REVIEW

The little imitator—porphyria: a neuropsychiatric disorder

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Abstract

Three common subtypes of porphyria give rise to neuropsychiatric disorders; acute intermittent porphyria, variegate porphyria, and coproporphyria. The second two also give rise to cutaneous symptoms. Neurological or psychiatric symptoms occur in most acute attacks, and may mimic many other disorders. The diagnosis may be missed because it is not even considered or because of technical problems, such as sample collection and storage, and interpretation of results. A negative screening test does not exclude the diagnosis. Porphyria may be overrepresented in psychiatric populations, but the lack of control groups makes this uncertain. The management of patients with porphyria and psychiatric symptoms causes considerable problems. Three cases are described to illustrate some of these issues. Advances in molecular biology permit identification of patients and latent carriers in the family. Care to avoid relapses and improved treatments have reduced the mortality.

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Porphyria is derived from the Greek word *porphuros* meaning *purple*. Protoporphyrin IX is the biologically active substance, an important feature of which is its metal binding capacity. Both chlorophyll and haem are metalloporphyrins and are involved in the processes of energy capture and utilisation in animals and plants. The description of the porphyrins by Nobel laureate Hans Fischer[1] in 1930 as:

"The compounds which make grass green and blood red."

indicates the central position of these substances in the biological sciences.

The porphyrias are a heterogeneous group of overproduction diseases, resulting from genetically determined, partial deficiencies in haem biosynthetic enzymes. Their manifestations are broad and their relevance in neuropsychiatric disorders may sometimes be overlooked.[2] Indeed, porphyria was described by Waldenström[3] as the "the little imitator," by contrast with syphilis, "the big imitator" of the early 20th century. Terminology is confusing and they have been categorised in several different ways: as acute, non-acute, hepatic, cutaneous, and neurovisceral, among others. The most useful clinical categorisation is based on symptoms (table 1), and divides the disease into cutaneous, neuropsychiatric, and mixed disorders.

Table 1 Biochemistry of the porphyrias (neuropsychiatric involvement in bold)

Pathway	*Enzyme*	*Disorder*	*Inheritance*	*Neuropsychiatric*	*Cutaneous*
Glycine + succinyl-CoA					
↓	ALA synthetase				
5-aminolaevulinic acid (ALA)					
↓	**ALA dehydratase**	**Plumboporphyria**	**Autosomal recessive**	+ + +	**0**
Porphobilinogen (PBG)					
↓	**PBG deaminase**	**Acute intermittent porphyria**	**Autosomal dominant**	+ + +	**0**
Hydroxymethylbilane					
↓	Uroporphyrinogen synthetase	Congenital erythropoietic porphyria	Autosomal recessive	0	+ + +
Uroporphyrinogen III (URO)					
↓	Uroporphyrinogen oxidase	Porphyria cutanea tarda	Autosomal dominant (20%) or acquired	0	+ + +
Coproporphyrinogen III (COPRO)					
↓	**Coproporphyrinogen oxidase**	**Hereditary coproporphyria**	**Autosomal dominant**	+ + +	+
Protoporphyrinogen IX (PROTO)					
↓	**Protoporphyrinogen oxidase**	**Variegate porphyria**	**Autosomal dominant**	+ +	+ + +
Protoporphyrin IX					
↓	Ferrochelatase	Erythropoietic protoporphyria	Autosomal dominant	0	+ + +
haem					

Most porphyrins are inborn errors of metabolism, but some—for example, porphyria cutanea tarda—may be acquired. The neuropsychiatric porphyrias (for example, acute intermittent porphyria) and the mixed porphyrias (for example, variegate porphyria and hereditary coproporphyria) may give rise to acute, potentially fatal, neurovisceral crises, with neuropathy, delirium, psychosis, autonomic instability, and abdominal pain. Variegate porphyria and hereditary coproporphyria also cause dermatological features, usually in the form of a bullous or erythematous rash. Plumboporphyria has only been described in a few cases but resembles acute intermittent porphyria clinically. Other conditions such as hereditary tyrosinaemia and lead poisoning may produce secondary abnormalities of porphyrin metabolism with similar clinical and biochemical features.

Eighty per cent of patients who have inherited haem biosynthetic enzyme deficiencies never develop symptomatic disease and are thought to be "latent porphyrics".[4] Relatively little progress has been made in predicting who will develop clinical features,[5] although women seem to be at much greater risk than men. The characterisation of individual molecular defects in the genes encoding the haem biosynthetic enzymes has led to the identification of homozygous forms—for example, harderoporphyria, the homozygous form of coproporphyria.[6] These are often associated with more florid clinical features.

Recent developments in molecular genetics make the accurate diagnosis of porphyria possible in the proband as well as allowing genetic counselling and screening in family members. Appropriate advice on avoiding potentially porphyrinogenic drugs has been shown to reduce the incidence of attacks.[7] The prevalence of the phenotype may be increasing,[7] making detection of apparently latent carriers more important. Whereas advances have been made in the diagnostic tests available, pitfalls in diagnosis are still common[8] resulting in the false belief that "porphyria has been excluded". Finally, a recent family study[9] found a higher incidence of generalised anxiety disorder in "latent" relatives of patients with acute intermittent porphyria, raising doubts as to the relation between phenotype and genotype in so-called "latent" carriers.

