12.5 The porphyrias 2032 Timothy M. Cox

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ESSENTIALS The porphyrias are a remarkable family of metabolic disorders char- acterized biochemically by overproduction of haem precursors, principally in the liver and bone marrow. The acute porphyrias are inborn errors of varying penetrance that affect enzymatic steps in a tightly regulated biosynthetic pathway for haem; nonacute acquired forms also occur in genetically predisposed individuals. Haem formation for erythropoiesis, while adaptable to physio- logical and pathological changes, is generally constant, but hepatic synthesis of haem undergoes extreme and rapid oscillations to meet dynamic changes in various pathophysiological states, and this in- fluences the clinical expression of porphyria, which is often latent. Acute porphyrias Clinical presentation—life-threatening neurovisceral attacks occur in four of the porphyrias: acute intermittent porphyria, varie- gate porphyria, hereditary coproporphyria, and Doss' porphyria (5-aminolaevulinate dehydratase deficiency). These present with ab- dominal pain, psychiatric symptoms, and signs of sympathetic and hypothalamic autonomic overactivity, sometimes accompanied by convulsions and motor and sensory deficits. They typically de- velop on exposure to environmental or endogenous factors that place a demand for hepatic haem biosynthesis, the most frequent being changes in reproductive steroid hormones either due to nat- ural hormone cycles or the administration of exogenous gonadal steroids, starvation, intercurrent infection, alcohol, and drugs. Acute porphyrias may also be associated with overproduction of photo- active metabolites and thus long-term photosensitivity, which is ag- gravated during acute attacks. Diagnosis—this is key to survival of an acute attack of porphyria, which can be suspected on the basis of the past history, in par- ticular of photosensitivity or the intermittent discoloration of urine, and family history, and is confirmed by finding excess water-soluble haem precursors in urine. Enzymatic studies can later be used to verify the exact type of suspected porphyria, with molecular analysis of genes encoding relevant haem synthetic enzymes used to identify at-risk individuals in affected pedigrees. Management—treatment of an acute porphyric attack mandates immediate withdrawal of inappropriate drugs and other precipitating factors; infusions of haem arginate or other licensed preparations of haem shorten life-threatening episodes and may be effective prophy- laxis for recurrent porphyria in women with periodic attacks. Genetic counselling informed by molecular analysis of cognate genes, and lifetime management advice should be offered to first-

degree rela- tives of patients in whom acute porphyria has been diagnosed. Beyond comprehensive genetic characterization of the acute porphyrias, promising developments in molecular therapy are coming to fruition, including RNA interference-mediated silencing of the rate-limiting biosynthetic enzyme, hepatic aminolaevulinate synthase 1. Nonacute porphyrias The nonacute porphyrias are photosensitivity syndromes caused by excess photoactive macrocyclic porphyrins triggered especially by visible light in the blue–violet range (380–420 nm). In the most severe form, manifestations are of severe blistering lesions on sun-exposed skin, particularly of the hands and face, with the formation of vesicles and bullae that may become infected. Healing may lead to loss of digits, scarring of the eyelids, nose, lips, and scalp, and occasionally blindness due to corneal scarring. Protoporphyria, either autosomal due to impaired incorporation of iron or X-linked due to overexpression of erythroid aminolaevulinate synthase, causes burning pain and erythema with oedema; blistering is absent. Diagnosis is based on finding excess formed porphyrins in blood and excreta. Sunlight exposure should be minimized until the porphyrin abnormality is corrected, for example, by phlebotomy to deplete iron excess that usually aggravates porphyria cutanea tarda, or by liver or haematopoietic stem cell transplantation in some (very rare) cases. The approved synthetic analogue of α-melanocyte- stimulating hormone, afamelanotide, increases skin pigmentation by increasing melanin production and significantly improves sunlight tolerance and quality of life in patients with at least one cutaneous form of (nonacute) porphyria, namely protoporphyria. Introduction The haem biosynthetic pathway holds great fascination for biochem- ists, who marvel at the evolution of ancient enzymes which interact to bring about the formation of the pigments of life, haemoglobin, the cytochromes, chlorophyll, and the cobalamins (vitamin B12). It is 12.5 The porphyrias Timothy M. Cox

