Seminar

The acute porphyrias

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Public attention has been drawn to the acute porphyrias in the past few years by speculation that they affected the character of George III and the creative genius of Vincent van Gogh. During the same period, there have been important advances in the understanding of the molecular basis of the acute porphyrias and in diagnosis and the clinical management of patients and their families. Four types of porphyria are classified as acute because they produce acute neurovisceral crises (panel).[1] Here, we outline current knowledge of the three autosomal dominant types: acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria.

Classification of the acute porphyrias

Acute intermittent porphyria
Autosomal dominant; acute attacks only; no cutaneous manifestations. Three families with homozygous/compound heterozygous variant reported.

Hereditary coproporphyria
Autosomal dominant; acute attacks with skin lesions (blisters, fragility) in about one-third of patients; skin lesions without acute attacks are rare. Three families with homozygous/compound heterozygous variant reported.

Variegate porphyria
Autosomal dominant. Of 61 UK patients, 45 (73%) presented with skin lesions (blisters, fragility) alone, seven (12%) with acute attacks alone, and nine (15%) with both together. 12 families with homozygous/compound heterozygous variant reported.

5-aminolaevulinic acid dehydratase deficiency porphyria
Autosomal recessive; presents at any age with severe acute attacks, neuropathy or both. Four families reported.

Biochemical and molecular genetics

Biochemical background

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

Molecular genetics

The porphyrias show extensive allelic heterogeneity.[2] More than 90 mutations that cause acute intermittent porphyria have been identified in the porphobilinogen deaminase gene.[3,4] Mutations in exon 1, which encodes the additional 17 aminoacids at the N-terminus that distinguish the ubiquitous from the erythroid isoenzyme of this enzyme,[3] are responsible for a rare variant of acute intermittent porphyria in which only the ubiquitous isoenzyme is defective.[5] Other mutations are distributed throughout the gene in exons common to both isoenzymes, with some clustering in exons 10 and 12; these mutations decrease enzyme activity in all tissues. The structure of *Escherichia coli* porphobilinogen deaminase has been solved at 0·176 nm resolution and provides a useful model for predicting the functional effects of human mutations (figure).[6] Most mutations in acute intermittent porphyria are restricted to one or a few families. However, one mutation (Trp198Stop), presumably inherited from a common founder, underlies the high prevalence of acute intermittent porphyria in northern Sweden (1 per 1500 people). There is no evidence that any specific genotype determines either the pattern or severity of the acute attack, or major differences in clinical penetrance between families.[4]

Preliminary data indicate that variegate porphyria may be as heterogenous at the DNA level as other porphyrias in most countries, with the notable exception of South Africa. About 10 000 South Africans of Afrikaans descent have variegate porphyria; genealogical evidence suggests that this acute porphyria was inherited from a single founder, a woman who emigrated from Holland in 1688.[7] These families share the same mutation (Arg59Trp) in the protoporphyrinogen oxidase gene.[8] The existence of such a large group with the same mutation provides a unique opportunity to study the interaction of other inherited and environmental factors in the acute porphyrias.

Homozygous forms of acute intermittent porphyria, variegate porphyria, and hereditary coporporphyria, which are frequently associated with growth and psychomotor retardation, have been reported,[1] as has more than one type of acute porphyria in the same individual or family.[1,9]

Clinical features

Prevalence

Acute porphyria occurs in all races. In most European countries, apart from Sweden, the estimated prevalence of clinically overt acute porphyria is 1–2 per 100 000 inhabitants.[10,11] Most of these individuals have acute

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Type of porphyria	Enzyme deficiency	Gene		Haem precursor overproduction
		Chromosome	Size (number of exons)	
Acute intermittent porphyria	PBG deaminase	11q24·1–24·2	10 kb (15)	Urine: PBG and ALA Faeces: normal porphyrin excretion
Hereditary coproporphyria	Coproporphyrinogen oxidase	3q12	14 kb (7)	Urine: PBG, ALA, coproporphyrin III (acute phase) Faeces: coproporphyrin III
Variegate porphyria	Protoporphyrinogen oxidase	1q23	4·7 kb (13)	Urine: PBG, ALA (acute phase); coproporphyrin III (acute, cutaneous phases) Faeces: protoporphyrin IX greater than coproporphyrin III Plasma: porphyrin-protein conjugate with fluorescence emission peak at 624–26 nm

PBG=porphobilinogen; ALA=aminolaevulinate.