Historical aspects

The first description of acute porphyria as a clinical syndrome was in 1889 by Stokvis.[10] The attack occurred after the administration of sulphonal, a drug which had been introduced as a hypnotic a year earlier. Congenital erythropoietic porphyria was recognised as an inborn error of metabolism by Garrod in 1923.[11] Important work on the description of the clinical condition originated in areas where the incidence of porphyria was high—for example, acute intermittent porphyria in Sweden[12] and variegate porphyria in Cape Town.[13,14] Porphyria has become topical in the United Kingdom in the past few decades as a result of the hypothesis of McAlpine and Hunter[15] that George III's frequent bouts of insanity were due to porphyria, although this view is still controversial.[16,17] Porphyria has also been implicated in van Gogh's illness[18] and in the obstetric history of Queen Anne.[19]

Waldenström in Sweden[20] and Dean in South Africa[13] have commented on the rarity of manifest porphyria before the introduction of porphyrinogenic drugs such as barbiturates and sulphonamides. In South Africa, where the 20 original Free Burghers have multiplied 12 500 fold since the 17th century, this autosomal dominant condition did not confer life threatening disadvantages on people with the genotype. The widespread use of potentially porphyrinogenic drugs and greater alcohol consumption may have led to increased clinical manifestation of the underlying genetic defect.[7]

Epidemiology

The estimated gene frequency of acute intermittent porphyria is 1–2 in 10 000[20]; however, there is great regional variability. The prevalence of variegate porphyria among the Afrikaans population of South Africa, where the introduction of the disorder has been traced back to a Dutch immigrant in 1688,[13] is 1 in 250. The resultant high awareness of variegate porphyria may have resulted in an underestimate of the importance of acute intermittent porphyria.[16] Other than in South Africa, acute intermittent porphyria seems to be the most common, with ratios of acute intermittent porphyria:variegate porphyria: hereditary coproporphyria of 100:15:7 in Germany[21] and 100:50:26 in Czechoslovakia.[22] In addition to the three autosomal dominant subtypes of porphyria mentioned above, plumboporphyria, an autosomal recessive condition which presents with neuropsychiatric symptoms, has been described in six cases worldwide[23] and a localised cluster of cases, known as "Dobson's complaint" (a combination of the enzyme deficits responsible for acute intermittent porphyria and variegate porphyria with a similar clinical picture) has been described in Cheshire, UK.[24] An outbreak of "secondary porphyria" occurred in Turkey after the exposure of 4000 people to a fungicide, hexachorobenzene, resulting in a mixed porphyric picture in many people as well as the death of many infants through breast milk transmission.[25] Porphyria is less common before adolescence and after the menopause, and symptomatic cases are four times more common in women, with a particular preponderance premenstrually.[26]

Waldenström[12] first showed the presence of excess porphyrin metabolites in asymptomatic relatives of patients with acute intermittent porphyria and proposed the now accepted hypothesis of autosomal dominance with variable penetrance. Mustajoki and Koskelo[27] measured porphobilinogen deaminase (PGB-D) activity in healthy Finnish blood donors in an attempt to calculate the prevalence of the genotype in the population. They found

unequivocally low values in 0·4% and borderline concentrations in a further 0·4%, suggesting a high rate of latent carriers. Thus the frequency of the responsible genes in the population is high and more than 80% of those who inherit the genetic defect do not develop symptoms.[4]

The prevalence of porphyria in psychiatric populations was first investigated by Kaelbling *et al*,[28] who found that 35 of 2500 psychiatric patients admitted to a short term intensive care psychiatric unit had a positive screening Watson-Schwarz reaction. Twelve of these were considered to have manifest acute intermittent porphyria on clinical grounds (point prevalence 0·48%). A similar study in Australia,[29] using quantitative PBG analysis alone, found a prevalence of 0·16%. The results of these earlier studies can be criticised because of the use of a single test, which is now known to have a high rate of false positive and false negative results.[30] Tishler *et al* screened nearly 4000 psychiatric inpatients and calculated a point prevalence of 0·21%. In this study, screening was based initially on the Watson-Schwartz reaction, with 24 hour urine analysis of 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG) in those with a positive result. Of the 70 who screened positive, eight were thought to have manifest acute intermittent porphyria on the basis of further tests, including assay of the enzyme PBG deaminase. In a further 10 positive patients, acute intermittent porphyria was thought not to be aetiologically related to their symptoms, despite abnormal enzyme concentrations, because of the absence of raised urinary porphyrin precursors. Most of the patients described in these studies had diagnoses of schizophrenia, schizoaffective disorder, or atypical psychoses.

