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The acute porphyrias

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Introduction

Most doctors have painful memories of learning about porphyria in medical school, although relatively few retain useful knowledge about the condition, recalling it only in desperation as a diagnosis for any patient with recurrent, unexplained symptoms. The porphyrias were first identified as cutaneous diseases in the 19th century, when a series of case reports described patients with skin photosensitivity and red urine. The emerging field of organic chemistry allowed this red substance to be identified as 'haematoporphyrin', which had previously been synthesised from dried blood. Subsequently, there were reports of patients who developed acute visceral symptoms and red urine, also containing haematoporphyrin, after taking drugs such as sulfonal. Thus, a group of conditions gradually emerged that seemed to involve defects in haemoglobin synthesis. They caused a mixture of cutaneous photosensitivity and acute pain, and became known as porphyrias.[1] Progress in clinical chemistry in the 20th century allowed the different types of porphyria to be characterised, and molecular genetics has added clarity over the past 20 years. Although these conditions are now fairly well understood at the biochemical and molecular level, clinical management is still limited and few effective therapeutic interventions are available.

Pathophysiology

Porphyrias are caused mostly by inherited abnormalities in one of the enzymes responsible for the synthesis of haem from the relatively simple molecules glycine and succinyl CoA. The acute porphyrias are usually single-gene disorders that have autosomal dominant inheritance, causing partial reduction of enzyme activity. Eighty percent of haem synthesis takes place in the erythron, with most of the remainder in the liver. The enzymes in the synthesis pathways are identical in the two organs, apart from the first enzyme, amino laevulinic acid synthase (ALAS). In the erythron, ALAS2 is a constitutional, non-inducible enzyme, whereas hepatic ALAS1 is inducible and controlled by negative feedback from haem itself.

The pathology of the porphyrias predominantly results from the build-up of toxic metabolic precursors rather than from actual haem deficiency. The symptoms fall into two main group: photosensitivity and neurovisceral symptoms. Photosensitivity results from the accumulation of porphyrins and protoporphyrins in the plasma, red cells and subcutaneous tissues. These generate superoxide and hydroxyl radicals when exposed to sunlight, causing the pain and tissue damage that are characteristic of cutaneous porphyrias.[2]

The acute neurovisceral symptoms are thought to arise predominantly through the direct action of porphyrin precursors and metabolites on the peripheral and central nervous symptoms. The exact identity of the supposed neurotoxin is unclear. The leading candidate is 5-aminolaevulinic acid (ALA), the second molecule in the haem-synthesis pathway; there is *in vitro* evidence that it can be neurotoxic. However, although ALA concentrations rise sharply during an acute attack, these levels remain elevated long after the symptoms have improved, often for many months or years. Acute neuronal haem deficiency has also been proposed as a mechanism, without much supporting evidence.

The sudden onset of symptoms is characteristic of acute porphyria. Attacks are thought to occur when there is an increase in demand for hepatic haem synthesis, resulting in induction of ALAS1. The inherited deficiency in one of the enzymes results in a rapid accumulation of metabolic precursors with toxic consequences, but because of the enzyme deficiency, there is little or no increase in haem synthesis and no negative feedback to decrease the rate of ALAS1 synthesis. Factors that are known increase haem demand can precipitate acute attacks; these include variations in progesterone and oestrogen levels, starvation, alcohol and certain drugs that induce cytochrome P450 enzymes. Glucose has been shown to play a direct role in determining the rate of ALAS1 transcription, explaining the effects of starvation. Fasting causes an increase in PPAR -coactivator 1 (PGC-1) synthesis by the cAMP/ cAMP-responsive element binding protein (CREB) pathway; PGC-1 activates the transcription factors nuclear respiratory factor 1 (NRF-1) and FOXO1, which increase transcription of ALAS1. Conversely, glucose causes increased insulin levels, which reduce PGC-1 induction and antagonise its activation of FOXO1.[3]

Different types of acute porphyria

Acute intermittent porphyria

Acute intermittent porphyria (AIP) is the most severe form of acute porphyria, resulting from autosomal dominant deficiency of porphobiliniogen deaminase. In Europe, about 1–2 people per 100,000 inherit the condition; although in northern Sweden, the allele frequency reaches one per 1,000 because of genetic isolation and a founder effect.

