Public attention has been drawn to the acute porphyrias in the past few years by speculation that they affected the character of George III and the creative genius of Vincent van Gogh. During the same period, there have been important advances in the understanding of the molecular basis of the acute porphyrias and in diagnosis and the clinical management of patients and their families. Four types of porphyria are classified as acute because they produce acute neurovisceral crises (panel). Here, we outline current knowledge of the three autosomal dominant types: acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria.

Biochemical and molecular genetics

Biochemical background

The inherited defect in each of the autosomal dominant acute porphyrias is the complete or near complete inactivation of one of a pair of allelic genes that encodes for an enzyme of the biosynthetic pathway for haem (table 1). The consequent 50% reduction in enzyme activity provokes a compensatory increase in substrate concentration, which is brought about through the negative feedback regulation by haem of the rate-controlling initial enzyme of the pathway, 5-aminolaevulinate synthase (ALA-S). Substrate accumulation and increased ALA-S activity in response to the enzyme deficiency are most prominent in the liver, in which haem supply is finely regulated to adjust to internal and external stimuli—for example, drugs that induce cytochrome P450s. The increase in synthesis and excretion of porphobilinogen that characterises the acute attack reflects primary (acute intermittent porphyria) or secondary (variegate porphyria and hereditary coproporphyria) limitation of the rate of hepatic haem synthesis at porphobilinogen deaminase—the enzyme that has the lowest activity of those that convert aminolaevulinate to haem.

Molecular genetics

The porphyrias show extensive allelic heterogeneity. More than 90 mutations that cause acute intermittent porphyria have been identified in the porphobilinogen deaminase gene. Mutations in exon 1, which encodes the additional 17 aminoacids at the N-terminus that are responsible for a rare variant of acute intermittent porphyria in which only the ubiquitous isoenzyme is defective. Other mutations are distributed throughout the gene in exons common to both isoenzymes, with some clustering in exons 10 and 12; these mutations decrease enzyme activity in all tissues. The structure of Escherichia coli porphobilinogen deaminase has been solved at 0.176 nm resolution and provides a useful model for predicting the functional effects of human mutations (figure). Most mutations in acute intermittent porphyria are restricted to one or a few families. However, one mutation (Trp198Stop), presumably inherited from a common founder, underlies the high prevalence of acute intermittent porphyria in northern Sweden (1 per 1500 people). There is no evidence that any specific genotype determines either the pattern or severity of the acute attack, or major differences in clinical penetrance between families.

Preliminary data indicate that variegate porphyria may be as heterogeneous at the DNA level as other porphyrias in most countries, with the notable exception of South Africa. About 10 000 South Africans of Afrikaans descent have variegate porphyria; genealogical evidence suggests that this acute porphyria was inherited from a single founder, a woman who emigrated from Holland in 1688. These families share the same mutation (Arg95T rp) in the protoporphyrinogen oxidase gene. The existence of such a large group with the same mutation provides a unique opportunity to study the interaction of other inherited and environmental factors in the acute porphyrias.

Homozygous forms of acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, which are frequently associated with growth and psychomotor retardation, have been reported, as has more than one type of acute porphyria in the same individual or family.

Clinical features

Prevalence

Acute porphyria occurs in all races. In most European countries, apart from Sweden, the estimated prevalence of clinically overt acute porphyria is 1–2 per 100 000 inhabitants. Most of these individuals have acute
intermittent porphyria. Variegate porphyria is about one-third as prevalent as acute intermittent porphyria in the UK; it usually presents with skin lesions alone (panel) and is less often the cause of recurrent attacks. Even in South Africa, most acute attacks are now caused by acute intermittent porphyria. Hereditary coproporphyria is the rarest of the three disorders.

Gene frequencies for these disorders are higher than the prevalence of overt cases. Biochemical studies of relatives of patients with symptomatic acute porphyria suggest that at least 90% of individuals with acute intermittent porphyria or variegate porphyria are clinically latent which gives a frequency of 1–2 per 10 000 individuals for acute intermittent porphyria. A study by Mustajoki and colleagues showed that screening blood donors for inherited porphobilinogen deaminase deficiency gives an even higher rate of 1 per 500 donors. This prevalence is close to that reported by Tishler et al. in a similar, but uncontrolled, study of psychiatric inpatients, which is often quoted as evidence of an increased frequency of acute intermittent porphyria among such patients. The occurrence of homozgyous variants, sporadic presentation of acute intermittent porphyria in about 25% of cases, and allelic heterogeneity combined with a low rate of new mutations are all features consistent with a high prevalence of latent acute porphyria in the population.