These estimates seem to represent an increased prevalence of both latent and manifest porphyria in psychiatric populations. However, there are significant methodological problems with the studies to date; in particular, given the wide geographical variability, the absence of control groups. It remains unclear whether porphyria was *causally* related to the psychiatric disorder seen. An alternative explanation is that porphyria modifies an already present psychiatric disorder in a way which makes patients more likely to be admitted to hospital, such as by worsening symptoms or inducing apparent "drug resistant" or refractory cases. Equally, no systematic follow up studies have been performed on the effect of removing porphyrinogenic agents from such patients' medication regimens, although case reports suggest that early improvements may occur.[31 32]

Biochemistry

The haem biosynthetic pathway is tightly controlled by several mechanisms allowing rapid adjustment when demand for haem, the end product, changes. The first enzyme in the pathway, ALA synthase, is an important part of this regulation and seems to be tissue specific, with different genes encoding both liver and erythroid isoenzymes. Thus the hepatic isoenzyme of ALA is inducible when demand for haem rises but the erythroid isoenzyme is produced to subserve the more constant demand for haemoglobin synthesis. Hepatic haem biosynthesis is under negative feedback through the activity of ALA synthase. Enzyme turnover is high, which permits rapid adjustment.[33] Feedback can be mediated at the stages of transcription and transport into mitochondria, as well as by post-translational activity of the enzyme itself. The system is exquisitely sensitive to rapid oscillations in haem demand.[23]

In the porphyrias, a partial enzyme deficiency leads to overproduction of precursors such as ALA and PBG, which may induce the clinical picture by acting as false neurotransmitters. Alternatively, the clinical picture may be caused by haem deficiency.[34] The recent development of a mouse model for acute intermittent porphyria[35] should help to resolve this issue. Table 1 shows the biosynthetic pathway for haem with the porphyria subtypes caused by enzyme deficiency along this pathway. Secondary porphyria results in a similar biochemical and clinical picture to the mixed porphyrias. The exclusion of toxins—for example, alcohol, lead or hexachlorobenzene—as a cause is important. Hereditary tyrosinaemia type 1, due to a partial deficiency of the enzyme fumaryl acetoacetate hydrolyase, results in a secondary deficit of ALA dehydratase, causing a similar clinical and biochemical picture to plumboporphyria.[36] Lead inhibits ALA dehydratase, as well as several other enzymes in the haem biosynthetic pathway and may produce both an acute crisis as well as a chronic neuropathy with intellectual decline and other mental changes.[37]

Pathogenesis

Both neurological and gastrointestinal symptoms are thought to result from neuronal dysfunction. Histological findings in peripheral and autonomic nerves include oedema, irregularity of the myelin sheaths, thinned and irregular axons, axonal vacuolisation, and degeneration and cellular infiltration.[38] Electrophysiology shows muscle denervation and decreased motor nerve conduction velocities.[39] The pathogenesis of the cerebral manifestations, however, remains unclear. The main hypotheses are metabolic abnormalities, ischaemia, demyelination, and oxidative stress. Pathology of the CNS includes vacuolisation of neurons, focal perivascular demyelination, and reactive glial proliferation.[40] Unfortunately, postmortem pathological findings bear little relation to the clinical features in life, supporting the theory that many of the clinical features may be caused by profound metabolic abnormalities.

One hypothesis is that ALA may disturb neurophysiological mechanisms through its structural similarity to γ-aminobutyric acid (GABA).[41] Others have proposed that multifocal ischaemia is responsible, through vaso-

spasm. Black *et al*[42] showed reversible angiographic changes, indicating arterial vasospasm in porphyric encephalopathy. King and Bragdon[43] described the MRI findings in a 20 year old woman with an acute, drug induced attack of acute intermittent porphyria characterised by abdominal pain, nausea, visual hallucinations, lethargy, and seizures. On the eighth day MRI showed multiple high signal intensity lesions, predominantly in frontal and parietal lobes. When she was asymptomatic 10 days after treatment, the lesions had resolved. Thunell *et al*[44] proposed that oxidative stress was important in the clinical manifestations and free radical formation may contribute to the sometimes irreversible pathological changes.[40] Complement activation and mediators of inflammation have also been implicated.[45] In variegate porphyria and hereditary coproporphyria, free radicals produced by the absorption of solar energy result in erythema or bullous lesions.[23] Skin histology is characterised by homogeneous PAS positive thickening and IgG deposition in vessel walls.

Precipitating agents

A partial deficiency in one of the enzymes of haem biosynthesis is not usually sufficient to result in the clinical syndrome. Many people with the genetic abnormality never develop symptoms, despite exposure to high doses of porphyrinogenic agents, and it is likely that there are other factors which modify the response of the body. Most of the agents which predispose to the clinical picture of porphyria deplete intracellular haem, which is thought to be due to increased production of the haemoprotein cytochrome *P*-450. This may be caused by induction of the cytochrome *P*-450 enzyme system, depletion of free haem due to direct inhibition of its synthesis, or direct degradation of haem.[46]

