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Update review of the acute porphyrias

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Summary

Acute porphyrias are rare inherited disorders due to deficiencies of haem synthesis enzymes. To date, all UK cases have been one of the three autosomal dominant forms, although penetrance is low and most gene carriers remain asymptomatic. Clinical presentation is typically with acute neurovisceral attacks characterised by severe abdominal pain, vomiting, tachycardia and hypertension. Severe attacks may be complicated by hyponatraemia, peripheral neuropathy sometimes causing paralysis, seizures and psychiatric features. Attacks are triggered by prescribed drugs, alcohol, hormonal changes, fasting or stress. The diagnosis is made by finding increased porphobilinogen excretion in a light-protected random urine sample. Management includes administration of intravenous human haemin and supportive treatment with non-porphyrinogenic drugs. A few patients develop recurrent attacks, a chronic illness requiring specialist management. Late complications include chronic pain, hepatocellular carcinoma, chronic renal failure and hypertension. In the UK, the National Acute Porphyria Service provides clinical advice and supplies haemin when indicated.

Keywords: acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, haemin, National Acute Porphyria Service.

The acute porphyrias belong to a wider group of porphyrias (Table I), each of which results from deficiency of a specific enzyme of the haem synthesis pathway, apart from X-linked erythropoietic protoporphyria, which is due to gain of function mutations (Kauppinen, 2005; Sassa, 2006; Puy *et al*, 2010). Clinical features depend on where the block in this pathway occurs, and the resulting accumulation of haem precursors or porphyrins, which are predominantly from the bone marrow and liver. Porphyrias may be considered in two groups: acute porphyrias, presenting with acute neurovisceral attacks, and cutaneous porphyrias, characterised by photosensitive skin lesions, although there is overlap.

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There are 4 acute porphyrias (Elder *et al*, 1997; Hift *et al*, 2012; Bissell & Wang, 2015) of which the recessive delta aminolevulinic acid (ALA) dehydratase deficiency porphyria (ADP) is exceedingly rare, with only a handful of case reports in the literature. Acute intermittent porphyria (AIP) is the most common acute porphyria in European populations and typically most severe. Variegate porphyria (VP) and hereditary coproporphyria (HCP) are rarer and may present with acute attacks or photosensitive skin lesions or both. Acute attacks in each case are considered to result from overproduction of a neurotoxic haem precursor from the liver, although the exact pathophysiology is not fully understood.

Haem synthesis and regulation

Haem-containing proteins have essential and diverse biological functions including oxygen transport, electron transfer and catalysis. Haem synthesis (Fig 1) takes place in all nucleated cells, but 80–90% of haem is made in developing red cells in the bone marrow where it is used for haemoglobin, with most of the remainder produced in hepatocytes for various haem-containing proteins, particularly the microsomal cytochrome P450 enzymes. Regulatory mechanisms differ at these two sites: erythroid haem synthesis depends mainly on the availability of iron, while hepatic haem synthesis is regulated by the free haem pool (Karim *et al*, 2013).

The first step in haem synthesis is the formation of ALA within the mitochondria catalysed by 5-aminolevulinic acid synthase (ALAS). This enzyme exists as 2 isoforms, ubiquitously expressed ALAS1 and erythroid ALAS2 (Bishop *et al*, 1990). ALAS1 is rate limiting in hepatic haem synthesis and tightly regulated by intracellular haem (Ajioka *et al*, 2006), which is the basis for the therapeutic effect of haemin in acute porphyria attacks, and the target for a new RNA silencing therapy undergoing clinical trials (Chan *et al*, 2015). *ALAS1* transcription may also be induced directly through activation of nuclear receptors responding to xenobiotic and steroid challenge and to transcription factors activated by fasting (Thunell, 2006).

Genetics of acute porphyrias

AIP, VP and HCP are inherited as autosomal dominant disorders with wide allelic heterogeneity. Approximately half of

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Table I. Mode of inheritance, enzyme defect, and clinical presentation in the acute and cutaneous porphyrias.

	Inheritance	Gene/enzyme	Clinical presentation	
			Acute attacks	Skin symptoms (both)
Acute porphyrias				
ALA Dehydratase deficiency porphyria	AR	*ALAD*/ALA dehydratase	100%	None
Acute intermittent Porphyria	AD	*HMBS*/Hydroxymethylbilane synthase	100%	None
Hereditary coproporphyria	AD	*CPOX*/Coproporphyrinogen oxidase	>95%*	<5%* (20–30%)
Variegate porphyria	AD	*PPOX*/Protoporphyrinogen oxidase	40%†	60%† (20%)
Cutaneous porphyrias				
Porphyria cutanea tarda	AD‡	*UROD*/Uroporphyrinogen decarboxylase	None	100%
Congenital erythropoietic porphyria	AR	*UROS*/Uroporphyrinogen synthase	None	100%
Erythropoietic protoporphyria	AR	*FECH*/Ferrochelatase	None	100%
X-linked erythropoietic protoporphyria	XL	*ALAS2*/ALA synthase 2	None	100%

AR, autosomal recessive; AD, autosomal dominant; XL, X-linked.
*Elder *et al* (2013).
†Whatley *et al* (1999).
‡20% inherited, 80% acquired.

all variants are missense or nonsense mutations. The Human Gene Mutation Database (Stenson *et al* 2014) lists 403 variants in the hydroxmeythyl bilane synthase (HMBS) gene (*HMBS*) causing AIP, 177 variants in the protoporphyrinogen oxidase (PPOX) gene (*PPOX*) causing VP, and 65 variants in the coproporphyrinogen oxidase (CPOX) gene (*CPOX*) causing HCP. Genetic differences have not proved useful in predicting clinical outcome or penetrance (Bonkovsky *et al*, 2014).