Variegate porphyria

Variegate porphyria (VP) is caused by protoporphyrinogen oxidase deficiency, and usually causes acute symptoms that are less

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severe than those caused by AIP. There is variable accumulation of plasma porphyrins, which in some people cause cutaneous photosensitivity, with blistering, skin fragility, and hypertrichosis in sun exposed areas. Variegate porphyria affects about 1 per 100,000 Europeans, but is much more prevalent amongst white South Africans because of a founder effect that has been traced back to one particular couple originating from the Netherlands.

Hereditary coproporphyria

This is probably the least severe acute porphyria. It is thought to be rarer than AIP and VP, although many cases are probably undiagnosed because of the lack of symptoms and the need to test faeces to confirm the diagnosis. It is caused by coproporphyrinogen oxidase deficiency and, like VP, is associated both with acute attacks and skin fragility with blisters.

ALA dehydratase porphyria

This is the only autosomal recessive acute porphyria. It is sometimes called Doss porphyria or plumboporphyria because biochemically it resembles lead poisoning, causing high urinary levels of ALA but normal porphobiliniogen (PBG). It is typically severe and associated with acute and chronic neuropathy, although it is very rare with fewer than ten cases having been described worldwide.[4]

Patterns of disease caused by acute porphyria

Latent acute porphyria

Many people inherit acute porphyria but remain asymptomatic throughout their lives. Such cases of latent porphyria are typically identified during screening of the relatives of symptomatic patients. Approximately 80% of men and 50% of women with AIP follow this pattern, with latency significantly more prevalent in HCP and VP. Latent disease is almost silent biochemically, although it might be possible to detect minor abnormalities, such as a slight increase in urinary PBG in AIP or a plasma porphyrin peak in VP. Enzyme assays might also detect low levels of activity, although this approach has limited sensitivity and specificity. DNA analysis is the best method of identifying individuals with latent porphyria, although even this is not 100% sensitive with 5–10% of patients having no mutation that can be identified by standard analysis, possibly as a result of large deletions or intronic mutations.

Active acute porphyria: single or infrequent attacks

Acute symptoms almost never occur in prepubertal children, and typically happen for the first time between the late teens and thirties. Most patients who suffer an acute attack do so only once, or very infrequently. Usually, the patient recovers uneventfully from the first attack and learns to avoid potential precipitating factors, with a subsequent avoidance of problems. The frequency and severity of attacks usually decrease with increasing age, and significant problems are unusual after the menopause.

Active acute porphyria: recurrent attacks

A small minority of patients with AIP, probably less than 5%, suffer recurrent disabling attacks of acute pain. This typically occurs in young women, with each attack occurring in the premenstrual period. This pattern can continue for many years and is usually incompatible with a normal or happy life. It is not known why this occurs in some patients and there is known link to biochemical defects caused by the porphyria mutation. Lifestyle factors might be important in some cases. Such recurrent attacks can result in significant and progressive neuropathy, potentially causing chronic pain, respiratory failure and even death. This severe pattern of disease is very rare in VP and HCP, and when it does occur, it is usually associated with significant co-incidental disease or unusual life-style factors such as heavy alcohol consumption or use of recreational drugs.

Clinical features of an acute attack

Precipitating factors

Several factors have been identified as precipitants of acute symptoms.

Drug exposure: certain drugs increase hepatic demand for haem, typically by inducing P450 cytochromes. Porphyrinogenic drugs include progesterones, oestrogens and barbiturates. Some drugs are known to be safe, although many medicines fall into a grey area where little good evidence is available. For most medical problems, however, a medicine is available that is effective and safe for those with porphyria.

