Best Practice & Research Clinical Gastroenterology 24 (2010) 593–605

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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The acute hepatic porphyrias: Current status and future challenges

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Keywords:
Acute hepatic porphyria
Acute intermittent porphyria
δ-Aminolevulinic acid dehydratase deficiency porphyria
Haem biosynthesis
Hereditary coproporphyria
Porphyria
Variegate porphyria

The porphyrias are predominantly inherited metabolic disorders, which result from a specific deficiency of one of the eight enzymes along the pathway of haem biosynthesis. Historically, they have been classified into hepatic and erythropoietic forms, based on the primary site of expression of the prevailing dysfunctional enzyme. From a clinical point of view, however, it is more convenient to subdivide them into acute and non-acute porphyrias, thereby primarily considering the potential occurrence of life-threatening acute neurovisceral attacks. Unrecognised or untreated, such an acute porphyric attack is associated with a significant mortality of up to 10%. The acute hepatic porphyrias comprise acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and δ-aminolevulinic acid dehydratase deficiency porphyria. Making a precise diagnosis may be difficult because the different types of porphyrias may show overlapping clinical and biochemical characteristics. To

Abbreviations: AIP, Acute intermittent porphyria; ALA, δ-aminolevulinic acid; LAD, δ-aminolevulinic acid dehydratase; EPI, European Porphyria Initiative; HCC, Hepatocellular carcinoma; HCP, Hereditary coproporphyria; PBG, Porphobilinogen; VP, Variegate porphyria.

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1521-6918/$ – see front matter
doi:10.1016/j.bpg.2010.08.010

date, the therapeutic possibilities are limited and mainly symptomatic. In this overview we report on what is currently known about pathogenesis, clinic, diagnostics, and therapy of the acute hepatic porphyrias. We further point out actual and future challenges in the management of these diseases.

Introduction

The porphyrias are a group of rare metabolic disorders, each arising from a predominantly hereditary catalytic dysfunction of one of the eight enzymes along the porphyrin-haem biosynthetic pathway (see Fig. 1 in the chapter on porphyria cutanea tarda by Frank and Poblete-Gutiérrez, this issue). Traditionally these disorders are subdivided into erythropoietic and hepatic forms, according to the major site of expression of the underlying enzyme deficiency [1,2]. However, from a general clinician's point of view it is more appropriate to classify the porphyrias into acute and non-acute forms, thereby emphasising the presence or absence of potentially life-threatening acute porphyric attacks (Table 1). Therefore, we will adhere to the latter classification throughout this review.

The group of the acute hepatic porphyrias comprises acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and δ-aminolevulinic acid dehydratase (ALAD) deficiency porphyria (Table 1) [2,3]. Because in all these porphyrias the most common clinical symptoms observed during a porphyric attack mimic those of an acute abdomen, the acute hepatic porphyrias are of interest for a broad group of specialists, including e.g. internists, gastroenterologists, surgeons, gynaecologists, and anaesthesiologists [4]. Two variants of the acute hepatic porphyrias, VP and HCP, can also manifest with cutaneous symptoms on the sun-exposed areas of the body. They are therefore also referred to as neurocotaneous porphyrias and, consequently, the acute hepatic porphyrias are also of relevance for dermatologists [2,5]. If an acute porphyric attack is suspected, biochemical tests are used to confirm the temptative diagnosis. When the results are inconclusive, DNA analysis might be helpful. The genetic defects underlying the different types of acute porphyrias are well characterised (Table 2), facilitating molecular diagnosis and genetic counselling for affected families [6].

In this review we provide a comprehensive view of the acute hepatic porphyrias and tackle some of the imminent challenges in the management of these disorders.

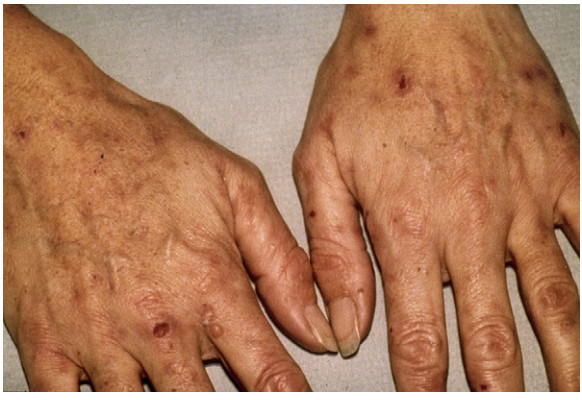

Fig. 1. Cutaneous symptoms in variegate porphyria. Intact blister, erosions, crusts, miliae, and hyperpigmented scarring on the back of the hands. Note that the cutaneous lesions cannot be distinguished clinically from those encountered in porphyria cutanea tarda and hereditary coproporphyria.