Founder effects are reported in several populations. For example, AIP has a much higher prevalence in Northern Sweden than in other European countries, with more than 50% of cases carrying the *HMBS* p.Trp198X mutation (Lee & Anvret, 1991). VP is particularly prevalent in the Afrikaner population of South Africa with the *PPOX* p.Arg59Trp mutation being responsible for more than 90% of cases (Meissner *et al*, 1996).

Natural history of acute porphyrias

Clinical penetrance in the dominant acute porphyrias (AIP, VP and HCP), is low with most family studies suggesting that only 10–20% of gene carriers will have an acute attack in their lifetime (Elder *et al*, 1997; Puy *et al*, 2010) although a clinical penetrance exceeding 40% has been reported in northern Sweden (Bylesjö *et al*, 2009). Gene carriers for acute porphyria who have never had an acute attack are termed latent and although most of these individuals remain well, they are all assumed to be equally susceptible to attacks precipitated by various environmental triggers, and predisposed to by as yet unidentified genetic factors (Badminton & Elder, 2005).

Although there is believed to be no sex difference in gene carriage, acute attacks affect females 5 times more often than males (Elder *et al*, 2013). Attacks are extremely rare before puberty and unusual after the menopause with the majority presenting between the ages of 20 and 40 years (Elder *et al*, 1997; Bonkovsky *et al*, 2014). Most symptomatic patients have just one or a few acute attacks in their lifetime, often within a period of a few years, and make a full recovery. At the other extreme, a few patients (mostly female) have a severe chronic illness with recurrent attacks every few weeks resulting in significant disability.

Clinical manifestations are reported to be more frequent and severe in AIP than in VP and HCP (Bonkovsky *et al*, 2014), and attacks are up to 14-fold more common in AIP than in VP (Hift & Meissner, 2005). Most attacks of AIP are precipitated by hormonal factors, while in VP, pre-menstrual attacks (and hence recurrent attacks) are unusual with drugs reported as the most important trigger (Hift & Meissner, 2005).

The proportion of patients experiencing acute attacks has apparently fallen over the past 3 decades, probably due to improved family screening and counselling (Elder *et al*, 2013). The prognosis for full recovery is good even following a severe attack, although rarely attacks are fatal (Kauppinen, 2005; Stein *et al*, 2012).

Incidence and prevalence of acute porphyrias

A 3-year prospective study of newly diagnosed symptomatic patients with inherited porphyrias in 11 European countries reported an annual incidence for symptomatic acute porphyria of 0·2 per million (0·13 per million for AIP, 0·08 per million for VP and 0·02 per million for HCP) (Elder *et al*, 2013).

Estimates of prevalence vary widely and do not always distinguish between latent (never had symptoms) and overt (previous or currently symptomatic) disease. The European study (Elder *et al*, 2013) estimated the prevalence of patients with overt acute porphyria (all types) as about 10 per million. Prevalence of overt AIP was 5·4 cases per million,