Table 1: **Autosomal dominant acute porphyrias**

intermittent porphyria. Variegate porphyria is about one-third as prevalent as acute intermittent porphyria in the UK; it usually presents with skin lesions alone (panel) and is less often the cause of recurrent attacks. Even in South Africa, most acute attacks are now caused by acute intermittent porphyria. Hereditary coproporphyria is the rarest of the three disorders.

Gene frequencies for these disorders are higher than the prevalence of overt cases. Biochemical studies of relatives of patients with symptomatic acute porphyria suggest that at least 90% of individuals with acute intermittent porphyria or variegate porphyria are clinically latent which gives a frequency of 1–2 per 10 000 individuals for acute intermittent porphyria. A study by Mustajoki and colleagues[12] showed that screening blood donors for inherited porphobilinogen deaminase deficiency gives an even higher rate of 1 per 500 donors.[12] This prevalence is close to that reported by Tishler et al[13] in a similar, but uncontrolled, study of psychiatric inpatients, which is often quoted as evidence of an increased frequency of acute intermittent porphyria among such patients. The occurrence of homozygous variants, sporadic presentation of acute intermittent porphyria in about 25% of cases,[14] and allelic heterogeneity combined with a low rate of new mutations[4,14] are all features consistent with a high prevalence of latent acute porphyria in the population.

Factors that may precipitate the acute attack

Drugs and the menstrual cycle are the most common precipitants of the acute attack,[1,10,15,16] and recurrent attacks that occur in the late luteal phase are sometimes a major problem in acute intermittent porphyria. Factors such as alcohol, fasting, stress, and infection have also been implicated. It is impossible to predict accurately whether specific drugs will provoke an acute attack in a particular individual.[15] Drugs should be prescribed only after reference to a drug list,[10,16] but these recommendations are not absolute and do not substitute for sound clinical judgment. The risk of an attack is highest for drugs that are known to have repeatedly provoked acute attacks and for patients who have or have had symptoms.[15,16]

The acute attack

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

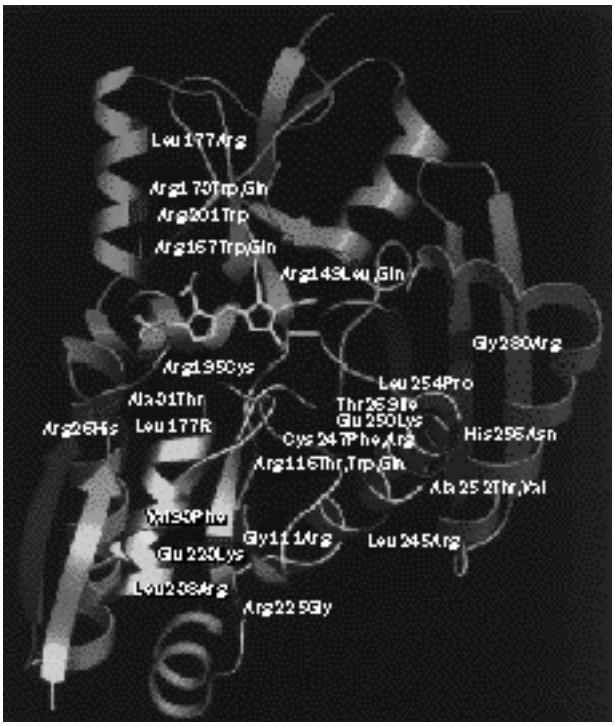
Though tachycardia and hypertension are described as features of the acute attack, the pulse rate and blood pressure are often only moderately raised, and these signs are of poor diagnostic value. Vomiting and constipation are common; the latter is rarely a presenting symptom. These features of acute porphyria—pain, tachycardia, hypertension, and partial ileus—have been attributed to an autonomic neuropathy. Dehydration is common and responds rapidly to fluid replacement. Hyponatraemia, probably caused in some patients by inappropriate secretion of vasopressin,[1] may also be present. The sodium concentration may decline to dangerously low levels, which can lead to convulsions.