12.5 The porphyrias 2033 unfortunate that, because of complexities in their chemical structure and nomenclature, the important diseases associated with their dis- turbed haem metabolism are perceived as obscure. These consider- ations apply particularly to the acute porphyrias, which are rare but distressing syndromes that mimic other acute illnesses but for which recognition may be critical for the patient’s survival; too often their inherited nature is overlooked and the diagnosis is not established until permanent disability (or even death) supervenes. The porphyrias are rare diseases caused by disturbances in the multistep pathway for the formation of haem, a pigment essential for oxygen transfer and the energy-yielding reactions of electron trans- port. The formation of haem is tightly regulated so that acquired or hereditary defects of any of its component reactions lead to the over- production of haem precursors. Potentially photoactive macrocyclic compounds and toxic precursors of pyrroles thus accumulate. Most of the human porphyria syndromes result from uncommon genetically determined deficiencies of unitary enzymes of the haem biosynthetic pathway, but certain toxins including lead, iron, and hydrocarbons influence the pathway and cause porphyria in sus- ceptible individuals. Similarly, the metabolism of endogenous molecules, including steroid hormones, and xenobiotics including alcohol and many therapeutic drugs, disturb the delicate biochem- ical equilibrium in asymptomatic patients with latent porphyria. Catastrophic gene–environment interactions in previously fit indi- viduals may precipitate sporadic attacks of acute porphyria. Haem metabolism General perspective In healthy adults, daily formation of haem requires the incorpor- ation of about 25 mg of iron into protoporphyrin IX to generate ap- proximately 275 to 300 mg of haem de novo. About 15% of haem biosynthesis occurs in the liver and 80% in the erythroid marrow, with the main bulk of haem being biochemically coordinated in haemoglobin and, to a lesser extent, as myoglobin in the muscles. The remaining haem is mostly present in enzyme proteins, including

catalase, tryptophan pyrrolase, nitric oxide synthase, guanylate cyclase, prostaglandin synthase, nucleotide phosphodiesterases, and cytochromes (in the endoplasmic reticulum cytochrome P450 system as well as the mitochondrial electron transport chain). Hepatic synthesis of haem is subject to rapid and wide fluctu- ations but haem formation in the erythropoietic bone marrow is, under most circumstances, constitutive and stable. However, haem synthesis may be increased, either as the erythron expands and proliferates to meet the demands of blood loss or haemolysis, or in response to intrinsic disease of the bone marrow—or conditions where there is tissue hypoxia or inappropriate erythropoietic drive (see Chapters 22.6.2 and 22.6.4). Very little free haem is present in the cytosol or plasma compart- ment, in the latter of which it is avidly bound to the glycoprotein, haemopexin. Haem proteins undergo appreciable turnover and the haem component is rapidly degraded by distinct haem oxygenases in many tissues, especially those populated by macrophages. Haem oxygenases break open the porphyrin ring to liberate iron, thereby generating linear pyrroles that are metabolized further to biliverdin and bilirubin pigments with the stoichiometric release of carbon monoxide. Many tissues use this one-way destructive route to dis- pose of haem, formation of which in health is balanced by fastidious control of de novo biosynthesis. The routes for the formation and deg- radation of haem are distinct (Fig. 12.5.1). Unlike the biosynthesis of other essential building blocks (e.g. cholesterol and other sterols, purines and pyrimidines, sphingolipids, and glycosphingolipids), once formed there is no means to recycle haem or recover its com- plex macromolecular precursors through salvage reactions. Functions and formation of haem Haem serves as a key prosthetic group in haem proteins, including cytochromes, myoglobin, and haemoglobin, by which it fulfils its essential biological roles as a transporter of oxygen and electrons in the respiratory chain. It is also essential for transcription fac- tors that regulate circadian activities, binding reversibly to a nuclear receptor (Rev-erbα) which is a crucial regulator of the core clock functions in biological rhythms. Haem suppresses the action of Rev-erbα on expression of proteins involved in maintenance of glu- cose homeostasis and gluconeogenesis. A molecular understanding of these recently discovered interactions holds much promise for elucidating how acute attacks of porphyria are induced by starva- tion, sepsis, endogenous hormonal factors, and xenobiotics. Haem biosynthesis requires eight coordinated reactions that are catalysed by cytoplasmic and mitochondrial enzymes which ex- change substrate intermediates between intracellular compartments (Fig. 12.5.1). 5-aminolaevulinate synthetase The first committed, essential, and rate-limiting precursor, 5-amino-laevulinate, is generated by condensation of glycine and the Krebs cycle intermediate, succinyl coenzyme A. This re- action is brought about by one or other of the two isozymes of 5-aminolaevulinate synthetase (ALAS): the gene for the ‘hepatic’ enzyme, ALAS1, maps to the autosome chromosome 3 and is ubi- quitously expressed; the gene for the distinct erythroid isoform, ALAS2, is found on the X chromosome and undergoes dosage compensation in females by lyonization. These enzymes them- selves are localized in the mitochondrial matrix. Expression of the Fig. 12.5.1 Main pathways for haem biosynthesis and degradation in humans.

