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Clinical Remission of Delta-Aminolevulinic Acid Dehydratase Deficiency Through Suppression of Erythroid Heme Synthesis

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Delta-aminolevulinic acid dehydratase-porphyria (ADP) is an autosomal recessive disorder of heme biosynthesis, caused by delta-aminolevulinic acid dehydratase deficiency (ALAD).[1] We report an important change in pathophysiological concepts and subsequent therapeutic options for patients with ADP, based on a review of previous cases and the treatment effects in a reported case.

Case Report

A Dutch patient was admitted 2 days after birth, with sudden onset of tetraplegia and respiratory insufficiency. During this episode the etiology remained unresolved. He partially recovered, and his childhood was marked by walking difficulties due to bilateral ankle contractures, impaired hearing, mild intellectual disability, and autism. As an adult, he was independent with regard to activities of daily living, with domestic assistance, and performed volunteer work for 2 days a week.

During a second episode, at age 44 years, he presented with abdominal pain, nausea, vomiting, and progressive asymmetrical weakness of both extremities. ADP was diagnosed based on increased urinary delta-aminolevulinic acid (ALA) levels, normal porphobilinogen levels, and low ALAD enzyme activity (10%-13% of the mean of normal). Lead poisoning, tyrosinemia, and other acute porphyrias were excluded. DNA sequencing detected two compound heterozygous mutations in the *ALAD* gene (Supporting Fig. S1).

He was treated with heme arginate 250 mg (Normosang; Orphan Europe). Following recurring attacks and disappointing recovery, prophylactic weekly heme therapy was initiated (plasma ALA then decreased to 1,977 nmol/L). The frequency of attacks decreased, but attacks still recurred. After several months, he developed resistant hypertension, and his neurological status slowly deteriorated with increasing weakness of all extremities, in parallel with a marked rise in plasma ALA (13,412 nmol/L).

A literature search on ADP was performed. Although ADP is considered a hepatic acute porphyria, there were more cases in which standard therapy was not satisfactory.

Notably, Thunell et al.[2] reported on a boy in whom liver transplantation did not cure his ADP and postulated that the disease might be erythroid in origin. Also, the only late-onset case, of a Belgian patient, supported this hypothesis; he developed ADP due to a monoclonal erythroid disease,[3] polycythemia vera.

Abbreviations: ADP, delta-aminolevulinic acid dehydratase-porphyria; ALA, delta-aminolevulinic acid; ALAD, delta-aminolevulinic acid dehydratase.

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Potential conflict of interest: Nothing to report.

TABLE 1. Detailed Description of ADP Cases

	Present Case	Germany 1	Germany 2	Sweden	Belgium	Germany 3	USA	Germany 4
Phenotype								
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Age at onset	<1 year	15 years	15 years	<1 year	63 years	15 years	12 years	7 years
Acute symptoms	Abdominal pain	Abdominal pain, vomiting, constipation	Pain in extremities, vomiting	Recurrent abdominal pain, vomiting	n/a	Abdominal pain	Abdominal pain, vomiting, constipation	Abdominal pain, vomiting, diarrhea
Motor weakness (arms and/or legs)	Yes	Yes	Yes	Yes	Yes	n/a	Yes	No
Respiratory failure	Yes	Yes	Yes	Yes	No	No	No	No
Therapeutic response								
Response of symptoms to heme	Partial response*	Partial response	Partial response	No response*	No response to heme (some response to iv glucose)	Partial response*	Only initially good response*	n/a
Response of ALA to heme	~30% reduction but later raised despite continued treatment	~15% reduction, remained elevated	>50% reduction, remained elevated	~50% reduction but later raised again despite continued treatment	~66% reduction of urinary ALA	~50% reduction, ALA remains elevated	n/a	n/a
Long-term follow-up	Progression of disease on heme therapy, improvement following blood transfusion and hydroxycarbamide (hydroxyurea)	Patient alive and well 25 years later	Patient alive and well almost 30 years later	No improvement after liver transplantation Died from pneumonia at age 9 years	Died due to hematological malignancy (polycythemia vera)	n/a	Significant continuing motor weakness (wrists and ankles)	n/a

Full information (e.g., biochemical data, clinical details) on all cases and related references are presented in Supporting Table S1. Patients after the present case are presented in order of publication. Cases of special interest for the "erythroid overproduction" hypothesis are in bold. All patients with ADP seem to have an unsatisfactory response to standard therapy for the acute porphyrias. Especially the failure of liver transplantation to cure a Swedish boy and the coinciding of ADP with a monoclonal erythroid disease in a 63-year-old Belgian man support the hypothesis that overproduction of ALA can originate from both the liver and the bone marrow.
*Patient has received prophylactic heme treatment.
Abbreviations: iv, intravenous; n/a, not available.

On top of weekly heme, we initiated weekly blood transfusions and hydroxycarbamide 1,000 mg once daily, to reduce erythroid heme synthesis. Within 2 weeks, symptoms improved and blood pressure returned to normal. Three months later he was still improving. He has no abdominal pain or weaknesses. Plasma ALA dropped from 10,270 to 3,298 nmol/L.

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Summary of Case Series

Data and references from all cases are presented in Table 1 (see also Supporting Table S1).

All DNA-confirmed ADP patients were male. Seven patients experienced porphyric symptoms during childhood. Six patients presented with abdominal pain, one with pain in his extremities. Only the late-onset patient presented with neuropathy of the extremities but no pain. Acute neuropathy was seen in various degrees in all patients, ranging from muscle weakness to severe paralysis. Four patients with paralysis required mechanical ventilation for transient respiratory failure.

Seven patients were treated with glucose and/or heme for attacks. Heme treatment was partially effective at reducing acute attack symptoms; it reduced abdominal pain and stabilized neurological symptoms. Three patients with a partial response were given weekly infusions to prevent attacks. In all 3 patients urinary ALA levels remained elevated. Liver transplantation had no effect in one case.

Discussion

We report on an ADP case with abdominal pain and progressive neurological symptoms despite prophylactic heme therapy to reduce hepatic ALA production. We demonstrate that these symptoms could be improved by also suppressing *erythroid* heme synthesis, through blood transfusions and hydroxycarbamide.

Patients with ADP seem to have a diminished response to standard therapy for acute hepatic porphyrias, despite hepatic 5′-aminolevulinate synthase 1 mRNA being increased.[4] The failure of liver transplantation to cure 1 patient and the late manifestation coinciding with a monoclonal myeloproliferative neoplasm support the hypothesis that in ADP patients ALA can also be overproduced by bone marrow. ADP appears to be an erythrohepatic porphyria.

Suppression of erythroid ALA by blood transfusions and hydroxyurea may be considered, as reported here.

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Supporting Information

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