The severe attack may progress to a motor neuropathy which may resemble a Guillain-Barré syndrome. In some patients, onset of the neuropathy may be preceded by disappearance of the abdominal pain, which may lead the physician to erroneously assume that the patient is recovering. Mild sensory changes often accompany the motor neuropathy, particularly, a "bathing trunk" distribution of hypoaesthesia over the trunk and thighs. In milder cases, particularly with repeated attacks of acute intermittent porphyria, the features are of a distal neuropathy with foot drop and wrist drop. Occasionally, sensory or sympathetic features such as dysaethesia or causalgia are prominent. Progression to neuropathy is seen less frequently than in the past (table 2).[15] Abnormal behaiviour and confusion, with agitation and hallucinations, are common in some patients during the acute attack. There is little evidence that porphyria produces chronic psychiatric illness, apart from generalised anxiety.[17]

Diagnosis of the acute attack

Most difficulties in the diagnosis of an acute attack arise in patients who do not have a family history of porphyria, particularly if the combination of symptoms is atypical. A high index of clinical suspicion is important to avoid delayed diagnosis, which may lead to inadvertent use of contraindicated drugs and a poorer prognosis.

Increased urinary excretion of porphobilinogen confirms the diagnosis of an acute attack (table 1). Excretion of aminolaevulinate is also increased but to a lesser extent. Screening tests for porphobilinogen based on the insolubility of organic solvents of the red product of its reaction with *p*-dimethylaminobenzaldehyde in acid (Ehrlich's reagent) have been criticised because they lack sensitivity and produce occasional false-positive results.[18] A positive screening test is useful in an emergency, but



Model of human porphobilinogen deaminase with some of the mutations that cause acute intermittent porphyria
The dipyrromethane cofactor at the active site is shown in yellow. We thank N Srinivasan and R Sowdhamini (Birkbeck College, London, UK) for the figure.

should always been confirmed by a specific, quantitative assay.[19] A negative screening test does not exclude an acute attack. If clinical suspicion persists, quantification of porphobilinogen and measurement of faecal and plasma porphyrins are essential. Excretion of porphobilinogen may fall below the detection limit of screening tests soon after the onset of symptoms, particularly in variegate porphyria and hereditary coporporphyria, and the diagnosis may be missed if this approach is not followed. The type of acute porphyria is established by measurement of faecal and plasma porphyrins (table 1);[19] enzyme assays at this stage may mislead and should not be used in place of porphyrin analysis. Fluorescence emission spectroscopy of plasma simplifies the differentiation of variegate porphyria from other acute and cutaneous porphyrias.[20]

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

Pathogenesis of the acute attack

Increased ALA-S activity, overproduction of aminolaevulinate, and relative haem deficiency in the liver are biochemical featues of all acute porphyrias and also of the identical syndrome that occurs in hereditary tyrosinaemia. How these changes are triggered and the pathogenesis of the neuronal dysfunction that produces the symptoms are little understood.[21] Some drugs and alcoholic beverages may increase the intrahepatic requirement for haem by inducing the synthesis of cytochrome P450. The mechanisms for other drugs and hormones and the explanation for differences between individuals in their susceptibility to develop acute attacks are not known.[15] Investigation of the pathogenesis of the neuropathy has been hampered by lack of an experimental model. Current theories implicate aminolaevulinate as a neurotoxin (for which the evidence is controversial[21]), neurotransmitter disturbance secondary to deficiency of haem and tryptophan dioxygenase in the liver, or depletion of haem in nerve cells.[22] The recent development of a transgenic porphobilinogen deaminase deficient mouse provides a system in which these hypotheses can be tested.[22]

Management of the acute attack

The acute attack

Most patients will require admission to hospital. Only drugs clearly shown to be safe in porphyria should be prescribed; all others should be withdrawn. Pain will respond to opiates, though high doses may be required. Sedation with chlorpromazine is often helpful. Vomiting may be suppressed with prochlorperazine or metaclopramide. Administration of dextrose or laevulose in large amounts has been shown to suppress synthesis of aminolaevulinate.[23] However, intravenous dextrose may aggravate hyponatraemia and must be used with caution. Maintenance of an adequate calorie intake can be achieved more safely by nasogastric feeding. Intravenous haematin has largely replaced carbohydrate as the specific therapy of choice for the acute attack; it suppresses hepatic ALA-S by negative feedback and is highly effective in reducing aminolaevulinate and porphobilinogen excretion.[21] The only placebo-controlled