 gene encoding ALAS1 is rate limiting for the formation of haem and is increased in response to a key regulator of mitochondrial biogenesis that stimulates activity of the Krebs cycle, the transcrip- tion factor peroxisome proliferator-activated receptor coactivator 1α (PGC-1α). To preclude the build-up of toxic porphyrin inter- mediates when the supply of iron is restricted, transcription of aminolaevulinate synthase is regulated by the presence of iron- binding elements. Terminal differentiation of erythroid cells depends upon tran- scriptional activation of ALAS2 by the erythroid factors, especially GATA1, and activation of ALAS2 appears to

be a prerequisite for in- duction of the other genes that encode the enzymes of haem biosyn- thesis. ALAS2 mRNA harbours an iron-response element that binds iron-regulatory proteins (IRP1 and -2), thereby blocking translation of the ALAS2 mRNA; these iron-sulphur binding proteins are de- stabilized when iron is present and translation can proceed. These elaborate molecular control processes serve to coordinate haem bio- synthesis with iron availability in erythroid cells and in this way the risk of toxic injury from the convergence of highly reactive biochem- ical intermediates generated from different corners of the cellular machinery can be minimized. Pyridoxal 5-phosphate (derived from vitamin B6) is an essential cofactor for ALAS isozymes. Deficiency of pyridoxine or interfer- ence with its metabolism leads to sideroblastic anaemia. 5-Aminolaevulinate dehydratase After its formation, 5-aminolaevulinate is exported to the cyto- plasm where the abundant cysteine-rich (heavy metal-sensitive) enzyme, 5-aminolaevulinate dehydratase, catalyses the formation of hydroxymethylbilane (alternatively known as preuroporphyrinogen), which spontaneously forms the monopyrrole porphobilinogen. 5-Aminolaevulinate dehydratase is a multimeric enzyme with re- active sulphydryl groups that are particularly sensitive to the toxic effects of heavy metals, especially lead, so that activity of this enzyme is a sensitive measure of environmental and industrial toxicity. The enzyme is inhibited competitively by the metabolite succinylacetone, concentrations of which rise to inhibitory levels in patients who have the defect of aromatic amino acid degradation tyrosinaemia type I. Patients with tyrosinaemia type I and lead poisoning have neurovisceral manifestations that resemble the acute porphyrias, and it appears likely that overproduction of aminolaevulinate, as a result of arrest at the 5-aminolaevulinate dehydratase reaction, con- tributes to this effect. Porphobilinogen deaminase and uroporphyrinogen III synthetase Four molecules of porphobilinogen are enzymatically condensed to yield the macrocyclic tetrapyrrole uroporphyrinogen III in a com- plex reaction brought about by porphobilinogen deaminase and uroporphyrinogen III synthetase. These enzymes act coordinately to reverse the orientation of one porphobilinogen molecule to yield uroporphyrinogen III, an isoform member of the III series of por- phyrins that are the sole precursors of haem in biological systems. Uroporphyrinogen III decarboxylase, coproporphyrinogen III oxidase, protoporphyrinogen oxidase, and ferrochelatase The cytoplasmic enzyme uroporphyrinogen III decarboxylase decarboxylates the four acetate substituent side chains of uro-porphyrinogen to yield coproporphyrinogen III, which is then reimported into the mitochondrion for further oxidative decarb- oxylation. Coproporphyrinogen III oxidase modifies the two propi- onate side chains to vinyl groups yielding protoporphyrinogen IX, the penultimate precursor of haem. Protoporphyrinogen oxidase removes six hydrogen atoms to yield protoporphyrin IX, which is the substrate for the final step in haem biosynthesis. The insertion of ferrous ions into the porphyrin macrocycle to form ferroprotohaem (haem) is catalysed by the mitochondrial enzyme ferrochelatase. Control of haem synthesis The highly regulated control mechanism of haem biosynthesis en- sures that the free concentrations of the toxic intermediates involved in the pathway are kept low unless there is a metabolic arrest at one of the biosynthetic reactions; under these circumstances, an over- production of the intermediate compounds occurs which can be used for diagnosis. This overproduction predisposes to the develop- ment of the particular clinical porphyric syndrome. A knowledge of the enzymatic steps and of the differential solu- bility of the haem precursors facilitates appropriate diagnostic testing for the precise identification of suspected porphyria. In general, over- production of the early precursors such as 5-aminolaevulinic acid is a common feature of those syndromes associated with neurovisceral manifestations or acute attacks of porphyria. Aminolaevulinate, in par- ticular, represents a common biochemical marker of such attacks and those syndromes that mimic the acute porphyrias, such as hereditary