Hormonal variation: variations in the levels of progesterones and oestrogens are established precipitants of acute pain, with high levels of progesterone seeming to be the most porphyrinogenic. Pain can be caused by exposure to hormone replacement therapy and the oral contraceptive pill. Attacks are also more likely in the premenstrual period and, to a lesser extent, in pregnancy and the puerperium.

Carbohydrate starvation: low carbohydrate intake stimulates hepatic haem synthesis by inducing PGC-1α. Some patients find that an increase in glucose intake when early symptoms occur can avert an incipient attack, and intravenous glucose is sometimes used to shorten an acute episode.

Alcohol consumption: alcohol induces ALAS1 activity, but most patients with acute porphyria can consume moderate amounts of alcohol with no adverse effects. Alcoholic binges are more likely to provoke acute symptoms, with the direct effects of alcohol being exacerbated by the reduced food intake related to nausea.

Other factors: the majority of attacks probably have no clear precipitating factors. Many patients identify stress and tiredness as being important, and often there is a combination of events that leads to the acute episode.

Symptoms and clinical findings

The cardinal feature of an attack of porphyria is acute pain, involving the abdomen in more than 90% of cases and the back and upper legs about 25% of the time. Other common symptoms include vomiting and constipation.[5] Overt neurological symptoms, such as weakness, numbness and convulsions, are uncommon, occurring in fewer than 10% of acute attacks. Hypertension and tachycardia are present in the majority of attacks.

Diagnosis of an acute attack

The signs and symptoms of acute porphyria are not specific, and statistically, the symptoms that are associated with porphyria are far more likely to have surgical causes such as appendicitis or cholecystitis. If porphyria has already been diagnosed and previous attacks have occurred, the diagnosis is more straightforward, although again it is important to exclude coincidental surgical, gynaecological, vascular or infective causes of the acute illness. If the symptoms are the first presentation of previously undiagnosed porphyria, then typically it will take several weeks or months to exclude more common causes of the symptoms and make the diagnosis.

The acute symptoms of porphyria are accompanied by markedly increased urinary excretion of PBG and ALA, typically at least ten times greater than the upper limit of normal. The exceptions are very rare cases of ALA dehydratase porphyria, in which only ALA excretion is increased. Interpretation of these results is complicated, however, by the fact that urinary levels of PBG and ALA remain elevated long after the symptoms have improved. In AIP, PBG excretion can remain greater than 10 times the upper limit of normal for up to 15 years after the last attack, and so the accurate diagnosis of subsequent symptoms is essentially clinical. In VP and HCP, ALA and PBG levels return to normal more quickly, but can remain elevated for several months.

Management of acute porphyria

Management of latent porphyria

The increased use DNA testing is identifying more individuals who have latent porphyria. Management involves education about acute porphyria, particularly about avoidable precipitating factors, and reassurance that the condition is likely to remain latent. It is important to discuss the risks of taking the oral contraceptive pill with women; some will already be taking the pill and in many cases continue without any difficulties, particularly if there are no biochemical abnormalities. Some latent patients might wish to be reviewed annually, whereas others prefer an open appointment allowing them rapid access to porphyria services should problems develop.

Management of an episode of acute porphyria

Pain is the main clinical problem and adequate analgesia typically requires opioids, which are usually given parenterally and by patient-controlled analgesia. Antiemetics and laxatives are also generally helpful. Intravenous fluids should be used cautiously because of the tendency towards hyponatraemia, and electrolytes should be monitored daily. Adequate carbohydrate intake, of at least 200 g glucose per day, is important and can be given as 2 l of dextrose saline per 24 hours. If pain is severe, requiring hospital admission and opiates, treatment with haem arginate is likely to be beneficial. This should be given as early as possible during the course of an attack. It is given as an intravenous infusion at a dose of 3 mg/kg on four successive days, and causes a rapid but transient fall in PBG levels. Haem arginate has been shown to shorten the duration of pain, and its main side-effect is thrombophlebitis at the site of infusion. It can also reduce the risk of severe neuropathy.