Many patients presenting with acute attacks have ingested a known porphyrinogenic drug which could account for the attack.[47] A committee has been set up to compile a database on the porphyrinogenicity of drugs.[48] The current list of drugs thought to be porphyrinogenic is long and details can be found in the British National Formulary[49] or obtained from the Porphyria Research Group in Cardiff (Porphyria Research Unit, Department of Medical Biochemistry, Heath Park, Cardiff CF4 4XN, UK). Common culprits include antibiotics such as sulphonamides and, erythromycin, sedatives such as barbiturates, benzodiazepines and sulpiride, hormone products such as the oral contraceptives, anabolic steroids, hormone replacement therapy and tamoxifen, antiepileptics such as phenytoin and carbamazepine, drugs of abuse including cocaine and amphetamines, as well as many commonly prescribed drugs such as antihistamines, diuretics, baclofen, metoclopramide, many of the tricyclic antidepressants, and diclofenac. Table 2 shows a list of drugs which are generally thought to be safe and can be used in the treatment of an acute porphyric attack.

Alcohol has long been noted to precipitate acute attacks of porphyria in some patients. Ethanol, although a good inducer of the cytochrome *P*-450 system in vitro, it is a less potent inducer in intact rats.[50] In humans, there is wide variability in alcohol tolerance among porphyric patients.[51] The evidence that alcohol itself is porphyrinogenic is conflicting. Thunell *et al*[50] failed to show a relation between the amount of alcohol consumed, or the frequency of ingestion and the development of porphyric symptoms in acute intermittent porphyria. The intake of some alcoholic beverages, especially red wine and whisky, was significantly related to symptoms. They proposed that long chain alcohols and polyphenolic compounds such as tannins were responsible for inducing porphyric attacks rather than ethanol itself.

Starvation may induce the activity of hepatic ALA synthase, an effect which is overcome by the administration of glucose. Thus dieting and eating disorders may precipitate an acute attack. The mechanism of this effect is uncertain, but calorie restriction has been shown to be associated with a significant rise in urinary excretion of ALA and PBG, which is reversed by increased carbohydrate intake.[52] Glucose may inhibit ALA synthase.[23] Oestrogen and progesterone aggravate porphyria[52] and cyclic attacks most commonly occur in the luteal phase. The relation between cigarette smoking and recurrent attacks may be due to metabolic induction of haem.[53] The claim that stress, surgery, and infection are precipitants has not been supported by published data. Acute porphyria was previously thought to be rare before adolescence, possibly because children are less likely to be exposed to precipitants such as drugs or alcohol. There are recent reports of acute attacks in children, often related to the use of potentially porphyrinogenic medication.[54–56]

Table 2 Drugs probably safe in porphyria

Symptoms	*Safe treatment options*
Pain	Narcotics—for example, codeine, morphine Paracetamol, aspirin
Hypertension/tachycardia	Propranolol
Anxiety/sleeplessness	Propranolol, lorazepam, chloral hydrate
Nausea/vomiting	Chlorpromazine, promazine, cyclizine
Delirium/psychosis	Phenothiazines—for example, chlorpromazine, trifluoperazine, droperidol
Seizures	Lorazepam, paraldehyde, bromides, Gabapentin
Depression	Lofepramine
Infection	Penicillins, aminoglycosides
Constipation	Lactulose, neostigmine

Clinical manifestations

The clinical manifestations of the porphyrias are variable and the potential for misdiagnosis is great (table 3).[12 57–59]

In patients with recognised acute attacks, the premorbid personality and mental health of patients between attacks seems normal.[60] The clinical course may be chronic or acute on chronic,[61] and episodes may be self limiting or progressive. The variability of the clinical course as well as the episodic nature and

Table 3 Signs and symptoms in acute porphyria (most data refer to acute intermittent porphyria)

	Percentage of cases			
Signs and symptoms	Waldenström 1957[12] n = 321	Goldberg 1959[57] n = 50	Stein and Tschudy 1970[58] n = 46	Mustajoki and Nordmann 1993[59] n = 51
Abdominal pain	85	94	95	96
Mental symptoms	55	58	40	19
Constipation	48	84	48	78
Pain elsewhere	—	52	50	25
Vomiting	59	88	43	84
Muscle weakness	42	68	60	8
Hypertension	40	54	36	57
Tachycardia	28	64	80	79
Fever	37	14	9	—
Respiratory paralysis	14	10	9	—
Convulsions	10	16	20	1
Sensory loss	9	38	26	—

bizarre features mean that porphyria may go undiagnosed and be put down to somatisation, conversion disorder, or to other psychiatric disorders. Several authors have described patients long incarcerated in mental hospitals who are eventually diagnosed with porphyria,[58 61 62] although there are no reports on the outcome of these patients.

Of the 29 attacks in 25 patients analysed by Ridley,[38] 10 patients died. Sudden death suggesting cardiac arrythmias was the most common cause of death. Later studies have shown lower mortality rates. Kauppinen and Mustajoki,[63] analysing their series of 206 patients, found that both the mortality associated with attacks and the risk of further attacks has greatly reduced over time, commensurate with better recognition, improved treatment regimens, and counselling of patients to prevent risk taking behaviour. Their group has also confirmed findings by Hardell[64] showing an increased incidence of hepatocellular carcinoma (which accounted for 8·3% of deaths in their porphyric patients) and chronic renal failure (which accounted for 4% of deaths). In patients who survive a severe acute attack, complete recovery is the rule, although recovery may be protracted. Distal weakness and sensory loss are the most persistent features.

