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Acute intermittent porphyria

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Acute intermittent porphyria (AIP) is characterised by neurovisceral crises the most common clinical presentation of which is abdominal pain. It is an autosomal dominant condition with incomplete penetrance and is potentially life-threatening. The key point in management is to suspect and confirm the diagnosis as early as possible in order to treat the attack and to avoid inappropriate treatments which may exacerbate the crisis.
In this chapter we briefly outline the haem biosynthetic pathway and how deficiencies in individual enzymes give rise to the different porphyrias. We then describe the clinical features and diagnosis of AIP, followed by a discussion of pathogenesis, highlighting advances in the molecular biology of AIP and introducing the debate as to whether neurovisceral crises might result from porphyrin precursor neurotoxicity or from haem deficiency. Finally we discuss management, including family screening, avoidance of triggering factors, analgesia, maintenance of a high calorie intake, and administration of haem derivatives.

Key words: acute intermittent porphyria; haem; porphyrin; delta-aminolaevulinic acid; porphobilinogen; porphobilinogen deaminase.

Acute intermittent porphyria (AIP) is well placed in a volume entitled 'Unusual causes of abdominal pain'. While the prevalence of a mutant AIP gene may be as high as 1 per 500,[1] penetrance is incomplete and the prevalence of symptomatic disease is only 1–2 per 100 000.[2] Although AIP is a multisystem disease with a wide variety of clinical features, its most common presentation is with abdominal pain. The other acute porphyrias—variegate porphyria, hereditary coproporphyria and the porphyria associated with deficiency of the enzyme δ-aminolaevulinic acid (ALA) dehydratase ('plumboporphyria')—are even less common than AIP and are less severe, but all share

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the same neurovisceral crises (all can cause abdominal pain). Variegate porphyria and hereditary coproporphyria differ from the other two acute porphyrias in that they may present with cutaneous photosensitivity. The management of neurovisceral crises is the same for each of these acute porphyrias.[3,4]

The acute porphyrias are potentially life-threatening, especially when unrecognised. The key issue in management is to suspect the diagnosis and, once the diagnosis has been made, to prevent further attacks, both in the index case and in family members through screening. In this chapter we describe the biochemical defects in the haem biosynthetic pathway associated with AIP and with the other porphyrias and outline the clinical features and diagnostic tests. We then highlight recent advances in our understanding of pathogenesis: advances in molecular and cellular biology continue to provide further insights into the mechanisms of disease, as well as influencing our methods of diagnosis and screening. Finally we shall discuss management, both preventative and of the acute attack, and how this has changed over recent years.

It is outwith the scope of this review to describe the different porphyrias and their classification in any detail, but to put AIP into context it is worth highlighting that porphyrias can be classified on the basis as to whether they are acute or non-acute and (if non-acute) whether excess porphyrins are concentrated in the liver (hepatic) or in the bone marrow (erythropoietic) (Figure 1). All the acute porphyrias, except that associated with ALA dehydratase deficiency (which is extremely rare) are autosomal dominant conditions.

THE HAEM BIOSYNTHETIC PATHWAY AND THE PORPHYRIAS

The haem biosynthetic pathway is shown in Figure 1. A series of eight enzymes (four mitochondrial, four cytosolic) catalyses the series of reactions which begins with the condensation of glycine and succinate to form ALA and which ends with the insertion of ferrous iron into protoporphyrin to form haem.

The key points about this cycle with respect to the understanding of the porphyrias are as follows:

1. The different porphyrias result from inherited deficiencies of the different enzymes as shown in Figure 1. In AIP the 'culprit' enzyme is porphobilinogen (PBG) deaminase.
2. The rate-controlling enzyme of the pathway is ALA synthase, which has a low basal activity and which is under negative feedback control by haem. In acute porphyria its activity is increased, in an attempt to compensate for the 'downstream' block.
3. PBG deaminase, the enzyme deficient in AIP, acts as a second rate-controlling enzyme. Therefore in variegate porphyria and hereditary coproporphyria the porphyrin precursors ALA and PBG are produced in excess (albeit at much lower levels than in AIP) even although the enzyme deficiency is later on in the pathway, and this is useful in the diagnosis of the acute attack.
4. The different sites of enzyme deficiency within the haem biosynthetic pathway result in the different porphyrias being associated with different patterns of urinary and faecal porphyrin and precursor excretion. This is useful diagnostically. For example, high faecal levels of coproporphyrin are found in hereditary coproporphyria, and of protoporphyrin in variegate porphyria.