BRIEF OBSERVATION

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Role of Delta-aminolevulinic Acid in the Symptoms of Acute Porphyria

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ABSTRACT

BACKGROUND: Attacks of neuropathic pain, usually abdominal, are characteristic of the acute porphyrias and accompanied by overproduction of heme-precursor molecules, specifically delta-aminolevulinic acid and porphobilinogen. The basis for the acute symptoms in these diseases has been speculative.

METHODS: We review genetic acute porphyria, hereditary tyrosinemia, and an acquired condition, lead poisoning. All perturb heme synthesis and present with a similar pain syndrome.

RESULTS: Although each of these conditions has characteristic urine biochemistry, all exhibit excess delta-aminolevulinic acid. Moreover, in all, treatment with hemin reduces delta-aminolevulinic acid and relieves symptoms. In contrast, use of recombinant porphobilinogen deaminase to knock down porphobilinogen in acute porphyria was ineffective.

CONCLUSIONS: There is now convincing evidence that delta-aminolevulinic acid is the cause of pain in the acute porphyrias. The efficacy of hemin infusion is due mainly, if not entirely, to its inhibition of hepatic delta-aminolevulinic acid synthase-1, the enzyme that catalyzes delta-aminolevulinic acid formation. Delta-aminolevulinic acid synthase-1 is a rational target for additional therapies to control symptoms in acute porphyria.

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KEYWORDS: Abdominal pain; Acute porphyria; Ayurveda; Delta-aminolevulinic acid; Lead poisoning

The acute porphyrias comprise 4 diseases,* each representing a genetic defect in the pathway of heme synthesis that potentially limits production of heme (Figure 1). Expression is most important in hepatocytes, where a critically low level of intracellular heme triggers overproduction of the precursor molecules, delta-aminolevulinic acid, and porphobilinogen. The symptoms of acute porphyria include abdominal pain, nausea, and tachycardia.[1] In an attack, delta-aminolevulinic acid and porphobilinogen are invariably elevated in plasma and urine.[1] Specific treatment is intravenous hemin (Panhematin or Normosang, Recordati Rare Diseases Inc, Lebanon, NJ).[1,2]

Hereditary tyrosinemia and lead poisoning also affect the heme synthetic pathway (Figure 1). In tyrosinemia, the genetic defect in tyrosine metabolism results in hepatocellular accumulation of succinylacetone, which potently inhibits aminolevulinic acid dehydratase.[3] In lead poisoning, the metal directly inhibits the same enzyme by binding to sulfhydryl groups. In either condition, the pathway is activated as in acute porphyria, but the result is overproduction of aminolevulinic acid only; porphobilinogen remains normal, reflecting the impaired conversion of delta-aminolevulinic acid to

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*The principal acute porphyrias include acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. A fourth type, delta-aminolevulinic acid dehydratase deficiency, is a rare recessive form and not considered in this article.

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porphobilinogen (Figure 1). In a case of tyrosinemia, neurologic crisis was treated with hemin infusion to good effect.[4] The present article includes a case of lead poisoning in which the symptoms similarly responded to hemin.

CASE SUMMARY

A previously healthy woman, aged 32 years, sought evaluation for fluctuating abdominal pain and nausea that had been present since the age of 26 years. Extensive testing had been unrevealing except for anemia (hemoglobin, 8.6 g/dL) and elevated urine coproporphyrins (2070 µg/g creatinine; reference range, 23-130 µg/g). She was referred to our tertiary facility for presumed acute porphyria. Urine delta-aminolevulinic acid and porphobilinogen had been requested but were still pending. Without the latter data, the porphyria diagnosis was provisional only. However, in light of her worsening symptoms, she was started on daily intravenous hemin as for acute porphyria.[1,2] With the third infusion, she reported marked improvement in pain and nausea. After 2 additional infusions, her symptoms nearly resolved, and she was discharged to outpatient follow-up. When reports from pretreatment testing arrived, they were notable for urine delta-aminolevulinic acid 29.4 mg/g creatinine (normal <7.5 mg/g) and porphobilinogen 2 mg/g creatinine (normal <2 mg/g). The blood lead level was 83 µg/dL (mean level in US adults, <1 µg/dL). A repeat blood lead level 2 weeks later was 91 µg/dL. Red blood cell Zn-protoporphyrin was 285 µg/dL (normal <40 µg/dL). Urine delta-aminolevulinic acid and porphobilinogen became undetectable after the second hemin infusion.

CLINICAL SIGNIFICANCE

- Acute porphyria, tyrosinemia, and lead poisoning all present similarly, with a clinical picture that is dominated by abdominal pain, nausea, and neuropathy. All 3 exhibit striking elevation of delta-aminolevulinic acid in the urine or blood.
- Pain resolves with treatment that shuts down overproduction of this heme pathway intermediate, confirming its pathogenic role.
- Future therapy for the acute porphyrias should target overproduction of delta-aminolevulinic acid.

The patient was Asian Indian, born and raised in the United States. On further questioning, she described using approximately 40 traditional (Ayurvedic) medications over several years for her abdominal symptoms. She provided samples of those taken during the 6 months before her hospitalization. Analysis by the California Department of Public Health's Food and Drug Laboratory Branch showed that all the samples had detectable lead, 4 with distinctly high levels; some also had mercury (Table 1). In retrospect, abdominal imaging at the referring hospital had shown 2 radio-opaque objects in the proximal colon approximately 8 mm in diameter (Figure 2), which matched the sixth item in Table 1 (Vatchintamani Rasa, Brihat). Chelation therapy was begun according to current guidelines for lead intoxication.[5] As the blood lead level decreased from 91 µg/dL to less than 10 µg/dL, her

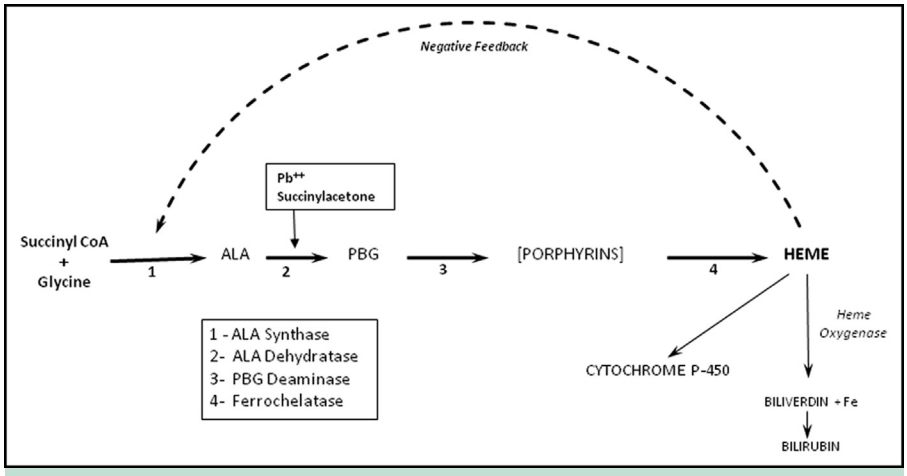

Figure 1 Schematic pathway of heme synthesis and use, showing the enzymes mediating formation of delta-aminolevulinic acid, porphobilinogen, and the initial porphyrin (uroporphyrinogen), respectively. Also shown is the regulatory feedback loop involving the end product of the pathway, heme, and delta-aminolevulinic acid synthase activity. Inhibition of delta-aminolevulinic acid dehydratase by lead (Pb^{++}) is indicated. ALA = aminolevulinic acid; CoA = co-enzyme A; PBG = porphobilinogen.