Physical symptoms and signs

The neuropathy in porphyria is primarily motor. Weakness begins in the proximal muscles, arms more commonly than legs. Paresis is often focal and cranial nerve involvement may occur, especially the IIIrd, VIIth, and Xth nerves.[38] Clinical progression, which may be gradual or stepwise, can continue for up to four weeks after withdrawal of the precipitating agent and recovery may be protracted. The pattern of involvement is very variable, may be unilateral ðr bilateral, and may vary from day to day. Reflexes are usually diminished, but extensor plantars may occur. Guillain-Barré syndrome[65] and lead poisoning are important differential diagnoses. Sensory involvement, usually in the form of dysthaesiae, occur in a third of cases, and may have a bizarre distribution,[58] which may lead to the suspicion of conversion disorder, but is usually rapidly followed by more unequivocal neurological signs. Sphincter disturbance is common and seizures occur in nearly a quarter of cases. Autonomical neuropathy is responsible for many of the systemic features of acute porphyria including abdominal pain, vomiting, constipation, hypertension, and tachycardia. Abnormal autonomic cardiac reflexes have been shown to occur during an attack, but regress on remission[66] and abnormal gastrointestinal mobility has also been found.[67] Seizures may be focal or generalised and may rarely be the presenting feature of porphyria.[68] A recent epidemiological survey found that seizures are less common than previously thought, with a lifetime prevalence of 5·1% among patients with manifest acute intermittent porphyria and 2·2% of all those with the genotype.[69] In the United Kingdom, 75% of cases of variegate porphyria have skin lesions alone, the remainder dividing equally between mixed and neuropsychiatric alone. In hereditary coproporphyria, skin lesions alone are uncommon. Cutaneous features in variegate porphyria and hereditary coproporphyria comprise photosensitivity, skin fragility, bullous lesions, facial hypertrichosis, and hyperpigmentation in addition to the neuropsychiatric features, which are otherwise indistinguishable from those of acute intermittent porphyria.

Psychiatric symptoms

Most of the larger case series have been undertaken by neurologists or physicians, thus "mental symptoms" are not fully characterised and their incidence is likely to have been underestimated. Anxiety, restlessness, insomnia, and depression and psychosis occur often and may be persisting features.[23] Detailed psychiatric assessment has been limited to small series or case reports. In one family, acute attacks of acute intermittent porphyria presented as aggressive, impulsive behaviour with depressed mood and suicidal attempts.[32] Others have described schizophrenic symptoms such as social withdrawal, auditory hallucinations, persecutory delusions, and catatonia[31]; affective symptoms with emotional lability, insomnia and grandiose delusions; and conduct disorder with disruptive behaviour, encopresis, and hyperactivity.[54] Conversion disorder, chronic fatigue syndrome, and somatisation disorder may also be suspected.[70] The occurrence of monthly luteal phase attacks in women, in whom the disorder seems to be more common,[71] may lead to the false diagnosis of premenstrual tension or cycloid psychoses being made and the exacerbation with alcohol may lead to false suspicions of excessive alcohol intake.[32] Pain control may pose particular problems in acute attacks, and morphine derivatives are often prescribed, and drug dependency has been recorded and may cause considerable management problems.[72]

Santosh and Malhotra[73] detailed the progression of psychiatric symptomatology in a 14 year old Indian patient, who initially developed an illness characterised by psychomotor retardation, muteness, and fearfulness along with a mild fever and severe abdominal pain.

On subsequent admissions after confirmation of acute intermittent porphyria, he presented with a variety of symptom clusters including: hypomania with elation, distractibility and social disinhibition on one occasion; catatonia with echolalia, posturing and abnormal motor behaviour on another, and delirium with focal neurological signs during a further episode. Between attacks his mental state was normal. Thus psychiatric symptoms mimic some psychiatric disorders and may vary in the same patient during different episodes.

Case reports

At the National Hospital for Neurology and Neurosurgery, a tertiary referral hospital, only three patients have been diagnosed as having porphyria in the past 10 years. These cases cannot be considered representative, but give a flavour of the diagnostic and management difficulties in patients with neuropsychiatric symptoms and porphyria.

A 54 year old woman with longstanding epilepsy was treated for many years with combinations of phenytoin, phenobarbitone, carbamazepine, and primidone. Over the preceding 20 years she developed progressive intellectual decline and had episodes of abdominal symptoms, weight loss, visual hallucinations, ataxia and muscular weakness occurring in association with increased fit frequency. She presented with delirium and vomiting, having been given co-trimoxazole for a urinary tract infection. Neurological examination disclosed generalised muscle wasting, finger-nose ataxia, global weakness, and normal tendon reflexes and a right extensor plantar. Urinary PBG and porphyrins were high (ALA was normal) and a diagnosis of acute intermittent porphyria was confirmed on enzyme studies. After diagnosis and treatment of her seizures with valproate and clonazepam, her mental state and fit frequency improved, but she died from an episode of status epilepticus a year later, not apparently related to a further porphyric attack.