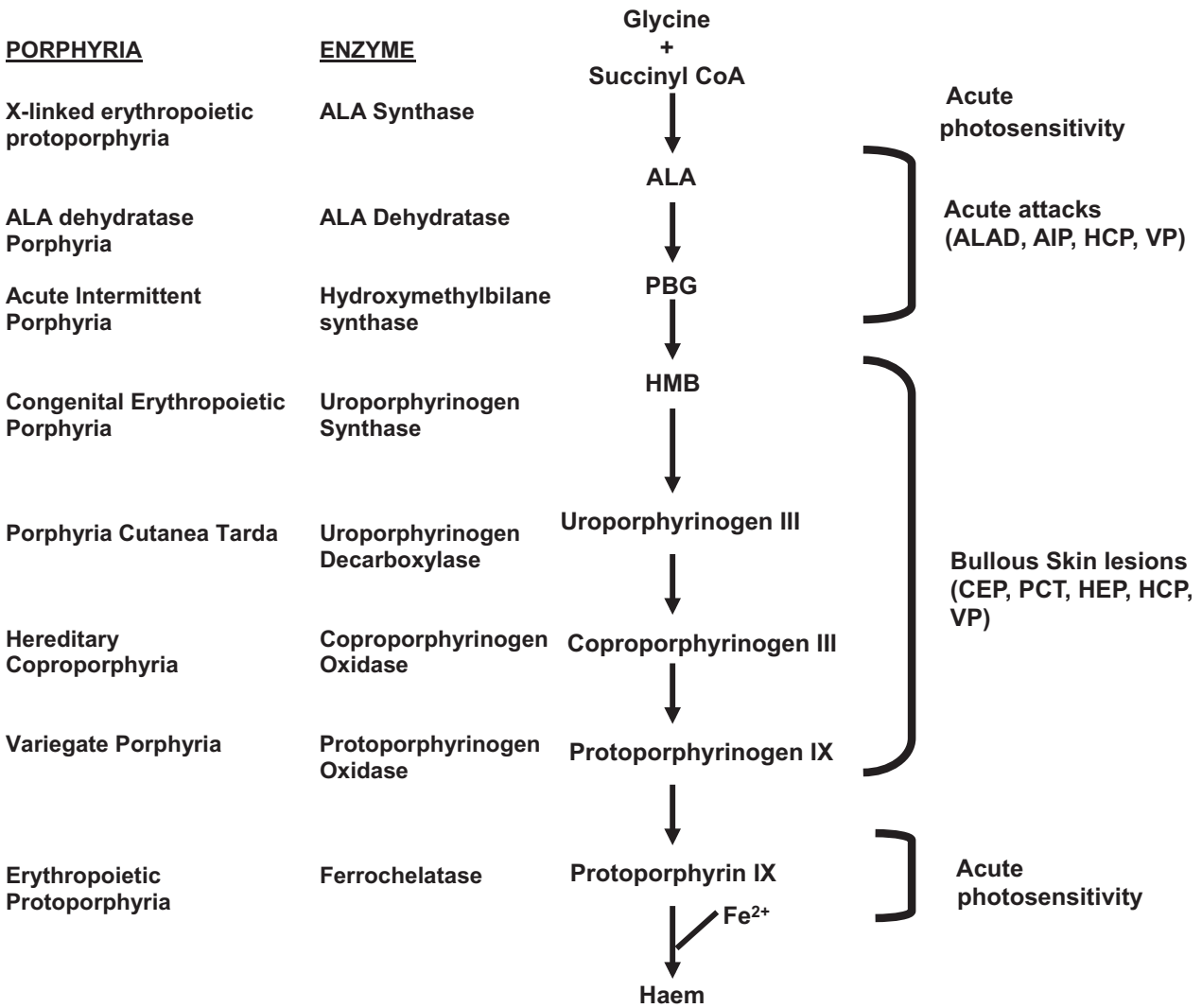

Fig 1. Haem synthesis pathway. AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAD, ALA dehydratase; CEP, congenital erythropoietic porphyria; HCP, hereditary coproporphyria; HEP, hepatoerythropoietic porphyria; HMB, hydroxymethylbilane; PBG, porphobilinogen; PCT, porphyria cutanea tarda; VP, variegate porphyria.

except in Sweden where it was 23 per million. VP is about half as prevalent as AIP in Europe (3·2 per million), but is much more common in South Africa where it is estimated to affect 3000 per million individuals of Dutch descent (Hift & Meissner, 2005).

Screening of a group of asymptomatic blood donors Nordmann *et al* (1997) suggested that pathogenic mutations causing AIP may be up to 100-fold higher than the prevalence of symptomatic disease. Recent genomic analysis has confirmed that the prevalence of probable pathogenic mutations causing AIP is about 560 cases per million (Chen *et al*, 2016).

Pathophysiology of acute attacks

In the dominant acute porphyrias, a functional gene is inherited from the unaffected parent, so residual enzyme activity is typically 50% and sufficient for haem homeostasis (Badminton & Elder, 2005). However, the partial enzyme deficiency becomes rate limiting when there is upregulation of ALAS1, resulting in increased metabolic flux through the pathway with accumulation and release of porphyrins and their precursors from the liver. Raised concentrations of ALA and porphobilinogen (PBG) are associated with inherited deficiency of HMBS in AIP, while in VP and HCP this is thought to result from allosteric inhibition of HMBS by accumulating coproporphyrinogen and or protoporphyrinogen (Meissner *et al*, 1993). A complex network of transcriptional pathways regulates hepatic ALAS1, and may explain the wide variation in susceptibility to attacks in acute porphyria gene carriers (Thunell, 2006).

The pathogenesis of attacks is still uncertain but it is believed that ALA exerts toxic effects on nerves, either directly, or by interacting with receptors for the structurally

similar neurotransmitter γ-aminobutyric acid (GABA), or by forming free radicals and reactive oxygen species (Brennan & Cantrill, 1981; Lin *et al*, 2011). Support for the key role of ALA in the pathogenesis of attacks comes from the observation that disorders associated with excess production of ALA but not PBG (hereditary tyrosinaemia, lead poisoning, ADP) have similar clinical presentations to acute porphyria. However plasma and urinary ALA levels do not correlate well with porphyria symptoms, and other unidentified biochemical pathways are likely to be involved (Marsden & Rees, 2014). The effectiveness of liver transplantation as a treatment for severe acute porphyria (Soonawalla *et al*, 2004), and the onset of acute attacks in a patient who received a liver transplant from a symptomatic AIP donor (Dowman *et al*, 2011) confirm the central role of the liver in the pathological process.

Triggers for acute attacks

Both prescribed and recreational drugs are important triggers for acute attacks in susceptible individuals (Hift *et al*, 2011). They act by inducing ALAS1, either directly or indirectly, by increasing demand for hepatic haem particularly through the consumption of cytochrome P450 enzymes. Well-known examples of unsafe drugs include hormonal contraception, some antibiotics (erythromycin, trimethoprim, rifampicin), anticonvulsants (such as phenytoin) and anaesthetics (such as barbiturates). Further information on drug safety can be found in the British National Formulary. It is not currently possible to predict which patients are susceptible to attacks, so latent and overt patients should be managed as equally at risk, and drug safety checked prior to prescribing any new drug. The UK Porphyria Medicines Information Centre provides advice about the safety of specific drugs and publishes a safe list that is updated annually (www.wmic.wales.nhs.uk/porphyria_info.php). A drug database for acute porphyria has been developed by the Norwegian and Swedish Porphyria Services and is available in several languages (http://www.drugs-porphyria.org/) (Thunell *et al*, 2007). Many drugs have not been definitely classified because of limited information. It may be necessary to prescribe drugs that are not classified as safe when there is no appropriate safe option and clinical benefit is assessed to outweigh risk. In this situation and for patients who are undergoing complex drug therapies, such as fertility treatment, cancer chemotherapy or treatment of human immunodeficiency virus infection, liaison with a specialist porphyria service is recommended.

