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Acute Porphyrias

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The acute hepatic porphyrias are acute intermittent porphyria (AIP), variegate porphyria (VIP), hereditary coproporphyria (HCP), and ALA dehydratase deficiency. They are marked as a group by the occurrence of neurovisceral attacks (neurologic manifestations and abdominal pain), and each is characterized by several of five "P's": (1) onset after puberty, (2) psychiatric abnormalities, (3) pain, (4) polyneuropathy, and (5) photosensitivity. During the latent period, symptoms and signs may be absent. However, acute episodes can be precipitated by four "M's": (1) medicines (including estrogens and alcohol) [see Tables 2a and 2b], (2) menstrual and premenstrual periods, (3) malnutrition (low carbohydrate ingestion or fasting), and (4) medical illnesses (especially infections). Although PCT also derives from a hepatic enzyme deficiency, it results only in photosensitivity and is discussed separately .

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The apparent contradiction between a fixed genetic abnormality and a relapsing clinical pattern is explained by the fact that hepatic ALA synthetase, normally the rate-limiting enzyme for heme synthesis, can be induced by certain endogenous (e.g., estrogen) and exogenous (e.g., starvation or drugs) stimuli, thereby precipitating acute clinical attacks of the disease. The basic defect in the various porphyrias is a partial deficiency of a non-rate-limiting enzyme. Such a defect may be well tolerated during normal levels of heme production in the liver; however, when ALA synthetase production is induced, increased precursor production overwhelms the defective step in the pathway. Intermediates proximal to the partial block accumulate and spill out of the liver into the circulation. Depending on the enzyme involved [see Table 1] and the extent to which ALA synthetase has been induced, the precursor surplus may consist of ALA and porphobilinogen (PBG) in combination with variable amounts of uroporphyrinogen, coproporphyrinogen, and protoporphyrinogen. Because porphyrinogens readily oxidize to their respective fluorescent porphyrins, the excretion of ALA, PBG, and porphyrin is usually measured. The progressive decarboxylation of porphyrinogen intermediates in the heme synthetic pathway leads to a corresponding loss of aqueous solubility. Therefore, coproporphyrin and protoporphyrin are excreted less by the kidney and more by the liver, necessitating fecal analysis.

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Precipitating factors are presumed to act by inducing hepatic ALA synthetase either by direct stimulation of the enzyme or by derepression of ALA synthetase synthesis secondary to diminution of available heme. Binding of heme