A 53 year old woman had a 31 year history of intermittent psychiatric disturbance characterised by emotional lability, agitation, ideas of reference, auditory hallucinations, and abdominal pain. The attacks tended to occur premenstrually and she required admission up to three times a year. Acute intermittent porphyria was diagnosed in a family member and urinary PBG was measured between attacks. This was normal. Several years later, she was reinvestigated during an attack and the diagnosis of acute intermittent porphyria was made on the finding of raised urinary porphyrins. At the time of admission she was euthymic, with no psychotic or neurological features, but evidence of mild cognitive underfunctioning. She was being treated with haloperidol and lithium. Urinary PBG and ALA were raised and enzyme studies confirmed the previous diagnosis of acute intermittent porphyria. Haloperidol was stopped and she was started on a high carbohydrate diet. ALA and PBG concentrations returned to normal. In the subsequent four years she has continued to have episodes of psychiatric disturbance, although less often, not all of which have been associated with a rise in ALA or PBG. Haematin has not been used. It is likely that she has an underlying bipolar affective disorder unrelated to her porphyria, but some attacks may have been made worse or more refractory in the past by treatment with porphyrinogenic drugs.

A 23 year old man had a history of two episodes of generalised pain, fever, confusion, vesicular rash, and nausea followed by the development of a paranoid psychosis. These had resolved over several months but no diagnosis had been reached. On admission, he had a three week history of abdominal pain, diarrhoea, fever, headache, delirium, psychosis, and bullous lesions on his legs. On mental state examination he had well systematised persecutory delusions, thought broadcasting, somatic passivity, and non-verbal auditory hallucinations. Neurological examination disclosed mild parkinsonism, increased tone on the left side, and bilateral brisk reflexes with downgoing plantars. He had been treated with thioridazine. Other than a mild neutrophilia, investigations were normal and repeated spot urine PBG and 24 hour ALA, PBG, and porphyrins were negative. He was treated initially with haloperidol and later sulpiride, neither of which helped, but within five days of being changed to chlorpromazine, he began to improve. A diagnosis of schizophrenia was made. His family continued to seek an alternative diagnosis and he was later investigated during a further episode in another centre abroad. Faecal coproporphyrinogens and 24 hour urinary coproporphyrinogens were raised and subsequent coproporphyrinogen oxidase assay confirmed the diagnosis of hereditary coproporphyria. He has had two further episodes, with similar clinical pictures. He has been treated with trifluoperazine as required and given haematin in the acute phase of his relapses. Episodes have been much more short lived and between attacks he remains well and functions at a high level, with no negative signs of schizophrenia.

These case histories illustrate several of the difficulties in the diagnosis and management of patients with porphyrias. Acute attacks may present with life threatening illness and problems may be exacerbated when patients are treated with medications which worsen their condition. This seems to be a particular problem with seizures, as so many antiepileptic agents are unsuitable when treating fits in porphyria.[74] An acute attack may cause psychiatric features indistinguishable from bipolar affective disorder or schizophrenia, but in our patients, abdominal symptoms—nausea, vomiting, or weight loss—were present as well. The clinical outcome is not necessarily good, despite the diagnosis having being made. There are several possible explanations for this; for example, patients may still be exposed to porphyrinogenic agents. However, it is likely that in some patients the porphyria is modifying the course of an underlying psychi-

atric or physical disorder. When there is a physical attribution conceivable for psychiatric symptoms, patients as well as physicians and psychiatrists often think that the physical disorder overrides the psychiatric one. It is important to recognise that psychiatric symptoms should not automatically be put down to porphyria, as this will tend to deprive patients of more conventional psychiatric management, both pharmacological and social. Finally, even when the diagnosis is foremost in the clinicians' minds, it can be missed if appropriate investigations, particularly those using faecal specimens and 24 hour urine samples are not undertaken, and repeated if clinical suspicion remains high.

Genetics

Most of the acute porphyrias are inherited in an autosomal dominant manner. Penetrance is low, with as many as 80% of carriers asymptomatic.[4] Occasional coinheritance of two porphyrias has been described.[26 75] To date, most genetic characterisation has been undertaken in acute intermittent porphyria. In this disorder, PGB deaminase activity is present at a concentration of about 50% of normal. Two isoenzymes are encoded by a single gene, which is located on chromosome 11q.[76] One of these isoenzymes is specific to red cells; the other is more ubiquitous. Three subtypes of acute intermittent porphyria are recognised. One (less than 5% of families) affects only the ubiquitous isoenzyme. This is important as assay of the erythroid enzyme is used diagnostically and a normal assay does not rule out this rare variant. In a further subtype, found in 15% of families, the product of the mutant allele cross reacts immunologically (CRIM positive) with antiserum to the normal enzyme, but with impaired activity. Only a few mutations are found in this subgroup. The final type, in which there is no immunological cross reactivity with the normal enzyme (CRIM negative), is found in 80% of families. This most common group is particularly heterogeneous, with more than 20 substitutions, deletions, and insertions described. Over 100 mutations of the PBG deaminase gene have now been identified although all but two occur in only a few families each. A recent analysis by Whatley *et al*[77] found that about a quarter of patients in the United Kingdom presented without a family history and 3% of all patients are caused by de novo mutations. An identical mutation has recently been described in 43 of 45 South African patients with variegate porphyria, however, it was not present in nine British patients with variegate porphyria. This is thought likely to represent the founder gene deficit associated with variegate porphyria in South Africa.[78]

