Porphyrias are rare diseases, and most clinicians will see only a few cases during their professional lives. Each of the seven types is caused by partial deficiency of a different enzyme in the heme biosynthesis pathway (1). Disease-specific mutations in the genes encoding these enzymes have been identified in all of the inherited porphyrias (2). The current repertoire of investigations for porphyria includes measurement of metabolites (heme precursors) that accumulate secondary to the enzyme deficiencies as well as enzyme assays and DNA analyses.

Four porphyrias can present with life-threatening acute neurovisceral attacks: δ-aminolevulinic acid dehydratase deficiency porphyria, acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP) (1). Attacks are often provoked by drugs, endocrine factors, alcohol, fasting, infection, or stress. In VP and HCP, skin lesions, typically erosions and bullae in sun-exposed areas, may accompany an acute attack or, particularly in VP, be the sole presenting symptom. δ-Aminolevulinic acid dehydratase deficiency porphyria is a very rare, autosomal recessive disease (3) and will not be discussed here. AIP, VP, and HCP are autosomal dominant disorders that show incomplete penetrance with symptoms developing in only ~30% of individuals who carry a gene with a disease-causing mutation. Screening families to identify such individuals is important because their risk of an acute attack can be decreased by counseling on avoiding potential precipitants (1, 4).

There are three main ways in which a patient with a suspected acute porphyria can present for investigation: with acute or cutaneous symptoms, during remission after a past illness attributed to acute porphyria, or with a family history of porphyria. Metabolite concentrations are invariably increased when symptoms caused by porphyria are present but may decrease to within reference values during remission and are frequently within the reference intervals, particularly before puberty, in individuals who have inherited an acute porphyria but have never had symptoms. It follows that the diagnostic accuracy (sensitivity and specificity) of the measured metabolite concentrations will differ according to the mode of presentation. In addition, the positive and negative predictive values of the test will depend on the sensitivity and specificity of the test as well as the pretest probability. For evaluation of family members, the pretest probability will usually be significantly higher than for patients presenting with symptoms and no family history. Previously, determination of the diagnostic accuracy of metabolite and enzyme tests for acute porphyria has been difficult because of the absence of any method for defining groups of affected and unaffected individuals with 100% accuracy. The introduction of tests for disease-specific mutations has helped to solve this problem (5–7). A recent report in this Journal used this approach to evaluate investigations for AIP (8), and in this issue Hift et al. (9) do the same for VP, capitalizing on its high prevalence in South Africa and the availability of a simple DNA test for the predominant R59W mutation.

When patients present with an acute neurovisceral attack, the concentration of porphobilinogen (PBG) in urine is increased, usually to >10 times the upper limit of the reference interval (10). It will usually remain increased for weeks in AIP but may occasionally decrease to values within the reference interval within 7 days in VP and HCP (8). Once the diagnosis of an acute attack of porphyria has been made, the next step is to determine the type of acute porphyria. Measurement of total fecal porphyrins, combined with separation of individual porphyrins by HPLC, is the most reliable method for distinguishing AIP from HCP in patients with current or recent symptoms and has advantages over enzyme measurements (10). In AIP, fecal porphyrins are within reference values or slightly increased with a coproporphyrin III/I ratio <2, whereas in HCP, coproporphyrin III excretion is increased. The European Porphyria Initiative is developing a consensus approach to the diagnosis of the acute porphyrías (4).

How should a diagnosis of VP be established? This has traditionally depended on analysis of metabolites in urine and feces with, more recently, measurement of protoporphyrinogen oxidase when these are uninformative. In 1980, Poh-Fitzpatrick (11) discovered that the plasma in VP contains a porphyrin–protein complex with a fluorescence emission peak at 624–627 nm that serves as a marker for the disease. Plasma fluorescence scanning has since become widely used for the diagnosis of porphyrias, particularly the differentiation of VP from other acute porphyrias and, when skin lesions are the only manifestation, from porphyria cutanea tarda. In all of the acute porphyrias except VP and in porphyria cutanea tarda a fluorescence emission peak around 620 nm may be present (10, 12). The test is simple but requires a fluorescence spectrometer with a red-sensitive photomultiplier (9).