The influence of endogenous female sex hormones is thought to explain why acute attacks mainly affect women of child bearing age. Progesterone is a potent inducer of ALAS1 (Anderson *et al*, 1979), and is believed to be more porphyrinogenic than oestrogens, explaining why attacks in women are more frequent during the luteal phase of the menstrual cycle, and why oral contraceptive pills frequently precipitate attacks (Andersson *et al*, 2003; Bonkovsky *et al*, 2014). Oral contraception should be avoided if possible, and subdermal contraceptive implants are particularly contraindicated (Harper & Sardh, 2014).

Reduction in carbohydrate intake (for instance due to fasting, dieting, illness or gastrointestinal upset) is a well-known trigger of attacks through indirect induction of ALAS1. Glucose downregulates ALAS in experimental conditions through effects on peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a protein which directly induces transcription of ALAS1 (Handschin *et al*, 2005).

Alcohol, particularly binge-drinking, may precipitate attacks, primarily through direct induction of ALAS1 (Doss *et al*, 2000). Other triggers include stress and infection (Elder *et al*, 1997). Cigarette smoking may increase the likelihood of recurrent attacks (Lip *et al*, 1991). Many attacks have no clearly identifiable precipitants.

Clinical presentation of an acute attack

Acute neurovisceral attacks may occur in all the acute porphyrias and are clinically indistinguishable. Recognition of an attack in a patient without a known diagnosis of acute porphyria is difficult and often delayed, as symptoms and signs are non-specific, particularly in the early stages of the illness, and because porphyrias are so rare. The diagnosis should be considered in patients with recurrent or prolonged episodes of unexplained abdominal pain, particularly when this is associated with neurological complications, psychiatric features or hyponatraemia.

Most of the clinical features of an attack (Elder *et al*, 1997; Badminton & Elder, 2002; Puy *et al*, 2010) arise from effects on the central, peripheral and autonomic nervous systems. The main symptom is severe, poorly localized abdominal pain (present in more than 90% of cases), sometimes with pain at other sites, especially the back and legs, and often accompanied by nausea, vomiting and constipation. Raised blood pressure and tachycardia are almost always present, but examination is often otherwise normal. Mental changes including agitation, depression, insomnia and confusion occur frequently in association with acute pain, and may also be present in the prodromal stages of an attack. Rarely these are more severe with psychosis, delusions and hallucinations. Mental changes resolve completely on remission.

Severe attacks, especially when diagnosis is delayed and exposure to porphyrinogenic factors is prolonged, may be complicated by neurological features including an axonal neuropathy, seizures and posterior reversible encephalopathy syndrome (Pischik & Kauppinen, 2009). A symmetrical motor neuropathy with weakness beginning proximally in the upper limbs is typical and may rarely progress rapidly to give complete paralysis, incontinence or urinary retention, swallowing difficulties and respiratory failure. Paralysis is

usually reversible with appropriate supportive treatment but requires many months of rehabilitation. Sensory disturbance may manifest as neuropathic pain, paraesthesiae or numbness. Focal neuropathy is unusual. Rare complications of attacks include cardiac arrhythmias, which may account for occasional reports of sudden death (Ridley, 1969), and rhabdomyolysis (Marsden & Peters, 2004).

Routine biochemical and haematological investigations are often normal, apart from hyponatraemia which occurs in up to 40% of attacks (Puy *et al*, 2010). In many cases this is attributed to the syndrome of inappropriate antidiuretic hormone, but renal or gastrointestinal sodium loss and over hydration may contribute. Severe hyponatraemia may lead to seizures.

Altered urine colour, darkening to red especially on exposure to light, is often striking (Fig 2) and is due to oxidation of PBG to uroporphyrin and porphobilin (Sassa, 2006). Although non-specific, this is a well-known feature of acute porphyria.

Laboratory diagnosis of an acute attack

In the dominant acute porphyrias, acute attacks are always accompanied by an increase in urinary excretion of ALA, PBG and porphyrin. Measurement of urine PBG and porphyrin are the first-line tests in a patient with a suspected acute attack of porphyria (Woolf *et al*, 2016), and normal results in an acutely unwell patient excludes acute porphyria as a cause of those symptoms. In VP and HCP, urine PBG excretion may return to normal within days to weeks, so the increase can be missed if sample collection is delayed, although urine porphyrin elevation persists for longer. In lead toxicity or the very rare ADP, urine porphyrin and ALA excretion are increased without a significant increase in PBG.

PBG is best analysed (Woolf *et al*, 2016) in a fresh random 10 ml urine sample collected without preservative, and protected from prolonged exposure to bright light. Urgent testing in new patients will typically require specific arrangements to be made with the biochemistry laboratory but should be available within 24 h of sample receipt. Analysis by a quantitative method is preferred and the result should be expressed as a ratio of the concentration of PBG to the concentration of creatinine (Aarsand *et al*, 2006).

Fig 2. Fresh (A) and light exposed (B) urine samples from a patient presenting with an acute attack of porphyria.

In a patient without a previous diagnosis of acute porphyria who presents with clinical features of an attack (for instance unexplained abdominal pain and vomiting), the finding of a significantly increased urine PBG concentration is sufficient to initiate treatment. The extent to which urine PBG concentration must change to confirm an acute attack is not defined, but there is usually at least a 10-fold increase over the upper limit of normal in an attack of AIP (Sandberg & Elder, 2004; Puy *et al*, 2010; Harper & Sardh, 2014; Bissell & Wang, 2015).