tyrosinaemia type I and lead poisoning. In patients with cutaneous photosensitivity, overproduction of the formed porphyrin macro- cycles can also be detected in plasma, urine, and faeces in which they are distributed according to their aqueous solubility (Table 12.5.1). The profile of molecules that are overproduced in a given syn- drome may be predicted from the level at which the enzymatic ar- rest occurs as flux through the pathway is stimulated by diminished negative feedback. In those porphyrias where the principal site of production appears to be in the liver, including the acute porphyrias and porphyria cutanea tarda, fluctuations through the biosynthetic pathway as a result of regulatory effects from environmental or en- dogenous factors can occur very rapidly; indeed minute-to-minute oscillations in biosynthetic haem fluxes have been recorded in the liver. Thus, in starvation and on challenge with xenobiotic reagents (which place a demand for the production of haem to meet the needs for new cytochrome formation), as well as with endogenous hor- monal changes, enhanced flux through the pathway leads to toxic overproduction of 5-aminolaevulinic acid. By the same token, rapid repression of the haem biosynthetic pathway in the liver can be in- duced by the administration of exogenous haem, a useful agent in the control of acute attacks and which rapidly corrects the disturbed metabolism (see next paragraph).
Table 12.5.1 Solubility and routes of excretion of haem precursors Plasma Urine Faeces 5-Aminolaevulinate ++ +++ − Porphobilinogen ++ +++ − Uroporphyrins I and III + ++ + Coproporphyrins I and III + + +++ Protoporphyrin IX + − +++

 Haem formation in the erythron is more rapid than that in the liver but is not subject to sudden oscillations in synthetic rates. Nonetheless, in patients with erythropoietic porphyrias such as congenital porphyria, enhanced rates of red cell destruction when hypersplenism supervenes or in response to light exposure greatly exacerbate the overproduction of porphyrin intermediates and aggravate photosensitivity due to increased porphyrin release. Short-term experiments indicate that exogenous haem may par- tially repress the endogenous haem biosynthetic pathway in eryth- roid tissue, but this has not proved to be useful for long-term relief in the erythropoietic porphyrias. Blood transfusion to suppress erythropoiesis or definitive replacement of bone marrow by trans- plantation has, however, proved to be successful in controlling the devastating manifestations of congenital erythropoietic porphyria. Classification and epidemiology of the porphyrias The porphyrias have been classified into hepatic and erythropoietic types depending on the main site of overproduction of haem pre- cursors. For clinical purposes, however, a useful operational defin- ition of the porphyric syndromes distinguishes the acute from the nonacute porphyrias. Classification Acute porphyrias cause life-threatening neurovisceral manifestations which are typically precipitated by sporadic environmental factors. All but one of these disorders is inherited as a dominant condition, but a striking feature is their clinical heterogeneity with great variation in expressivity and penetrance—the latter often termed ‘latency’. Nonacute porphyrias are characterized by photosensitivity syn- dromes due to overproduction of macrocyclic porphyrins which cause light-induced skin injury. Several of the acute porphyrias may also cause overproduction of porphyrin intermediates that are either intrinsically fluorescent or readily oxidized to become fluorescent. These porphyrias may at times be accompanied by marked photo- sensitivity and blistering skin reactions, which are usually exacer- bated during the acute attacks. Epidemiology The frequency and epidemiology of the porphyrias are areas of con- tinued uncertainty: estimated prevalence of all porphyrias is from 1 in 300 to 1 in 200 000 in different populations. Difficulties arise because there are many types of porphyria and, being rare, often episodic, and of low penetrance, they frequently escape formal diagnosis. It is also regrettable that biochemical complexity and scientific nomenclature intimidates