Symptom / sign	Goldberg, 1959 (n=50)*	Stein, Tschndy, 1970 (n=46)*	Mustajoki, Nordmann,[25] 1993 (n=51)	Hift, 1986–95 (n=92)†
Abdominal pain	94	95	96	98
Non-abdominal pain	52	50	25	. .
Vomiting	88	43	84	85
Constipation	84	48	78	28
Psychological symptoms	58	40	19	2
Convulsions	16	20	. .	5
Muscle weakness	68	60	8	7
Sensory loss	38	26	. .	2
Hypertension (diastolic blood pressure >85 mm Hg)	54	36	57	68
Tachycardia (>80 per min)	64	80	79	57
Hyponatraemia (<135 nmol / L)	. .	. .	32	39

Figures are percentages of number of acute attacks. *See further reading section. †Unpublished data.

Table 2: **Symptoms and signs of acute porphyria**

study of this therapy suggested that the clinical benefit of intravenous haematin was modest.[24] Uncontrolled data suggest that haem arginate (Normosang, Leiras Medica, Finland) is highly efficacious, but it will not reverse an established neuropathy and must be given during the early stages of an attack.[25]

Administration of haematin may induce haem oxygenase, with consequent enhanced catabolism.[21] We observed apparent clinical tolerance to haem arginate in a few patients who required repeated courses at short intervals; efficacy was restored by the coadministration of tin protoporphyrin, an inhibitor of haem oxygenase.[26] However, tin protoporphyrin causes photosensitivity and its long-term toxicity is unknown. Zinc mesoporphyrin may be a safer alternative but requires evaluation.[21]

Recurrent acute attacks

Frequent recurrences of the acute attack are usually encountered in patients with acute intermittent porphyria who have attacks induced by menstruation or who repeatedly take inducing agents. With menstrually related attacks, attempts to regulate the menstrual cycle with sex steroids may exacerbate the porphyria. Some patients have responded well to hormonal suppression with gonadotrophin-releasing hormone agonists.[1,27] A functional menopause is induced by these agonists which may be accompanied by symptoms of oestrogen deficiency and accelerated osteoporosis. These effects may be reduced by cyclical adminstration or hormone replacement, but the safety and efficacy of different regimens need further investigation. In one patient, we found that supplemental oestrogen arrested the oestoporosis and was tolerated, whereas progesterone induced an immediate attack.

Outcome

With improvements in management, severe neuropathy and death are now less common than in the past.[15] Recurrent attacks are more common in acute intermittent porphyria than in variegate porphyria. Patients may develop hypertension or chronic renal failure.[28] Acute porphyrias may also be associated with an increased risk of hepatocellular carcinoma.[29]

Management of the patient and family

Success in caring for patients with the acute porphyrias lies less in crisis intervention at the time of the acute attack than it does in enabling affected patients and their families to keep to a minimum the risk of an attack. Family studies are essential to identify individuals with clinically latent porphyria so that they can be counselled about the need to avoid drugs and other factors that provoke acute attacks.[1,16,21] Identification of latent porphyria in children and most adults requires specialised enzymatic and other methods,[19] such as DNA analysis,[2–4,30] and is best undertaken in a referral centre. Most of those who inherit an acute porphyria will lead a normal life and many will be symptom-free; the lives of only a minority are blighted by the disease. No specific diet is indicated for porphyria, though sudden or prolonged calorie restriction may induce an acute attack and should be avoided, as should alcoholic beverages. Although early reports suggest a high incidence of acute attacks in pregnancy and the puerperium, pregnancy seems to pose little increased risk to patients who are known in advance to have porphyria and need not be discouraged.[18] Similarly, general anaesthesia and surgical operations carry little increased risk of an acute attack provided prior knowledge of the diagnosis enables agents that provoke acute porphyria to be avoided.

References

1 Kappas A, Sassa S, Galbraith RA, Nordmann Y. The porphyrias. In: Scriver CL, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. New York: McGraw-Hill, 1989: 1305–65.