Diagnosis

Most routine investigations are unhelpful in the diagnosis of porphyria. Liver function tests and lipids may be abnormal, but not invariably. More specialised investigations such as electrophysiology[39] or MRI[43] showing focal lesions may be informative, but not diagnostic.

A different approach should be taken to diagnosis of the *symptomatic* patients as opposed to that of the *asymptomatic* relative. The second should be undertaken at a specialist laboratory. The confirmation that porphyria is *aetiologically* related to a patient's symptoms (and not a case of latent porphyria) requires the demonstration of an excess of porphyrin precursors, indicating substrate accumulation at the same time as the occurrence of symptoms. The detailed investigation of porphyria is complex; thus it is important that clinicians have some understanding of the investigative options and pitfalls. Once the diagnosis has been made, referral to a specialist centre is advisable, for further characterisation of the disorder, and to offer appropriate further investigation of family members.

Several different sample types can be used in the investigation of a patient and these vary in usefulness depending on which subtype of porphyria is being investigated (table 4). Hereditary coproporphyria and variegate porphyria are due to enzyme deficits further down the biosynthetic pathway and the accumulated precursors are more fat soluble. These precursors are preferentially excreted in faeces, whereas in acute intermittent porphyria, abnormalities are predominantly in urine. Porphyrins are very light sensitive and therefore samples must be stored in the dark and transported to the laboratory as soon as possible. The porphyrin concentration in urine is reduced by 50% in 24 hours under normal

Table 4 Investigations in the neuropsychiatric porphyrias

	Urine				*Faeces*		*Blood*	
	ALA	*PBG*	*URO*	*COPRO*	*COPRO*	*PROTO*	*Enzymes*	*Notes*
Plumboporphyria	High in attack	May be raised in attack	Raised in attack	Raised in attack			↓ALA dehydratase	Rare
Acute intermittent porphyria	Very high in attack	Very high in attack	Usually raised in attack	May be raised	May be raised	May be raised	↓PBG deaminase (normal in a minority)	Enzyme may be normal in a minority of patients
Hereditary coproporphyria	Raised in attack	Raised in attack	May be raised in attack	Usually raised	Usually raised	Mildly raised	↓Coproporhyrinogen oxidase	Urine often normal between attacks
Variegate porphyria	Raised in attack	Raised in attack	Usually raised in attack	Usually raised	Mildly raised	Raised	↓Protoporphyrinogen oxidase	75% of attacks are cutaneous only

ALA = 5-Aminolaevulinic acid; PBG = porphobilinogen; URO = uroporphyrinogen; COPRO = coproporphyrinogen; PROTO = protoporphyrinogen.

lighting.[79] Additionally, urinary porphyrin precursors may only be present in excess for a few days during the acute attack and therefore samples should be collected as early as possible in the course of the illness. This is less likely to be a problem in hereditary coproporphyria or variegate porphyria, when faecal samples remain abnormal for a longer period, sometimes permanently.

The most common first line screening test used is urine analysis for PBG excretion. A qualitative test is usually first performed (for example, the Watson-Schwartz test), in which it is important to include a control to detect ingested red dyes from foods or medications.[80] It is often not appreciated that this test has a significant false positive and false negative rate.[30] Alternative screening investigations have been suggested,[81] but are not yet used universally. If this screening test is positive, samples of urine, faeces, plasma, and serum should all be sent to a specialised laboratory for more detailed analysis and characterisation of the type of porphyria.[79] The clinician should not be reassured, however, by the finding of a normal urinary PBG in the presence of clinical suspicion. More reliable information should be sought by repeating spot urine tests, and by analysing 24 hour urine collections and faecal samples (particularly to investigate the possibility of the rarer variegate porphyria and hereditary coproporphyria). The interpretation of results in variegate porphyria and hereditary coproporphyria is complex[82] and some workers have advocated the use of bile specimens instead of faecal specimens.[83]

Several methods are available in specialist centres for the further characterisation of the porphyrias. High performance liquid chromatography (HPLC) is used to separate out the differing patterns of excess porphyrins in urine, faeces, and plasma. It is also possible to assay the relevant enzymes in cytoplasm and mitochondria. In acute intermittent porphyria, PBG-D is usually reduced to 50% of normal but there is overlap with normal subjects,[84] and in some porphyric families the erythrocyte isoenzyme is normal.[85] In variegate porphyria and hereditary coproporphyria the relevant enzymes are more difficult to assay and more credence is put on faecal HPLC.[79]

When to consider porphyria

There are three means by which the diagnosis of porphyria may be missed. It is rare, and clinicians may be unaware of the wide ranging clinical presentation. Diagnostic screening is most sensitive when investigations are performed at the same time as symptoms. This means that the diagnosis should be considered during the early part of the acute admission. Finally, the low sensitivity of some laboratory screening tests means that a normal screening test does not exclude the diagnosis. Attempts should be made to repeat urine tests and obtain stool samples if clinical suspicion is high. Liaison with a biochemistry department with expertise in the porphyrias will be needed to interpret findings. Table 5 shows when the diagnosis of porphyria should be considered, but porphyria may coexist with other physical and psychiatric disorders.