many practitioners. These con- siderations also impede proper management, especially since costly technological sophistication and specialist referral is often needed for definitive diagnosis. Patients referred with skin manifestations to dermatologists are more readily identified, but the associated or subsequent neurovisceral manifestations in underlying porphyrias such as variegate or coproporphyria are not always recognized in the nonacute clinical context. Acute porphyrias There are regional variations in reported frequency of acute inter- mittent porphyria. A prospective study of newly diagnosed patients with genetic porphyrias from 11 European countries suggested an annual incidence for symptomatic acute porphyria of 0.2 per mil- lion. The incidence of symptomatic acute intermittent porphyria was similar in all countries (0.13 per million per year; 95% confi- dence interval 0.10–0.14), excepting Sweden (0.51; 95% confidence interval 0.28–0.86). Prevalence of overt acute intermittent porphyria was 5.4 cases per million. Higher figures have been reported in other studies: one in Norway gave the prevalence of acute intermittent porphyria to be approximately 4 in 100 000, with an overall annual incidence of 0.5 to 1 in 100 000, and the condition occurs in about 1 in 1000 of the Lapp population that is shared between Sweden, Finland, and Norway. Acute variegate porphyria is most common in the Afrikaner population of South Africa: traced to a Dutch settler in the 17th century, it has a prevalence of about 3 in 1000 persons. The condition has spread to all ethnic groups within the South African population, molecular analysis of which confirms the presence of a single dominant missense mutant allele of the protoporphyrinogen IX oxidase gene (p.R59W). There are iso- lated reports of high prevalence among the potters in the Bikaner district of Rajasthan, India. Nonacute porphyrias The most common condition in this category is porphyria cutanea tarda, with an estimated prevalence of approximately 1 in 10 000 in Norway. Protoporphyria, the second most frequent of the nonacute porphyrias, in which systemic features with cholestatic liver disease are rare (5%), is estimated to have a frequency of 1 in 75 000 to 1 in 200 000 births. Tables 12.5.2 to 12.5.4 set out the individual defects that charac- terize the clinical porphyrias and summarize the clinical features of these hereditary syndromes. Table 12.5.2 The porphyria syndromes Hereditary porphyria Acute porphyrias: • Acute intermittent porphyria • Variegate porphyriaa • Hereditary coproporphyriaa • Doss’ porphyria—aminolaevulinate dehydratase deficiency Nonacute porphyrias: • Congenital erythropoietic porphyria—Gunther’s disease • Protoporphyria • X-linked protoporphyria • Porphyria cutanea tardab—sporadic or familial • Hepatoerythropoietic porphyriac Acquired porphyria • Hexachlorobenzene porphyria • Lead poisoning (plumboporphyria) • Hereditary tyrosinaemia type 1 a Acute syndromes also accompanied by long-term skin photosensitivity. b Porphyria cutanea tarda is not a simple monogenic disorder; it is almost always provoked by environmental agents such as hepatitis C, oestrogens, iron excess, or alcohol. c Homozygous uroporphyrinogen III decarboxylase deficiency.

 Table 12.5.3 Main biochemical abnormalities in the porphyrias Disorder Enzyme defect Biochemical abnormality Acute intermittent porphyria Porphobilinogen deaminase Increased urinary porphobilinogen and 5-aminolaevulinate Variegate porphyria Protoporphyrinogen IX oxidase Increased urine 5-aminolaevulinate and porphobilinogen (especially acute attacks) Increased stool coproporphyrin III and protoporphyrin Hereditary coproporphyria Coproporphyrinogen III oxidase Increased urine 5-aminolaevulinate and porphobilinogen (especially acute attacks) Increased stool coproporphyrin III more than protoporphyrin Doss’ porphyria Aminolaevulinate dehydratase Increased urinary 5-aminolaevulinate Faecal porphyrins normal Porphyria cutanea tarda Uroporphyrinogen III decarboxylasea Increased urine uroporphyrin I and III Increased faecal hepatacarboxylic porphyrin and isocoproporphyrin Congenital erythropoietic