While urine PBG concentration falls back to normal within a week or two of the attack in VP and HCP (Puy *et al*, 2010), it may remain significantly elevated for up to 20 years, even in the absence of ongoing symptoms, in AIP (Marsden & Rees, 2014). Urine PBG excretion after recovery from an attack of AIP may be up to 50 times the upper reference limit (Andersson *et al*, 1995) making interpretation of results difficult (Aarsand *et al*, 2006).

Other biochemical attack markers have been investigated. Plasma ALA is a sensitive marker of clinical course in acute attacks (Sardh *et al*, 2009a) but the assay is available in only a few specialist laboratories. Urine ALA and urine porphyrin concentrations are both increased in acute attacks. However increased urine porphyrin is a common and non-specific finding in many acute illnesses, while urine ALA usually mirrors PBG and rarely provides additional information unless there is suspicion of lead toxicity or ADP.

Biochemical and genetic diagnosis of individual acute porphyrias

Further investigation of a newly presenting symptomatic patient requires analysis of plasma and faecal porphyrins to determine the type of acute porphyria (Woolf *et al*, 2016). A positive plasma porphyrin fluorescent emission screen with an emission peak greater than 624 nm is diagnostic of VP. Where the emission peak is less than 624 nm (usually around 620 nm), analysis of faecal porphyrins allows AIP and HCP to be clearly distinguished (Fig 3).

As investigation of family members is almost invariably required and as biochemical methods lack sensitivity and specificity for testing relatives, genetic testing of the proband to document the causative mutation should be requested. Mutation analysis of the relevant gene reveals a pathogenic variant in more than 95% of affected patients (Whatley *et al*, 2009). Once a causative mutation has been identified, cascade testing of at-risk family members can be undertaken on DNA extracted from blood or saliva. Family member testing may be organised and undertaken through regional genetic services, but all affected patients should be offered referral to a porphyria or metabolic specialist for counselling once a diagnosis is confirmed. Emerging technology based on next-generation sequencing may increase the importance of DNA analysis in

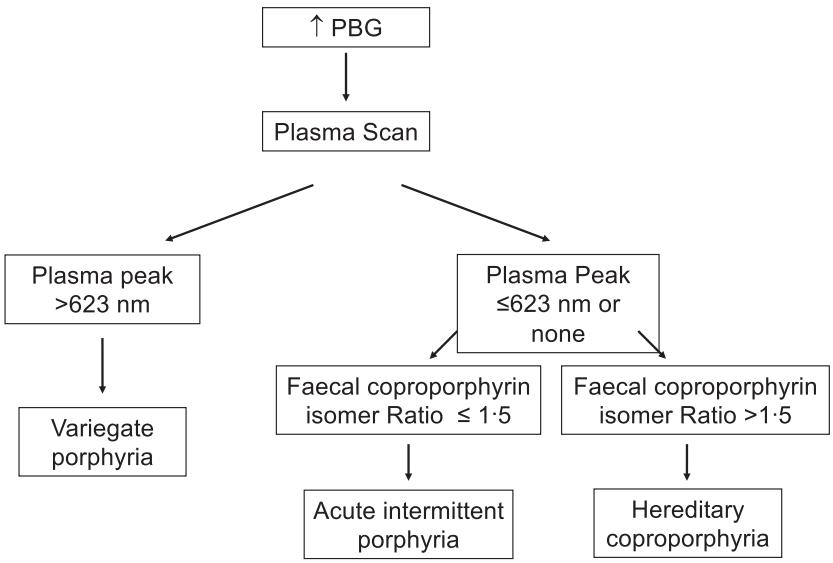

Fig 3. Suggested diagnostic pathway to determine type of acute porphyria following finding of a raised urine porphobilinogen (PBG) concentration.

the diagnosis of acute porphyria, with the potential to analyse rapidly and cheaply a large number of complex genes.

Genetic testing of symptomatic patients with normal urine, plasma and faecal porphyrins is rarely indicated and difficult to interpret, as finding a mutation does not confirm porphyria as the cause of symptoms. Conversely, failure to find a mutation in a patient with a historic diagnosis of active acute porphyria does not completely exclude acute porphyria as a cause of the previous illness (Whatley *et al*, 2009). Enzyme activity, which is reduced by 50%, can be measured in erythrocytes for HMBS, but requires nucleated cells for PPOX and CPOX activity and these assays are therefore less widely available. Erythrocyte HMBS activity also has some additional limitations; it does not identify reduced activity resulting from mutations within the region coding for the additional 17 amino acids present in the ubiquitous isoform, and there is an overlap between the activity range in affected and unaffected individuals, which can reduce the diagnostic certainty of these investigations (Thunell *et al*, 2000).

Management of an acute attack

The majority of patients with moderate or severe attacks require hospital admission for evaluation, treatment and monitoring. Other causes of symptoms should be excluded, particularly treatable conditions requiring urgent treatment, such as appendicitis, complications of pregnancy or pancreatitis. Precipitating factors should be identified and removed if possible, including checking medication for porphyrinogenicity.

Symptomatic and supportive treatment with drugs that are known to be safe in acute porphyria should be started as soon as possible. Pain is typically severe and opiates are usually indicated, often in large amounts. Administration of opiates at regular intervals, or via a Patient Controlled Analgesia pump is preferred. It is helpful to seek advice from a specialist pain management team.

Intravenous fluids are indicated if there is vomiting, dehydration or electrolyte imbalance; normal saline or glucose mixed with normal saline are the preferred options. Hyponatraemia is common and can develop rapidly; this should be evaluated through paired urine and serum measurements of sodium and osmolality, and assessment of extracellular fluid volume status, with appropriate treatment depending on the underlying cause.

