The Journal of Emergency Medicine, Vol. 49, No. 3, pp. 305–312, 2015

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2015.04.034

Best Clinical Practice

ACUTE PORPHYRIAS

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□ **Abstract—Background: Porphyrias are a group of eight metabolic disorders characterized by defects in heme biosynthesis. Porphyrias are classified into two major categories: 1) the acute or inducible porphyrias and 2) the chronic cutaneous porphyrias. The acute hepatic porphyrias are further classified into acute intermittent porphyria (AIP), hereditary coproporphyria, variegate porphyria, and porphyria due to severe deficiency of delta-aminolevulinic acid (ALA) dehydratase (ALADP). Discussion: AIP is the most common, and ALADP is the least common acute porphyria. The clinical presentations of acute porphyrias are nonspecific. There are no pathognomonic signs or symptoms. The most frequent presenting symptom is abdominal pain, but pain in the chest, back, or lower extremities may also occur. Hyponatremia is the most common electrolyte abnormality during acute attacks, and hypomagnesemia is also common. Both are risk factors for development of seizures, which occur in ~ 20–30% of acute attacks. Conclusion: Once suspected, the diagnosis of porphyria can be rapidly established by checking random urinary porphobilinogen. Initial management of acute porphyria includes discontinuation of all potentially harmful drugs and management of symptoms. Acute attacks should be treated emergently with intravenous heme and glucose to avoid considerable morbidity and mortality. Acute attacks last a few days, and the majority of patients are asymptomatic between attacks. Prognosis is good if the condition is recognized early and treated aggressively.** © 2015 Elsevier Inc.

□ **Keywords—acute porphyria; abdominal pain; haem metabolism; Panhematin; autosomal dominant**

INTRODUCTION

Porphyrias are a group of eight metabolic disorders, mainly inherited inborn errors of metabolism characterized by defects in heme biosynthesis. Porphyrias have varied presentation, with a broad spectrum of clinical manifestations that may be confused with other medical conditions.

Porphyrias are classified into two major categories: 1) the acute or inducible porphyrias, and 2) the chronic cutaneous porphyrias (1). There are two main ways of classifying the porphyrias; one is based upon clinical manifestations of the disease, and the other on the principal site of metabolic defect (Table 1). The discussion herein will be primarily limited to the evaluation and management of acute porphyrias, which are the major forms likely to present to emergency departments (EDs) and to be seen by emergency physicians. The acute hepatic porphyrias are four in number: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and porphyria due to severe deficiency of delta-aminolevulinic acid (ALA) dehydratase (ALADP) (1). Fortunately, most of the patients with acute porphyria, with possible exception of the very rare recessive form of ALADP, are asymptomatic most of the time. Acute porphyria symptoms rarely, if ever, occur prior to puberty, and most patients remain asymptomatic throughout their lives.

RECEIVED: 8 September 2014; FINAL SUBMISSION RECEIVED: 31 March 2015;
ACCEPTED: 18 April 2015

Table 1. Usual Schemes for Classification of the Porphyrias

Porphyrias	Inheritance	Gene Affected	Chromosomal Location	Comments
According to the clinical manifestations of disease				
Acute or inducible porphyrias				
ALADP	AR	ALAD [PBGS]	9q34	Very rare severe disease in infancy
AIP	AD	PBGD [HMBS]	11q23.3	Most severe form
HCP	AD	CPOX	3q12	May also have cutaneous feature
VP	AD	PPOX	1q22	May also have cutaneous feature
Cutaneous chronic porphyrias				
CEP	AR	URO3S	10q26.1–q26.2	Rare, usually manifests in infancy/ childhood
HEP	AR	UROD	1p34.1	Rare, usually manifests in infancy/ childhood
PCT (Type I)	Acquired	None known	None known	Disease of adults
PCT (Type II)	AR	UROD	1p34.1	Requires additional defects
EPP	AR	FECH	18q21.31	Common: onset in infancy
XLPP	X-linked	ALAS 1	Xp11.21	Gain of function mutations
According to the principal site of metabolic defect				
Acute hepatic porphyrias				
ALADP	AR	ALAD [PBGS]	9q34	Very rare severe disease in infancy
AIP	AD	PBGD [HMBS]	11q23.3	Most severe form
HCP	AD	CPOX	3q12	May also have cutaneous features
VP	AD	PPOX	1q22	May also have cutaneous features
Chronic hepatic porphyrias				
HEP	AR	UROD	1p34.1	Usually manifests in infancy
PCT (Type I)	Acquired	None known	None known	Disease of adults
PCT (Type II)	AR	UROD	1p34.1	Requires additional defects
Erythropoietic porphyrias				
CEP	AR	URO3S	10q26.1–q26.2	Rare, usually manifests in infancy/ childhood
EPP	AR	UROD	18q21.31	Common: onset in infancy

AD = autosomal dominant; AIP = acute intermittent porphyria; ALAD = ALA dehydratase; ALADP = ALA dehydratase deficiency porphyria; ALAS = ALA synthase; AR = autosomal recessive; CEP = congenital erythropoietic porphyria; CPOX = coproporphyrinogen oxidase; EPP = erythropoietic protoporphyria; FECH = ferrochelatase; HCP = hereditary coproporphyria; HEP = hepatoerythropoietic porphyria; HMBS = hydroxymethylbilane synthase; PBGS = porphobilinogen synthase; PBGD = porphobilinogen deaminase; PCT = porphyria cutanea tarda; PPOX = protoporphyrinogen oxidase; UROD = uroporphyrinogen decarboxylase; URO3S = uroporphyrinogen 3 synthase; VP = variegate porphyria; XLPP = X-linked protoporphyria.

The term "acute" in acute porphyria is used to signify life-threatening manifestations and not to indicate duration of disease. All acute porphyrias produce similar neurovisceral manifestations regardless of associated enzymatic defects, and hence, should be managed in a similar way. It is important early on to consider the diagnosis and perform the appropriate biochemical and genetic tests to either establish or to exclude diagnosis of acute porphyria.

DISCUSSION

Heme Biosynthesis

Acute porphyria is due to the deficiency of a specific enzyme involved in heme synthesis. The normal pathway of heme synthesis is shown in Figure 1.

The first step is condensation of glycine and succinyl CoA to form delta-aminolevulinic acid (ALA), catalyzed by the mitochondrial enzyme ALA synthase, the rate controlling step in heme synthesis. There are two forms of ALA synthase, the ubiquitous housekeeping form 1 and the erythroid-specific form 2. These two forms are products of separate genes and are under quite different regulation. ALA synthase-1 can be upregulated markedly by transcriptional and posttranscriptional mechanisms, and an "uncontrolled" upregulation of this enzyme in the liver is the biochemical sine qua non of acute porphyric attacks. Upregulation of ALA synthase-1 occurs due to three main known causes:

1. Lipophilic drugs and chemicals interact with nuclear receptors that, in turn, increase activation of drug-response elements in the upstream enhancer of ALA synthase-1 (2).
2. Deficiency of glucose or other gluconeogenic compounds that normally suppress gene expression of ALA synthase (the so-called "glucose effect") (3).
3. Deficiency of heme, the end product of the heme pathway shown in Figure 1, which not only represses transcription of the ALA synthase-1 gene,