In this issue of the Journal, Hift et al. (9) compare the sensitivity of plasma fluorescence scanning and fecal porphyrin analysis for the diagnosis of VP, using patient and control groups that are larger and more accurately defined than in previous studies (13, 14). Overall, the sensitivity of plasma fluorescence scanning in adults (≥16 years of age) was 84%. Clinical information was available for approximately one-third of the adults. Sensitivity was greater in those with symptoms, 85% in those with a family history and 100% in those without a family history, than in the asymptomatic group with a family history.
(76%), whereas specificity was close to 100% in all groups. It is likely that sensitivity would have been even higher in the symptomatic group with a family history had more rigorous criteria been used to exclude mutation-positive individuals with symptoms, such as abdominal pain, that were not being precipitated by porphyria at the time of testing. Previous estimates of sensitivity in asymptomatic adults have been 86% (13) and 50% (14). Sensitivity under the age of 16 years was 24%, a much higher percentage than found previously (13, 14); whether this is a special feature of VP caused by the R59W mutation is uncertain. The sensitivity and specificity of fecal porphyrin analysis was lower, and combining plasma fluorescence scanning with fecal porphyrin analysis did not improve diagnostic accuracy.

Although as expected for VP (1, 10, 15) the median concentrations of protoporphyrin and coproporphyrin were increased in feces, with the former exceeding the latter, coproporphyrin was found to be the better predictor of VP (9). However, protoporphyrin, as measured by the authors (9), includes other dicarboxylic porphyrins that may predominate in normal feces. Use of a more specific method, such as HPLC (16), which also gives better recovery of protoporphyrin and enables coproporphyrin isomers to be separated, might have given a different result. Interestingly, pseudopentacarboxylic porphyrin, a hydroxylated derivative of protoporphyrin probably formed during the extraction and esterification procedures used in their method, was almost as good a predictor as coproporphyrin. It seems unlikely, however, that use of an HPLC method would have had a major effect on the sensitivity of fecal porphyrin analysis.

The study of Hift et al. (9) provides strong support for the view that plasma fluorescence scanning should replace fecal porphyrin analysis for the diagnosis of VP. In practice, this means that fecal porphyrin analysis is required for the differentiation of porphyrias only if the plasma fluorescence scan does not show a peak at 624–627 nm. It must be emphasized, however, that the diagnostic accuracies reported by Hift et al. (9) probably reflect only the ability to distinguish VP patients from healthy persons, and not from patients with other porphyrias, because the inclusion criterion was that a mutation detection allows affected and unaffected individuals to be accurately distinguished, comparative clinical studies should allow a more accurate picture of the range of phenotypes directly caused by porphyria to be obtained.

How should families be screened to identify asymptomatic individuals who have inherited an acute porphyria? Sensitivities <85% have been reported for urinary PBG measurement for AIP (8), fecal porphyrin analysis for HCP (17), and plasma fluorescence scanning for VP (9). Enzyme measurements can be used, especially PBG deaminase for AIP, but their diagnostic accuracies are limited by an overlap of 10–20% between unaffected and affected individuals (8, 15). Because of their imperfect diagnostic sensitivities, none of these investigations can exclude porphyria. When the mutation that causes porphyria in a particular family can be identified, mutation detection provides a test that is 100% sensitive and 100% specific for that family. This approach, which should now be the method of choice, is limited only by the inability of current techniques to find mutations in 5–10% of families (5–7).

In families in which a mutation cannot be found, gene tracking by use of intragenic polymorphisms may be helpful; otherwise, enzyme and metabolite measurements can be used but need careful interpretation taking into account their sensitivities and specificities. Evaluation of relatives in a family with porphyria often represents presymptomatic testing and requires appropriate genetic counseling with informed consent.

A diagnostic problem arises, particularly in patients who are known to have inherited an acute porphyria, in deciding whether symptoms are produced by porphyria or some other disease. In patients with severe symptoms typical of a neurovisceral attack and a substantially increased urinary PBG concentration, the symptoms are likely to be attributable to acute porphyria, and they will be relieved by appropriate treatment. If PBG excretion is normal when symptoms are present, the symptoms are very unlikely to be caused by porphyria. However, in cases where less typical, milder, or chronic symptoms are present and urinary PBG excretion is increased, as it is in many AIP patients in clinical remission, diagnosis depends on clinical assessment and exclusion of other potential causes. Now that mutation detection allows affected and unaffected individuals to be accurately distinguished, comparative clinical studies should allow a more accurate picture of the range of phenotypes directly caused by porphyria to be obtained.

References


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