Table 5 When to consider the diagnosis of porphyria

Episodic psychiatric disorder in association with:
Bullous or fragile skin lesions
Unexplained recurrent abdominal symptoms
A menstrual relation to symptoms
Impaired consciousness or delirium
Alcohol induced symptoms
Atypical or variable features
Family history of unexplained death
Family history of psychiatric disorder
In patients with a psychiatric diagnosis of:
Treatment resistant psychosis
Schizoaffective disorder
Cycloid psychosis
Conversion disorder
Somatisation disorder and chronic fatigue syndrome
In the differential diagnosis of the following neurological disorders:
Encephalopathy
Motor neuropathy – for example, Guillain Barré syndrome
Refractory epilepsy
Migraine
Early onset dementia
Non-anatomical sensory symptoms

Management

TREATMENT OF THE ACUTE ATTACK

Some patients will respond to simple measures such as increased carbohydrate intake. This is most easily achieved with an intravenous glucose infusion—2000 kcal carbohydrate per 24 hours is recommended. In addition, withdrawal of precipitants and treatment of intercurrent infection is necessary. Table 2 shows a list of drugs which are thought to be safe and can be used for treatment of intercurrent problems and relief of symptoms. More severe episodes may require considerable supportive treatment, particularly if neuropathy or autonomic features are present. The use of intravenous haematin has been advocated for many years,[26] but administration is complicated by its instability in solution and extensive side effects (thrombophlebitis and coagulopathy). Recent work by Mustajoki and Nordmann[59] using haem arginate has shown a low rate of side effects and favourable response to treatment in all of 51 attacks of porphyria studied. A placebo controlled trial[86] found a non-significant trend in favour of haem arginate and this should now be considered the treatment of choice. It should be started as soon as possible after the onset of an attack, or even prophylactically and given as four daily courses. A further treatment option is the use of the metalloporphyrins such as tin or zinc porphyrins. These act as inhibitors of haem oxygenase, the enzyme responsible for the breakdown of both endogenous and administered haem. There are concerns with regard to the potential toxicity of these metals and their use is still experimental .[71]

PREVENTION OF ATTACKS

Patients who have had attacks of porphyria should be advised to avoid potentially porphyrinogenic agents, including drugs and alcohol—particularly whisky or red wine.[50] Unfortunately, doctors' advice is often unpalatable. Thunell *et al*[50] found that despite

counselling at centres of excellence, 87% of patients with inducible porphyria continued to drink alcohol, despite reporting that it resulted in clinical exacerbation of the disease. Patients should also be warned about the importance of maintaining a high carbohydrate diet and of the potential danger of intercurrent infections and dieting and emotional stressors. In women with attacks related to menstruation, suppressing ovulation with the luteinising hormone releasing hormone (LHRH) analogue, Buserelin, has been shown to reduce the number of attacks.[87] When exposure to a precipitant has taken place, haematin can be initiated prophylactically if the consequences are likely to be severe.

Identification of carriers

The identification of carriers in the family should be undertaken wherever possible. Both patients and carriers should be given advice on the likely precipitants of porphyria. In addition, carriers as well as patients should wear med-alert bracelets in case of the necessity for emergency treatment. It is currently unknown what proportion of asymptomatic carriers go on to develop symptoms and acute attacks can be fatal; therefore, advice should be given to all. Patient and carer support groups have been set up in conjunction with some centres and this has proved beneficial, particularly in the light of recent publicity about porphyria, which has resulted in patients fearing incipient madness.

Conclusion

The porphyrias are rare but important disorders. Their recognition is increasingly important in view of the widespread use of potentially porphyrinogenic agents. Whether porphyria is of relevance in chronic psychiatric illness remains controversial. No studies to date have satisfactorily considered the issue of a control population. The highly variable nature of neurological and psychiatric symptoms in acute porphyria adds to the difficulty in making a diagnosis. The potential for iatrogenic attacks in both unsuspected and diagnosed patients should be recognised. Treatment may worsen or prolong both psychiatric and neurological symptoms. There are particular problems associated with treating patients with coexistent porphyria and psychiatric disorder.

There is still widespread misunderstanding among clinicians with regard to the interpretation of laboratory results and the techniques currently used have unacceptably high false positive and false negative rates.

Finally, it is important that patients are diagnosed and family members screened to avoid unnecessary exposure to potentially dangerous drugs, thereby reducing morbidity and mortality from this disorder.[7]

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