Carbohydrate loading was the standard treatment for an acute attack of porphyria prior to availability of haemin, and the rationale is based on the inhibitory effect of glucose on ALAS1 (Welland *et al*, 1964; Felsher & Redeker, 1967). Oral carbohydrate is often beneficial in mild attacks, but the role of intravenous carbohydrate loading is controversial because of the potential risk of hyponatraemia leading to cerebral oedema and osmotic demyelination (Stein *et al*, 2012). Experts in the US (Anderson *et al*, 2005) and Sweden (Harper & Sardh, 2014) advise intravenous glucose providing at least 300 g carbohydrate daily together with monitoring for hyponatraemia, while guidelines from the UK (Stein *et al*, 2013) and South Africa (Hift & Meissner, 2005) recommend avoiding all intravenous solutions of glucose in water.

Human haemin was proposed as a treatment for acute attacks (Bonkowsky *et al*, 1971) based on its potential to suppress ALAS activity and reduce production of haem precursors (Bonkovsky *et al*, 1991). It has become the treatment of choice for all severe or prolonged attacks, especially when there is hyponatraemia, convulsions, psychosis or neuropathy. Two forms of human haemin are currently available, haem arginate (Normosang, Orphan Europe, Berkshire, UK), a stable form of human haemin in a complex with arginine, is used in Europe and many other countries, while a lyophilised form of human haemin (Panhematin, Recordati Rare Diseases, Lebanon, NJ, USA) is used in the USA, where haem arginate does not have Food and Drug Administration approval.

The only placebo-controlled trial of human haemin involving 12 patients did not show a statistically significant effect (Herrick *et al*, 1989), but clinical experience gathered in many different countries over the past 25 years suggests that patients treated with haemin at an early stage in their attack have faster resolution of symptoms, shorter hospital stays and a lower incidence of complications, including neuropathy and seizures, than those who did not receive haemin (Kostrzewska *et al*, 1991; Mustajoki & Nordmann, 1993; Nordmann & Deybach, 1993; Hift & Meissner, 2005; Anderson & Collins, 2006). Haemin will not reverse an established neuropathy, but may prevent onset or progression of nerve damage (Hift & Meissner, 2005; Puy *et al*, 2010).

The recommended dose of haemin varies between 1 and 4 mg/kg body weight, with doses above 6 mg/kg/day regarded as toxic. The recommended dose of haem arginate is 3 mg/kg (up to a maximum of 250 mg) daily for 4 consecutive days, although longer courses are sometimes used in severe attacks with neuropathy. Haem arginate should be reconstituted in 100 ml normal saline, although many clinicians prefer to use 100 ml 20% human serum albumin (Bonkovsky *et al*, 1991), which reportedly reduces the risk of local vascular complications. The solution is stable for 1 h and should be infused through an online filter over 30–60 min, after which the vein should be flushed immediately with saline. Haemin is an irritant and thrombophlebitis is the most common side effect. Infusions should therefore be given through a large peripheral vein or a central line to reduce the risk of damage to the superficial venous system.

The National Acute Porphyria Service is a highly specialised service providing clinical advice and haem arginate where appropriate for patients in mainland Britain with either one-off acute attacks or recurrent attacks of porphyria. A 24-h emergency service can be accessed by contacting the switchboard of the University Hospital of Wales (Tel 02920 747747) who will advise which centre is on call and provide the appropriate contact number.

Management of recurrent attacks

A minority of patients with acute porphyria develop recurrent attacks, usually defined as 4 or more attacks needing admission to hospital in 1 year. Severe recurrent acute attacks affect 3–5% of newly diagnosed symptomatic patients, and are more common in AIP and in females (Elder *et al*, 2013). In women with AIP, attacks sometimes occur regularly in the luteal phase of the menstrual cycle, although in many patients there is no obvious pattern or trigger. There is no agreement on what level of pain or combination of symptoms and signs is required to confirm a new attack in this group, so the diagnosis relies heavily on clinical judgement. Urine PBG excretion is persistently raised in patients with recurrent attacks of AIP, but careful urine PBG monitoring may be useful by allowing values when symptomatic to be compared with a recent baseline. Management of patients with recurrent attacks is challenging and outcomes are variable. A significant proportion of these patients, who are mainly young women, suffer a prolonged period of chronic pain, depression, neuropathy and disability. All patients with recurrent attacks should be referred to a specialist porphyria service for advice on management and long-term monitoring.

The most straightforward management approach is to treat each attack individually (as described above) following medical assessment to exclude other causes, preferably through direct admission to an acute medical unit with experience of managing that patient. This should include monitoring urine PBG at the start of each episode prior to the administration of haemin. This approach must be balanced against the risk of complications with each attack and the effect of repeated attacks and hospital admissions on quality of life. Most porphyria specialists would start discussing options to prevent repeated attacks if there is no improvement in the clinical pattern after 6–12 months.

Gonadotropin releasing hormone (GnRH) analogues preventing ovulation may be helpful in women with recurrent pre-menstrual attacks of porphyria (Anderson *et al*, 1984; Innala *et al*, 2010). The benefits need to be weighed against the risks of oestrogen deficiency. Menopausal side-effects may be reduced by addition of a low dose oestrogen patch, although this may increase the risk of acute attacks together with the increased risk of uterine carcinoma associated with unopposed oestrogens (Anderson *et al*, 2005). GnRH therapy should be started within the first few days of menstruation to reduce the risk of an attack triggered by transitory ovarian stimulation. Regular monitoring of bone mineral density, and additional gynaecology monitoring for patients on oestrogen replacement, should be arranged during the treatment period, and the decision to continue treatment should be reviewed every 1–2 years (Anderson *et al*, 2005; Stein *et al*, 2013; Harper & Sardh, 2014).