The majority of attacks resolve within a week, although a very small number last much longer and result in severe and progressive neuropathy that requires mechanical ventilation. There is no evidence-based management for this situation, although optimal respiratory support, treatment of infection and prolonged use of haem arginate are thought to improve prognosis. Death is rare as a consequence of an attack of acute porphyria, and most often seems to result from very delayed diagnosis and prolonged use of porphyrinogenic medication. Death can result from hyponatraemia, severe neuropathy causing respiratory failure and possibly autonomic neuropathy causing cardiac arrhythmias.

Management of recurrent attacks of porphyria

A small percentage of patients, mostly women, develop repeated attacks, often on a monthly basis associated with menstruation. This results in significant morbidity, inability to work and, in severe cases, progressive neuropathy. There is no established management that has a firm evidence-base. If the attacks are clearly linked to menstruation, suppression of the menstrual cycle using gonadotrophin-releasing hormone agonists, such as goserelin, is logical and anecdotally effective in some cases. Regular, prophylactic haem arginate is also used in some cases; this has been used in different regimes with variable effects but evidence of its efficacy is largely anecdotal.[6] Cimetidine has been proposed as a treatment because of its ability to inhibit haem oxygenase, but again there is little evidence of clinical benefit. Several patients with severe, recurrent attacks have been treated successfully with liver transplantation, although there have been some fatalities and significant complications.[7]

Porphyria and psychiatric illness

Historically, and in popular culture, acute porphyrias have been identified as causing psychiatric illness, most famously in the case of King George III of England. There is little evidence that acute porphyria does cause isolated psychiatric illness, although behavioural disturbances are recognised during acute attacks, and as for many chronic diseases, psychological problems may

be more common in sufferers than in the general population. On balance, there is little to support the diagnosis of acute porphyria in George III or any of his relatives.[8] Some patients have very strong, possibly delusional, beliefs that they have acute porphyria, despite repeated testing showing no evidence of the condition. Often, these patients have a primary psychiatric disorder and attribute their symptoms to porphyria because of the perception that this is a less stigmatised diagnosis, partly because of its royal overtones.

Future developments

The only specific treatment for acute porphyria is haem arginate, and this has limited efficacy during acute attacks and no proven benefit in preventing recurrent attacks. Further clinical trials might help to establish how this treatment is best used. Trials of specific enzyme replacement therapy in AIP showed no evidence of benefit because of difficulties with delivering the enzyme to the liver, although this approach might be refined in the future. Phase I studies of gene therapy are starting in Europe, with encouraging mouse data, and might offer significant benefit to patients with recurrent attacks.[9] Safer ways of performing liver transplantation and subsequent immunosuppression might widen the use of this treatment.

References

1 Goldberg A. The porphyrias. Historical perspective. *Clin Dermatol* 1998;16:189–93.
2 Sarkany RP. Making sense of the porphyrias. *Photodermatol Photoimmunol Photomed* 2008;24:102–8.
3 Handschin C, Lin J, Rhee J *et al.* Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. *Cell* 2005;122:505–15.
4 Doss MO, Stauch T, Gross U *et al.* The third case of Doss porphyria (delta-amino-levulinic acid dehydratase deficiency) in Germany. *J Inherit Metab Dis* 2004;27:529–36.
5 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004–8.
6 Kauppinen R. Porphyrias. *Lancet* 2005;365:241–52.
7 Dowman JK, Gunson BK, Mirza DF *et al.* Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. *Liver Transpl* 2012;18:195–200.
8 Hift RJ, Peters TJ, Meissner PN. A review of the clinical presentation, natural history and inheritance of variegate porphyria: its implausibility as the source of the 'Royal Malady'. *J Clin Pathol* 2012;65:200–5.
9 Unzu C, Sampedro A, Mauleón I *et al.* Sustained enzymatic correction by rAAV-mediated liver gene therapy protects against induced motor neuropathy in acute porphyria mice. *Mol Ther* 2011;19:243–50.

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