porphyria Uroporphyrinogen III synthase Increased urine, plasma, and red cell uroporphyrin I and coproporphyrin I Normal 5-aminolaevulinate and porphobilinogen Increased faecal coproporphyrin I Protoporphyria Ferrochelatase Increased protoporphyrin in stool and red cells (metal free) Caseinolytic mitochondrial matrix peptidase chaperone subunit (ClpXP) Increased protoporphyrin in stool and red cells (metal free) X-linked protoporphyria Aminolaevulinate synthase 2 Increased protoporphyrin in stool and red cells (heterozygous females mosaic) Hexachlorabenzene porphyria Uroporphyrinogen III decarboxylase Increased urinary uroporphyrin I and III and hepatocarboxylic and other acetic acid substituents Hereditary tyrosinaemia I Aminolaevulinate dehydrataseb (acquired deficiency) Increased urinary 5-aminolaevulinate and succinylacetone (toxic metabolite) Lead poisoning Aminolaevulinate dehydratase, ferrochelatase ± impaired iron delivery from transferrin Increased urinary 5-aminolaevulinate, raised red cell protoporphyrin and zinc protoporphyrin a Homozygous deficiency also responsible for hepatoerythropoietic porphyria. b Inborn deficiency of fumarylacetoacetate hydrolase leads to excess formation of the 5-aminolaevulinate hydratase inhibitor, succinyl acetone (4,6-dioxoheptanoate). Reference ranges: urine—total porphyrins 20 to 320 nmol/litre; 5-aminolaevulinate <52 µmol/litre (urine:creatinine porphobilinogen ratio <1.5); porphobilinogen <10.7 µmol/litre. Faeces—total porphyrins 10 to 200 nmol/g dry weight. Red cell—total porphyrins 0.4 to 1.7 µmol/litre. Laboratory ranges supplied by Porphyria Service, Department of Medical Biochemistry, University Hospital of Wales NHS Trust, Heath Park, Cardiff CF4 4XW (Professor G.H. Elder). Table 12.5.4 Principal manifestations of the porphyrias Acute intermittent porphyria Acute neurovisceral attacks Variegate porphyria Acute neurovisceral attacks Skin photosensitivity with fragility, scarring, hairiness, and pigment changes Hereditary coproporphyria Acute neurovisceral attacks, blistering skin lesions, photosensitivity Doss’ porphyria Acute neurovisceral attacks, susceptibility to lead exposure. (Only six confirmed cases reported) Porphyria cutanea tarda Blistering skin lesions on light exposure, pigment changes, atrophy, and scarring— also may be associated with manifestations of iron storage disease, also hepatitis C Congenital erythropoietic porphyria Haemolytic anaemia, hypersplenism, porphyrinuria, extreme photosensitivity with skin ulceration and injury; adult or late onset reported Hepatoerythropoietic porphyria Resembles congenital erythropoietic porphyria: blisters, photosensitive skin with scar formation, haemolysis, red urine Protoporphyria and X-linked protoporphyria Photosensitivity; early-onset, characterized by burning pain, oedema—scarring rare X-linked disease Occasional cholestatic liver disease, protoporphyrin gallstones—fulminant or subfulminant hepatic failure complicated by neurovisceral syndrome, especially in perioperative state Hexachlorobenzene porphyria Resembles sporadic porphyria cutanea tarda Lead poisoning Neurovisceral manifestations with signs of disordered red cell haemoglobinization Hereditary tyrosinaemia I Toxic neurovisceral disease

12.5 The porphyrias 2037 Pathogenesis Acute neurovisceral attacks These attacks occur in four of the porphyrias indicated in Tables 12.5.2 to 12.5.4. In all but one, the very rare Doss’ porphyria (aminolaevulinate dehydratase deficiency, a recessive disease), the inheritance is as an autosomal dominant trait. Clinical expression is characterized by recurrent acute, life- threatening attacks of neuropathy that include abdominal pain, psy- chiatric symptoms including anxiety, and signs of sympathetic and hypothalamic autonomic overactivity with tachycardia and systemic hypertension. The illness is sometimes accompanied by convulsions and principally motor rather than sensory deficits; the neurological features may be confused with Guillain–Barré syndrome. Acute decompensation is characteristically precipitated by drugs which induce hepatic haem formation and are metabolized by the hepatic cytochrome P450 system located in the endoplasmic re-