Prophylactic haemin, although an unlicensed therapy, is widely used to reduce the frequency of recurrent attacks in severely affected patients (Puy *et al*, 2010; Stein *et al*, 2013; Bonkovsky *et al*, 2014; Harper & Sardh, 2014). Prophylactic haemin should be administered via a central line if possible. In the UK most patients receive treatment at home (Stein & Cox, 2011). A UK audit of 22 patients (Marsden *et al*, 2015) showed a range of frequencies from 1 to 8 haem arginate infusions per month. Complications included vascular access problems, iron overload associated with long-term use and difficulty withdrawing treatment. Two thirds of patients had a reduction in pain, but a proportion of patients continued to have repeated hospital admissions, which may represent more severe disease, tachyphylaxis to haemin, development of a chronic pain syndrome or co-existence of other pathologies. The benefits and risks of regular haemin therapy should be assessed in individual cases.

Liver transplantation has been undertaken in at least 10 AIP patients in the UK and Ireland and is regarded as a curative treatment for patients with severe recurrent attacks

where medical management has been unsuccessful or where complications, such as loss of vascular access, make this impossible. The potential side effects of medical management need to be balanced against the short- and long-term risks of liver transplantation and prolonged immunosuppression. (Soonawalla *et al*, 2004; Seth *et al*, 2007).

Skin lesions in acute porphyria

Patients with VP and HCP may present with photosensitive skin lesions affecting exposed sites particularly the face and the back of the hands. This is due to deposition of porphyrins in the skin, which are activated by visible violet light with a wavelength peak at 400–410 nm resulting in a local phototoxic reaction. Affected skin is excessively fragile, leading to blisters, milia, and scarring (Badminton & Elder, 2002; Schulenburg-Brand *et al*, 2014). Skin symptoms in VP and HCP may accompany an acute attack, or may be the only clinical manifestation of porphyria, especially in VP. Skin lesions do not occur in AIP except when there is end stage renal failure (Sardh *et al*, 2009b).

Patients should be advised to keep exposed skin protected from light with suitable clothing and wear a wide-brimmed hat and gloves. Opaque sun creams blocking visible light are effective, but conventional sun creams blocking ultraviolet (UV)A and UVB rays are rarely helpful.

Management of acute porphyria in pregnancy

Women with acute porphyria are at increased risk of attacks during pregnancy and the post-natal period, probably due to hormonal effects (Brodie *et al*, 1977; Andersson *et al*, 2003; Marsden & Rees, 2010). There is some historical evidence for increased risk of miscarriage (Andersson *et al*, 2003) and perinatal death (Brodie *et al*, 1977; Tollånes *et al*, 2011) in patients with symptomatic acute porphyria. However pregnancy is usually well tolerated with a favourable outcome, particularly when the diagnosis of acute porphyria is already known and appropriate counselling has taken place (Anderson *et al*, 2005; Marsden & Rees, 2010; Bonkovsky *et al*, 2014; Harper & Sardh, 2014). Medication should be checked for safety, particularly during labour and delivery, although no clinically indicated medication or procedure should be restricted in an obstetric emergency. Regional (spinal or epidural) anaesthesia has been safely administered. There are no clinical trials of the safety of haemin in pregnancy but there is clinical experience of its use in patients who are pregnant or breast feeding without adverse effects to mother or baby (Badminton & Deybach, 2006; Marsden & Rees, 2010; Bonkovsky *et al*, 2014).

Counselling patients with acute porphyria

Patients and their families should be offered family screening, and both latent and overt patients should be provided with information about their condition and about patient support groups, such as the British Porphyria Association (www.porphyria.org.uk). All should be advised of measures they could take to avoid attacks, in particular the importance of checking that all prescribed or over-the-counter medicine is safe in acute porphyria, including access to an up-to-date list of safe drugs. Contraception should be discussed with women, including the risks of oral and depot hormonal contraception, and many porphyria specialists recommend the intrauterine device.

Patients should be encouraged to eat regular meals, and warned about the risk of extreme dieting. They should be encouraged to avoid excessive alcohol, smoking and recreational drugs.

Late complications in acute porphyria

An association between hepatocellular carcinoma (HCC) and acute porphyria, usually without underlying cirrhosis, was initially reported in Scandinavia (Lithner & Wetterberg, 1984; Kauppinen & Mustajoki, 1988; Andersson *et al*, 1996) and more recently in other countries (Andant *et al*, 2000; Schneider-Yin *et al*, 2009). The evidence for increased risk of HCC is strongest in AIP, but there are case reports in patients with VP (Germanaud *et al*, 1994) and HCP (Andant *et al*, 2000). Swedish AIP patients were shown to have an 8-fold higher incidence of HCC than patients in other European countries (Elder *et al*, 2013), but it is not clear if that represents a true excess risk or greater awareness. About one-third of patients with HCC have never had an acute attack (Innala & Andersson, 2011). Females are more affected than males and most patients are elderly. There is no evidence for cost effectiveness of systematic surveillance for HCC in patients with acute porphyria in any country except Sweden (Innala & Andersson, 2011; Stewart, 2012). However, many porphyria services offer screening through an annual liver ultrasound to patients aged over 50 years with past or current symptoms.