Factors that may precipitate the acute attack

Drugs and the menstrual cycle are the most common precipitants of the acute attack, and recurrent attacks that occur in the late luteal phase are sometimes a major problem in acute intermittent porphyria. Factors such as alcohol, fasting, stress, and infection have also been implicated. It is impossible to predict accurately whether specific drugs will provoke an acute attack in a particular individual. Drugs should be prescribed only after reference to a drug list, but these recommendations are not absolute and do not substitute for sound clinical judgment. The risk of an attack is highest for drugs that are known to have repeatedly provoked acute attacks and for patients who have or have had symptoms.

The acute attack

Acute attacks are about five times more common in women than in men, attacks are most frequent during the second to fourth decades and are rare before puberty. Abdominal pain is almost universal in acute porphyria (table 2). Pain is severe, constant, occurs in any quadrant and commonly in the back, buttocks, and thighs, and may require large amounts of opiates for its control. Pain is sometimes accompanied by guarding, but not by true peritonism. The incessant pleas of affected patients for opiates frequently lead to unwarranted suspicions of histrionic behaviour or addiction. Yet as the attack remits, the need for analgesia disappears, which confirms the severity of the initial pain.

Though tachycardia and hypertension are described as features of the acute attack, the pulse rate and blood pressure are often only moderately raised, and these signs are of poor diagnostic value. Vomiting and constipation are common; the latter is rarely a presenting symptom. These features of acute porphyria—pain, tachycardia, hypertension, and partial ileus—have been attributed to an autonomic neuropathy. Dehydration is common and responds rapidly to fluid replacement. Hypoaesthesia, probably caused in some patients by inappropriate secretion of vasopressin, may also be present. The sodium concentration may decline to dangerously low levels, which can lead to convulsions.

The severe attack may progress to a motor neuropathy which may resemble a Guillain-Barré syndrome. In some patients, onset of the neuropathy may be preceded by disappearance of the abdominal pain, which may lead the physician to erroneously assume that the patient is recovering. Mild sensory changes often accompany the motor neuropathy, particularly, a “bathing trunk” distribution of hypoaesthesia over the trunk and thighs. In milder cases, particularly with repeated attacks of acute intermittent porphyria, the features are of a distal neuropathy with foot drop and wrist drop. Occasionally, sensory or sympathetic features such as dysaesthesia or causalgia are prominent. Progression to neuropathy is seen less frequently than in the past (table 2). Abnormal behaviour and confusion, with agitation and hallucinations, are common in some patients during the acute attack. There is little evidence that porphyria produces chronic psychiatric illness, apart from generalised anxiety.

Diagnosis of the acute attack

Most difficulties in the diagnosis of an acute attack arise in patients who do not have a family history of porphyria, particularly if the combination of symptoms is atypical. A high index of clinical suspicion is important to avoid delayed diagnosis, which may lead to inadvertent use of contraindicated drugs and a poorer prognosis. Increased urinary excretion of porphobilinogen confirms the diagnosis of an acute attack (table 1). Excretion of aminolaevulinate is also increased but to a lesser extent. Screening tests for porphobilinogen based on the insolubility of organic solvents of the red product of its reaction with p-dimethylaminobenzaldehyde in acid (Ehrlich’s reagent) have been criticised because they lack sensitivity and produce occasional false-positive results. A positive screening test is useful in an emergency, but
should always been confirmed by a specific, quantitative assay. A negative screening test does not exclude an acute attack. If clinical suspicion persists, quantification of porphobilinogen and measurement of faecal and plasma porphyrins are essential. Excretion of porphobilinogen may fall below the detection limit of screening tests soon after the onset of symptoms, particularly in variegate porphyria and hereditary coproporphyria, and the diagnosis may be missed if this approach is not followed. The type of acute porphyria is established by measurement of faecal and plasma porphyrins (table 1); enzyme assays at this stage may misleading and should not be used in place of porphyrin analysis. Fluorescence emission spectroscopy of plasma simplifies the differentiation of variegate porphyria from other acute and cutaneous porphyrias.

In patients who have latent porphyria or are in remission, differentiation of an attack of acute porphyria from other causes of abdominal pain may be difficult, especially in those few patients who become addicted to opiates. In variegate porphyria and hereditary coproporphyria, porphobilinogen excretion will generally be normal in the absence of symptoms. In acute intermittent porphyria, concentrations are often raised during the symptomless phase and increase further during an acute attack.