ticulum. Neuropathological examination shows axonal degener- ation and central chromatolysis in anterior horn cells and in the brain. Electromyography may reveal denervation compatible with a primary axonal neuropathy of peripheral nerves. Although psy- chiatric symptoms often accompany the attacks, there is conflicting evidence that patients with acute porphyria have a greater risk of chronic psychiatric illness than other patients with long-standing episodic illnesses that affect the quality of life and are associated with physically disabling manifestations. Role of 5-aminolaevulinic acid The porphyric crises of 5-aminolaevulinate dehydratase deficiency are associated with lone overproduction of 5-aminolaevulinic acid, which is common to all porphyrias associated with acute manifest- ations. It has been suggested that toxic effects of other factors may contribute, but evidence supports the view that 5-aminolaevulinic itself, or a direct metabolite of this critical precursor of porphyrin synthesis, has a causal role in the acute porphyric attack. 1. Mutations in aminolaevulinate synthase 1 (ALAS1) have not been causally associated with human diseases. Mutations in the erythroid isozyme gene, ALAS2, cause two diseases: inactivating or low-activity mutations, as with deficiency of the cofactor pyridoxal 5-phophate, cause sideroblastic anaemia; mutations at the C-terminus of the gene are responsible for X-linked nonacute protoporphyria, in which there is a common four-nucleotide base deletion. 2. Acute, ‘nonsurgical’ abdominal pain, encephalopathy, and per- ipheral motor mononeuropathy are typical features of toxic lead exposure, which is associated with specific acquired bio- chemical abnormalities including elevated 5-aminolaevulinic excretion together with elevated free protoporphyrin—changes predicted by the effects on aminolaevulinate synthase and ferrochelatase, respectively (both sulphydryl-rich enzymes that are readily susceptible to inhibition by lead). As an addendum to these observations, it has been shown that individuals who are otherwise asymptomatic heterozygotes, identified from studies of pedigrees with 5-aminolaevulinate dehydratase deficiency (‘Doss’ porphyria’), are themselves exquisitely sensitive to en- vironmental lead exposure, thereby developing symptomatic plumboporphyria. 3. Hereditary tyrosinaemia type 1 is an inborn error of tyrosine metabolism due to the deficiency of fumarylacetoacetate hydro- lase: there is liver disease (with a high risk of hepatocellular carcinoma), renal tubular disease, and neurological manifest- ations. Acute neurological crises, with abdominal symptoms, painful extremities, and hypertension with hyponatraemia, occur episodically and may lead to fatal respiratory failure— widely referred to as porphyria-like syndrome. When man- aged by dietary restriction of tyrosine and phenylalanine, these episodes persist, but the illness is characterized by ele- vation of the secondary metabolite succinylacetone (5,7- dioxoheptanoate) and 5-aminolaevulinate concentrations in plasma and urine. Succinylacetone is a potent noncompeti- tive inhibitor of 5-aminolaevulinic dehydratase (Ki 30 nM), thus explaining the accumulation of 5-aminolaevulinate. The neurological crises in tyrosinaemic patients resolve rapidly on introduction of nitisinone, an inhibitor of 4- hydroxyphenylpyruvate dioxygenase which catalyses conver- sion of 4-hydroxyphenylpyruvate to homogentisic acid, thus blocking the proximal tyrosinaemia pathway and correcting the pathological generation of succinylacetone. If started early, the clinical manifestations are ameliorated but the long-term neurocognitive outcomes are often impaired. The structure of aminolaevulinate is analogous to the inhibi- tory neurotransmitters γ-aminobutyric acid and l-glutamate. It seems likely that 5-aminolaevulinate may interfere with the ac- tion of the γ-aminobutyric acidergic system, the best evidence for which appears to be its ability to inhibit melatonin production in the rat pineal gland in vivo, as has been described in patients with recurrent acute porphyric attacks. It has been further postulated that under the conditions of the acute attack there may be a de- ficiency of essential haem proteins, such as the cytochrome P450 isozymes in the liver, with further disturbances in

secondary me- tabolism; other possibilities include a decrease in the activity of hepatic tryptophan dioxygenase, leading to increased formation of 5-hydroxytryptamine (serotonin). At present there is no clear resolution between combined or in- dividual effects of acute porphyria on the production of neurotoxic pseudotransmitters (aminolaevulinate) or secondary local deficiency of haem. However, the beneficial results of liver transplantation in pa- tients with disabling recurrent attacks of acute intermittent porphyria indicate that the principal cause of the acute syndrome is the hepatic over- production of toxic haem precursors. In any event, there is convincing evidence of abnormal neurotransmitter function and increased sero- tonin production, as well as direct interference of γ-aminobutyric acid receptors by toxic concentrations of 5-aminolaevulinate. Supplying ex- ogenous haem during the acute attack, however, would be expected to correct both arms of this disturbed metabolism, which may account for the beneficial biochemical and clinical effects observed with its use. The recent development of a mouse model of porphyrinogen deaminase deficiency showing sensitivity to barbiturates serves as an authentic model of the biochemical and neuropathological mani- festations of acute porphyria and may clarify much about the patho- genesis. Finally, decisive evidence for causal role of aminolaevuinate or a related metabolite has emerged from the spectacular clinical and biochemical success of short-interfering RNA molecules (siRNAs) that are able to modulate synthesis and abundance of ALAS1.

