Hereditary coproporphyria: Comparison of molecular and biochemical investigations in a large family

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MS received 24.01.05 Accepted 21.04.05

Summary: Hereditary coproporphyria (HCP) is the least common of the three autosomal dominant acute porphyrias. To compare the sensitivity of metabolite measurements for the identification of asymptomatic HCP, we carried out a molecular and biochemical investigation of a large family in which HCP is caused by a previously unreported frameshift mutation (c.119delA). Thirteen of 19 asymptomatic family members, aged 10–72 years, were shown by mutational analysis to have HCP. The faecal coproporphyrin isomer III:I ratio was increased in all of these 13 family members; faecal total porphyrin concentration and urinary porphyrin excretion were increased in 11 and 8 of them, respectively. Plasma porphyrin concentrations were marginally increased in three individuals and plasma fluorescence emission scanning showed a porphyrin peak at 618 nm in two of these. Our results add to the evidence that an increased faecal coproporphyrin isomer III:I ratio is a highly sensitive test for the detection of clinically latent HCP in individuals over the age of 10 years; its sensitivity below this age remains uncertain. They also show that plasma fluorescence emission scanning is not useful for the investigation of families with HCP.

Hereditary coproporphyria (HCP; McKusick 121300) is the least common of the three autosomal dominant acute porphyrias. It results from partial deficiency of the mitochondrial enzyme, coproporphyrinogen oxidase (CPO; EC 1.3.3.3), which catalyses the oxidative decarboxylation of coproporphyrinogen III to protoporphyrinogen IX during the biosynthesis of haem (Brodie et al 1977; Martasek 1998). Thirty-four disease-specific mutations have now been reported in the CPO gene (Human Gene Mutation Database: www.hgmd.org), mostly restricted to one or a few families. Clinically, HCP is characterized by episodic acute neurovisceral attacks, typically consisting of severe abdominal pain, mental confusion and peripheral neuropathy (Brodie et al 1977; Martasek 1998). Approximately 30% of patients may also have skin lesions due to increased fragility on exposure to sunlight; presentation with skin lesions alone is uncommon (Brodie et al 1977). During the acute phase of the
illness, urinary excretion of the porphyrin precursor, porphobilinogen (PBG), is increased, as it is in the other autosomal dominant acute porphyrias, acute intermittent porphyria (AIP) and variegate porphyria (VP). However, HCP can be distinguished from AIP and VP by demonstrating increased faecal excretion ratio of coproporphyrin III to coproporphyrin I but without a similar increase in protoporphyrin excretion or a porphyrin fluorescence emission peak in plasma at 624–627 nm that occurs with VP (Deacon and Elder 2001).

The clinical penetrance of HCP is low. As in AIP and VP, symptoms are rare before puberty and most adults are asymptomatic but at risk of developing acute attacks in response to precipitants, such as drugs, alcohol, infection, fasting or changes in hormone balance (Brodie et al 1977; Kühnel et al 2000; Martasek 1998). Screening of family members once an index case has been identified is an important aspect of clinical management because asymptomatic relatives found to have inherited the disease can be advised to avoid those drugs and other factors that increase the risk of an acute attack. Asymptomatic, but affected, relatives can be identified by mutational analysis, measurement of the defective enzyme, or metabolite analysis. In AIP and VP, mutational analysis is more sensitive and more specific than other methods (Kauppinen and Fraunberg 2002; Whatley et al 1999); in both conditions, metabolite measurements are usually normal before puberty and normal in 25–40% of asymptomatic adults (Hift et al 2004; Kauppinen and Fraunberg 2002). There is little information about the sensitivity of metabolite measurements for the detection of asymptomatic HCP (Blake et al 1992; Kühnel et al 2000). The plasma porphyrin concentration may be increased when symptoms are present, giving a fluorescence emission peak at 615–620 nm (Deacon and Elder 2001), but not in their absence (Hindmarsh et al 1999). An increase in the ratio of coproporphyrin III to coproporphyrin I isomer in faeces appears to be a better indicator of asymptomatic HCP, at least in adults (Blake et al 1992; Gross et al 2002; Jacob and Doss 1995; Kühnel et al 2000; Lamoril et al 2001), but its sensitivity has not been determined in a group of asymptomatic individuals in whom the diagnosis of HCP has been unequivocally established by DNA analysis. Here we compare the use of measurements of urinary PBG, and porphyrins in urine, faeces and plasma, to detect asymptomatic disease in 13 individuals from one family, all of whom were shown to have HCP by demonstrating the presence of a previously unidentified mutation in the CPO gene.

**PATIENTS AND METHODS**

**Patients**

The index case was a 35-year-old caucasian male who presented with a history of unexplained severe abdominal pain. Whole blood, plasma, urine and faeces were collected for DNA analysis and measurement of urine PBG, and urine, plasma and faecal porphyrins. Samples were also obtained from all of his available relatives who gave informed consent to investigation.

**Analysis of haem precursors**

Urine PBG was measured using the BioRad kit method (BioRad Laboratories, Hemel Hempstead, UK). Total urine porphyrins were measured by fluorescence spectroscopy.