatic AIP, and it can lead to end-stage renal disease (ESRD).7 Development of ESRD decreases urinary excretion of PBG and ALA, further elevates plasma levels, and may increase symptoms. Plasma porphyrins may also increase sufficiently to cause blistering phototoxicity, and combined liver and kidney transplantation can correct the metabolic derangements of this hepatic porphyria and restore renal function.8

We report a rare and challenging case of AIP in a patient with ESRD on hemodialysis. The plasma PBG and ALA levels with hemin therapy and hemodialysis were compared.

Case description

A 43-year-old man, with AIP diagnosed in his early 30s, had experienced ~8 previous attacks. He also had stage 3 chronic kidney disease and HIV infection and had not taken antiretroviral medications for at least the past 3 months. He was admitted to the hospital with abdominal pain, severe muscle weakness involving the upper and lower extremities, dark urine, sepsis, acute on chronic kidney injury, and a CD4 count of 161. Random urine ALA concentration was 7.6 Umol/L (normal < 0.03), and PBG level was 366 Umol/L (normal < 1.5). Sequencing of the HMBS gene identified a novel alteration, c.478delC, in 1 of his HMBS alleles.

He was treated with broad-spectrum antibiotics for sepsis and with glucose loading and hemin (Panhematin, Recordati Rare Diseases, 4 mg/kg body weight daily) for the acute attack of porphyria. His hospital course was complicated by septic shock, progressive severe motor neuropathy ultimately leading to quadriplegia, respiratory failure requiring ventilator support, and worsening renal failure due to sepsis and acute tubular necrosis, requiring hemodialysis. He stabilized and became afebrile after 20 days of treatment with antibiotics and hemin, but remained anuric and profoundly weak, requiring continued hemodialysis and ventilator support. An unexplained cardiac arrest occurred 3 days after stopping hemin in the absence of apparent infection, electrolyte abnormalities, or ventilator dysfunction. After resuscitation, systemic circulation and mental status returned to their previous levels. Hemin was
We report a patient with AIP who developed a severe exacerbation associated with septic shock and acute on chronic kidney failure requiring hemodialysis. A heterozygous HMBS mutation was identified that, to our knowledge, has not been previously reported. Finding a novel mutation is not uncommon in this disease, in which >400 different HMBS mutations have been reported, many found only in individual families. An acute attack of porphyria was documented by the presence of compatible symptoms and signs, including abdominal pain and severe peripheral motor neuropathy, and substantial elevation of PBG in plasma.

The patient was treated for this severe attack with hemin, which is standard of care treatment, as well as with hemodialysis for acute renal failure, which gave us the opportunity to compare effects of both interventions on circulating levels of the porphyrin precursors ALA, which may be neurotoxic, and PBG. Our results indicate that hemodialysis can significantly lower ALA and PBG in AIP patients, as others have observed. Hemin was more effective in our patient with, for example, PBG falling from 34.46 to 2.15 μM with hemin alone and only to 12.43 with hemodialysis alone. With both treatments, the levels of PBG and ALA fell to even lower and near normal levels than with either treatment alone (Table 1), suggesting that the effects of these treatments were additive. Additional studies with more frequent sampling are needed in patients with AIP and renal failure who are treated with both hemin and hemodialysis to verify our findings.

The effects of hemodialysis in AIP are of interest in part because chronic renal disease is a common long-term complication of symptomatic AIP and can progress to require long-term hemodialysis or renal transplantation. Moreover, as in our case, patients with AIP may require hemodialysis if they develop acute renal failure. Hemodialysis has also been proposed as an alternative primary treatment of acute attacks in patients without renal failure, but it has not been systematically studied for this treatment indication. It is unknown whether partial removal of porphyrins with hemodialysis will improve symptoms, and the time course of reaccumulation of porphyrins after hemodialysis is unknown as well. Unlike hemin and investigational treatments such as RNA interference that downregulate hepatic ALA synthase-1, hemodialysis removes ALA and PBG from plasma but does not reduce hepatic production of ALA and PBG.

Further studies may find that hemodialysis may have a role in combination with other treatments in AIP.

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Authorship
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References

Table 1. Plasma PBG and ALA levels in a patient with anuria and a prolonged attack of AIP measured within 1 hour before and after hemodialysis and both during and after completion of a 14-day course of treatment with hemin (Panhematin, Recordati), 4 mg/kg IV once daily

<table>
<thead>
<tr>
<th></th>
<th>With hemin</th>
<th>Without hemin</th>
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<tr>
<td><strong>Porphobilinogen</strong></td>
<td></td>
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<tr>
<td>Before hemodialysis</td>
<td>2.15</td>
<td>34.46</td>
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<tr>
<td>After hemodialysis</td>
<td>0.64</td>
<td>12.43</td>
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<tr>
<td><strong>ALA</strong></td>
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<tr>
<td>Before hemodialysis</td>
<td>0.21</td>
<td>4.87</td>
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<tr>
<td>After hemodialysis</td>
<td>0.14</td>
<td>2.55</td>
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*With hemin: combined hemin and hemodialysis treatment; Without hemin: hemodialysis only*