2 Elder GH. Molecular genetics of disorders of haem biosynthesis. *J Clin Pathol* 1993; **46:** 977–81.

3 Deybach J-C, Puy H. Porphobilinogen gene structure and molecular defects. *J Bioenerg Biomembr* 1995; **27:** 197–205.

4 Puy H, Deybach J-C, Lamoril J, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet* (in press).

5 Chen C-H, Astrin KH, Lee G, Anderson KE, Desnick RJ. Acute intermittent porphyria: identification and expression of exonic mutations in the hydroxymethylbilane synthase gene. *J Clin Invest* 1994; **94:** 1927–37.

6 Brownlie PD, Lambert R, Louie GV, et al. The three-dimensional structure of mutants or porphobilinogen deaminase: toward an understanding of the structural basis of acute intermittent porphyria. *Protein Sci* 1994; **3:** 1644–50.

7 Dean G. The porphyrias: a story of inheritance and environment. London: Pitman, 1971.

8 Meissner PN, Dailey TA, Hift RJ, et al. A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. *Nat Genet* 1996; **13:** 95–97.

9 McColl KEL, Moore MR, Thompson GG, et al. Chester porphyria—biochemical studies of a new form of acute porphyria. *Lancet* 1985; ii: 796–99.

10 Moore MR, McColl KEL, Rimington C, Goldberg A. Disorders of porphyrin metabolism. New York: Plenum Press, 1987.

11 Mustajoki P, Koskelo P. Hereditary hepatic porphyrias in Finland. *Acta Med Scand* 1976; **200:** 171–78.

12 Mustajoki P, Kauppinen R, Lannfelt L, Lilius L, Koistinen J. Frequency of low erythrocyte porphobilinogen deaminase activity in Finland. *J Int Med* 1992; **231:** 389–95.

13 Tishler PV, Woodward B, O'Connor J, et al. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry* 1985; **142:** 1430–36.

14 Whatley SD, Roberts AG, Elder GH. De-novo mutation and sporadic presentation of acute intermittent porphyria. *Lancet* 1995; **346:** 1007–08.

15 Kauppinen R, Mustajoki P. Prognosis of acute porphyria: occurrence of acute attacks, precipitating factors, and associated diseases. *Medicine* 1992; **71:** 1–13.

16 Disler PB, Moore MR. Drug therapy in acute porphyrias. *Clin Dermatol* 1985; **3:** 112–24.

17 Patience DA, Blackwood DHR, McColl KEL, Moore MR. Acute intermittent porphyria and mental illness—a family study. *Acta Psych Scand* 1994; **89:** 262–67.

18 Buttery JE. Is the Watson-Schwartz screening method for porphobilinogen reliable? *Clin Chem* 1995; **41:** 1670–71.

19 Elder GH, Smith SG, Smyth SJ. Laboratory investigation of the porphyrias. *Ann Clin Biochem* 1990; **27:** 395–412.

20 Poh-Fitzpatrick MB. A plasma porphyrin fluorescence marker for variegate porphyria. *Arch Dermatol* 1980; **116:** 543–47.

21 Bonkovsky HL. Advances in understanding and treating 'The little imitator', acute porphyria. *Gastroenterology* 1993; **105:** 590–94.

22 Lindberg RLP, Porcher C, Grandchamp B, et al. Porphobilinogen deaminase deficiency in mice causes a neuropathy resembling that of human hepatic porphyria. *Nat Genet* 1996; **12:** 195–99.

23 Brodie MJ, Moore MR, Thompson GG, Goldberg A. The treatment of acute intermittent porphyria with laevulose. *Clin Sci Mol Med* 1977; **53:** 365–71.

24 Herrick AL, McColl KEL, Moore MR, Cook A, Goldberg A. Controlled trial of haem arginate in acute hepatic porphyria. *Lancet* 1989; i: 1295–97.

25 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993; **153:** 2004–08.

26 Dover SB, Moore MR, Fitzsimmons EJ, Graham A, McColl KEL. Tin protoporphyrin prolongs the biochemical remission produced by heme arginate in acute hepatic porphyria. *Gastroenterology* 1993; **105:** 500–06.

27 Anderson KE, Spitz IM, Bardin CW, Kappas A. A gonadotopin releasing hormone analogue prevents cyclical attacks of porphyria. *Arch Intern Med* 1990; **150:** 1469–74.
28 Church SE, McColl KEL, Moore MR, Youngs GR. Hypertension and renal impairment as complications of acute porphyria. *Nephrol Dial Transplant* 1992; **7:** 986–90.
29 Bengtsson NO, Hardell L, Porphyrias, porphyrins and hepatocellular cancer. *Br J Cancer* 1986; **54:** 115–17.
30 Kauppinen R, Mustajoki S, Pihlaja H, Peltonen L, Mustajoki P. Acute intermittent porphyria in Finland: 19 mutations in the porphobilinogen deaminase gene. *Hum Mol Genet* 1995; **4:** 215–22.