Pathogenesis of the acute attack

Increased ALA-S activity, overproduction of aminolaevulinate, and relative haem deficiency in the liver are biochemical features of all acute porphyrias and also of the identical syndrome that occurs in hereditary tyrosinaemia. How these changes are triggered and the pathogenesis of the neuronal dysfunction that produces the symptoms are little understood. Some drugs and alcoholic beverages may increase the intrahepatic requirement for haem by inducing the synthesis of cytochrome P450. The mechanisms for other drugs and hormones and the explanation for differences between individuals in their susceptibility to develop acute attacks are not known. Investigation of the pathogenesis of the neuropathy has been hampered by lack of an experimental model. Current theories implicate aminolaevulinate as a neurotoxin (for which the evidence is controversial), neurotransmitter disturbance secondary to deficiency of haem and tryptophan dioxygenase in the liver, or depletion of haem in nerve cells. The recent development of a transgenic porphobilinogen deaminase deficient mouse provides a system in which these hypotheses can be tested.

Management of the acute attack

The acute attack

Most patients will require admission to hospital. Only drugs clearly shown to be safe in porphyria should be prescribed; all others should be withdrawn. Pain will respond to opiates, though high doses may be required. Sedation with chlorpromazine is often helpful. Vomiting may be suppressed with prochlorperazine or metaclopramide. Administration of dextrose or laevulose in large amounts has been shown to suppress synthesis of aminolaevulinate. However, intravenous dextrose may aggravate hyponatraemia and must be used with caution. Maintenance of an adequate calorie intake can be achieved more safely by nasogastric feeding. Intravenous haematin has largely replaced carbohydrate as the specific therapy of choice for the acute attack; it suppresses hepatic ALA-S by negative feedback and is highly effective in reducing aminolaevulinate and porphobilinogen excretion. The only placebo-controlled
study of this therapy suggested that the clinical benefit of intravenous haematin was modest. 16 Uncontrolled data suggest that haem arginate (Normosang, Leiras Medica, Finland) is highly efficacious, but it will not reverse an established neuropathy and must be given during the early stages of an attack. 16

Administration of haematin may induce haem oxygenase, with consequent enhanced catabolism. 21 We observed apparent clinical tolerance to haem arginate in a few patients who required repeated courses at short intervals; efficacy was restored by the coadministration of tin protoporphyrin, an inhibitor of haem oxygenase. 22 However, tin protoporphyrin causes photosensitivity and its long-term toxicity is unknown. Zinc mesoporphyrin may be a safer alternative but requires evaluation. 23

Recurrent acute attacks
Frequent recurrences of the acute attack are usually encountered in patients with acute intermittent porphyria who have attacks induced by menstruation or who repeatedly take inducing agents. With masculinously related attacks, attempts to regulate the menstrual cycle with sex steroids may exacerbate the porphyria. Some patients have responded well to hormonal suppression with steroids may exacerbate the porphyria. Some patients have responded well to hormonal suppression with

References

13 Tisher PV, Woodward B, O’connor J, et al. High prevalence of

Outcome

With improvements in management, severe neuropathy and death are now less common than in the past. 25 Recurrent attacks are more common in acute intermittent porphyria than in variegate porphyria. Patients may develop hypertension or chronic renal failure. 26 Acute porphyrias may also be associated with an increased risk of hepatocellular carcinoma. 26

Management of the patient and family
Success in caring for patients with the acute porphyrias lies less in crisis intervention at the time of the acute attack than it does in enabling affected patients and their families to keep to a minimum the risk of an attack. Family studies are essential to identify individuals with clinically latent porphyria so that they can be counselled about the need to avoid drugs and other factors that provoke acute attacks. 1,16,21 Identification of latent porphyria in children and most adults requires specialised enzymatic and other methods, 13 such as DNA analysis, 13,20 and is best undertaken in a referral centre. Most of those who inherit an acute porphyria will lead a normal life and many will be symptom-free; the lives of only a minority are blighted by the disease. No specific diet is indicated for porphyria, though sudden or prolonged calorie restriction may induce an acute attack and should be avoided, as should alcoholic beverages. Although early reports suggest a high incidence of acute attacks in pregnancy and the puerperium, pregnancy seems to pose little increased risk to patients who are known in advance to have porphyria and need not be discouraged. 18 Similarly, general anaesthesia and surgical operations carry little increased risk of an acute attack provided prior knowledge of the diagnosis enables agents that provoke acute porphyria to be avoided.
Further reading

General


Biochemical and molecular genetics


Clinical features of acute porphyrias


Diagnosis and management