Several studies, suggest that patients with overt AIP have an increased risk of sustained hypertension and chronic kidney disease (CKD) (Church *et al*, 1992; Kauppinen & Mustajoki, 1992; Andersson *et al*, 2000; Marsden *et al*, 2008). The risk of CKD in AIP is independent of the presence of hypertension (Pallet *et al*, 2015). Recent experimental evidence implicates vascular toxicity of porphyrin metabolites in the pathogenesis of the typical tubulointerstitial lesions (Pallet *et al*, 2015).

Chronic pain is usually a late complication in patients with recurrent acute attacks (Bonkovsky *et al*, 2014; Harper & Sardh, 2014; Marsden *et al*, 2015) and flares of chronic pain may be difficult to distinguish from acute attacks. Chronic pain is poorly responsive to haemin (Anderson *et al*, 2005) and to opiates, but medication for neuropathic pain may be helpful (Santos *et al*, 2010), and patients may

benefit from referral to a specialist pain management service.

There is little evidence that porphyria is a cause of psychiatric illness, although it is a popular belief amongst doctors and the public. The claim that King George III of Great Britain suffered from a form of acute porphyria, and that this explained his "insanity" (Macalpine & Hunter, 1966), has been discredited (Hift *et al*, 2012), but the story has perpetuated the misconception that patients with acute porphyria have a higher risk of mental health problems. There is no evidence for a true excess risk of any chronic psychiatric illness in acute porphyria patients, with the possible exception of anxiety (Patience *et al*, 1994; Elder *et al*, 1997; Millward *et al*, 2005). Even the link with anxiety may partly be explained by the known high risk of anxiety disorders in women, young adults and individuals with chronic health conditions (Remes *et al*, 2016). Likewise, depression occurs more frequently in patients affected by acute porphyria than in the general population (Bonkovsky *et al*, 2014; Marsden *et al*, 2015), but no more frequently than in other chronic illnesses (Katon *et al*, 2007).

Delta-aminolevulinic acid dehydratase deficiency porphyria (ADP)

ADP or Doss porphyria (Sassa, 1998; Doss *et al*, 2004) is an autosomal recessive disorder and is extremely rare, with only 12 confirmed cases reported since first described. Acute attacks in ADP are associated with increased urine concentrations of coproporphyrin III and ALA, but PBG is only slightly increased. Clinical presentation is almost always in childhood with acute attacks often associated with severe neuropathy. Anecdotally, haem arginate treatment is effective.

Homozygous acute porphyria

Homozygous acute porphyrias are extremely rare and the clinical phenotypes differ from their heterozygous counterparts. Homozygous AIP presents in early childhood with developmental delay and severe neurological features (De Villeneuve *et al*, 1964; Beukeveld *et al*, 1990; Llewellyn *et al*, 1992; Hessels *et al*, 2004; Solis *et al*, 2004). Interestingly none of the reported patients had a documented acute attack although excretion of porphyrins, ALA and PBG in urine were extremely high. Neural or mitochondrial haem deficiency has been proposed as the pathogenic mechanism. No homozygous cases of the Swedish mutation, p.Trp198X have been reported, even in areas with a high carrier frequency, presumably because the homozygous form of this null mutation would be incompatible with life (Thunell, 2006). Homozygous VP presents with severe cutaneous manifestations from infancy, short stature and neurological abnormalities, but typically without acute attacks (Roberts *et al*, 1998). No homozygous case of the p.Arg59Trp variant has been described in South Africa.

Homozygous HCP has been described in a few cases, presenting with cutaneous manifestations and attacks of abdominal pain. Harderoporphyria has been reported in 3 families; it is a clinically distinct subgroup of homozygous HCP presenting in infancy with haemolytic anaemia and neonatal jaundice (Nordmann *et al*, 1983; Lamoril *et al*, 2001; Schmitt *et al*, 2005). Affected patients have a combination of null mutations and particular mutations that prevent conversion of harderoporphyrin to protoporphyrinogen IX, resulting in accumulation of harderoporphyrin in faeces.

Management of these very rare cases involves multidisciplinary care, typically involving paediatricians, neurologists, dermatologists and porphyria specialists. There is no evidence for use of haemin, and the roles of liver transplantation and haematopoietic stem cell transplantation are unclear.

Advances in management

Currently, haemin is the only licensed therapy for symptomatic patients with acute porphyria. Previous attempts at enzyme replacement therapy in AIP were safe but clinically ineffective as the enzyme was not taken up by the liver (Sardh *et al*, 2007).

A phase one study of gene therapy in AIP using a recombinant adeno-associated vector expressing porphobilinogen deaminase has recently been completed in 8 patients. There was no evidence of a reduction in excretion of ALA or PBG, although vector was still detectable in the liver 1 year after treatment. There was a suggestion that patients had less pain and used less haemin, although it is difficult to interpret this in the absence of a placebo arm (D'Avola *et al*, 2016).

Alternative forms of liver transplantation have been explored, including the use of hepatocyte transfusions in animal models (Yin *et al*, 2014), but have not yet shown to be clinically effective.

Perhaps more promisingly, a phase I clinical trial is ongoing of an RNAi molecule targeted at ALAS1 in patients with AIP, delivered to the liver through GalNAc conjugation. This has the potential to reduce ALAS1 activity and limit the accumulation of porphyrin precursors, such as ALA, which are thought to cause many of the symptoms in AIP (Chan *et al*, 2015).

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Author contribution

PS reviewed the literature and wrote the first draft. MB and DC wrote subsequent drafts. MB prepared figures and tables.

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