Further reading

General

Anderson KE. The porphyrias. In: Zakin D, Boyer TD, eds. Hepatology: a textbook of liver disease. Philadelphia: W B Saunders, 1995: 417–63.
Arnold WN. Vincent Van Gogh: chemicals, crises and creativity. Birkhauser: Boston, 1992.
Macalpine I, Hunter R. George III and the mad business. New York: Pantheon, 1969.
Warren MJ, Jay M, Hunt DM, Elder GH, Röhl JC. The maddening business of King George III and porphyria. *Trends Biochem Sci* 1996; **21:** 229–34.

Biochemical and molecular genetics

Grandchamp B, Lanoril J, Puy H. Molecular abnormalities of coproporphyrinogen oxidase in patients with hereditary coproporphyria. *J Bioenerg Biomembr* 1995; **27:** 215–20.
Jenkins T. The South African malady. *Nat Genet* 1996; **13:** 7–9.
Wood S, Lambert R, Jordan PM. Molecular basis of acute intermittent porphyria. *Mol Med Today* 1995; **1:** 232–39.

Clinical features of acute porphyrias

Eales L, Day RS, Blekkenhorst GH. The clinical and biochemical features of variegate porphyria—an analysis of 300 cases studied at Groote Schuur Hospital, Cape Town. *Int J Biochem* 1980; **12:** 837–53.
Goldberg A. Acute intermittent porphyria: a study of 50 cases. *QJM* 1959; **28:** 183–209.
Hift RJ, Meissner PN, Todd G, et al. Homozygous variegate porphyria: an evolving clinical syndrome. *Postgrad Med J* 1993; **69:** 781–86.
Llewellyn DH, Smyth SJ, Elder GH, et al. Homozygous acute intermittent porphyria caused by adjacent base transitions in the same codon of the porphobilinogen deaminase gene. *Hum Genet* 1992; **89:** 97–98.
Stein JA, Tschudy DP. Acute intermittent porphyria: a clinical and biochemical study of 46 patients. *Medicine* 1970; **49:** 1–16.
Waldenstrom J. The porphyrias in inborn errors of metabolism. *Am J Med* 1957; **22:** 758–73.
Xu W, Solis C, Bermejo AM, Astrin KH, Desnick RJ. Clinical and molecular delineation of severe homozygous dominant acute intermittent porphyria. *Pediatric Res* 1995; **37:** A155.

Pathogenesis

Bont A, Steck AJ, Meyer UA. The acute hepatic porphyrias and their neurologic syndromes. *Schweiz Med Wochenschr* 1996; **126:** 6–14.
Litman DA, Correia MA. L-tryptophan: a common demoninator of biochemical and neurological events of acute hepatic porphyria. *Science* 1983; **222:** 1031–33.
Puy H, Deybach J-C, Bogdan A, et al. Increased delta-aminolevlinic acid and decreased pineal melatonin production—a common event in acute porphyria: studies in the rat. *J Clin Invest* 1996; **97:** 104–10.

Diagnosis and management

Dover SB, Plenderleith L, Moore MR, McColl KEL. Safety of general anaesthesia and surgery in acute hepatic porphyria. *Gut* 1994; **35:** 1112–15.
Harrison GG, Meissner PN, Hift RJ. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48:** 417–21.
Lip GY, McColl KE, Goldberg A, Moore MR. Smoking and recurrent attacks of acute intermittent porphyria. *BMJ* 1991; **302:** 507–08.
Meissner PN, Hift RJ, Schmid R, Porphyria. In: Kirsch RE, Robson CR, Trey C, eds. Diagnosis and management of liver disease. London: Chapman and Hall, 1995: 225–44.
Robert TL, Varella L, Meguid MM. Nutrition managment of acute intermittent porphyria. *Nutrition* 1994; **10:** 551–55.
Sassa S. Diagnosis and therapy of acute intermittent porphyria. *Blood Rev* 1996; **10:** 53–58.