 The findings in mice that model acute intermittent porphyria have been decisively translated into a human RNA interference agent (givosiran) that specifically targets hepatic ALAS1 gene expression. Not only was this drug able to prevent the biochemical abnormal- ities, it markedly reduced the paralysis associated with barbiturate challenge in affected animals and in humans. Photosensitivity In living cells, most of the macrocyclic precursors of the haem biosyn- thetic pathway are present as their reduced porphyrinogen precursors which are not photoreactive. However, when these tetrapyrroles (uroporphyrinogen, coproporphyrinogen, and protoporphyrinogen) are produced in excess, they diffuse into plasma and tissues where they react with ambient oxygen to form their parent porphyrins, which are spectacularly fluorescent. Porphyrins absorb light maximally in the Soret region (400–420 nm) and between 500 and 600 nm (both within the visible light range of 380–700 nm); they re-emit this light energy at lower wavelengths to give pink, orange, or red fluorescence. The double-bond resonance structure of these macrocyclic compounds promotes the formation of singlet oxygen by the transfer of absorbed energy to ground-state oxygen through light activation, and it appears that generation of singlet oxygen brings about the photodermatoses associated with the porphyrias. Porphyrias associated with overpro- duction of formed macrocyclic haem precursors are thus associated with photosensitivity. The particular skin reactions that develop differ between the particular enzyme defects, which may be explained prin- cipally by the degree of hydrophobicity of the overproduced porphy- rins and their solubility in cellular membranes. The first tetrapyrrole that serves as an immediate precursor to haem is uroporphyrinogen III, formation of which requires coordinated action of the two cytoplasmic enzymes uroporphyrinogen I synthase (porphobilinogen deaminase) and uroporphyrinogen III cosynthase. In the absence of adequate cosynthase activity there is a marked overproduction of porphyrins of the I series, which do not form bio- logically active ferroprotohaem. Deficiency of uroporphyrinogen III cosynthase leads to the very rare but disabling syndrome of Gunther’s disease (congenital erythropoietic porphyria), characterized by ex- treme photosensitivity, haemolysis, and the passage of pink urine containing abundant porphyrins of the I isoform. Persistently high concentrations of these toxic molecules in body fluids lead to staining of the teeth and bones and extreme photosensitive damage, often with cruel and painful skin

disfigurement and hair loss. Porphyria cutanea tarda is caused by deficiency of uro porphyrinogen decarboxylase, defects of which involve complex interactions between heredity and environmental factors. The en- zyme activity is markedly decreased in the presence of excess tissue iron and, although rare familial cases of porphyria cutanea tarda occur, most patients have a sporadic disease that is provoked by exposure to environmental toxins such as alcohol, oestrogens, hy- drocarbons, iron (often associated with mutations in the haemo- chromatosis gene HFE), and hepatitis C. At the time of writing, the pathogenic relationship between these external factors and the manifestations of uroporphyrinogen decarboxylase deficiency is unclear. Skin biopsies show subepidermal bullas and electron mi- croscopy reveals vacuoles in the cells of the superficial dermal epi- thelium. In this disease, as in protoporphyria, the endothelium of the dermal capillary is thickened and the vessels are surrounded by complement and mucopolysaccharide deposits. The final step in the haem biosynthetic pathway involves insertion of ferrous iron into the protoporphyrin nucleus generated enzymatically from protoporphyrinogen IX by protoporphyrinogen IX oxidase. This last step occurs in the mitochondrion. Ferrochelatase depends on the iron–transferrin cycle for the delivery of iron from plasma transferrin. In the bone marrow, when the iron supply is deficient, freely available zinc may be preferentially converted to zinc protoporphyrin ra- ther than ferroprotohaem, thus offering a convenient means to monitor iron-deficient erythropoiesis. Similarly, industrial lead exposure, which inhibits both iron delivery and the activity of the sulphydryl enzyme ferrochelatase, causes accumulation of zinc protoporphyrin and free protoporphyrin in erythroid precursors and reticulocytes. Deficiency of ferrochelatase leads to the accu- mulation of free protoporphyrin in liver tissue, plasma, and the skin where it induces marked photosensitivity. The accumula- tion of excess protoporphyrin in red cell precursors leads to the characteristic fluorocytes (young red cells containing excess free protoporphyrin) that are the easily recognized hallmark of patients with burning photosensitivity caused by protoporphyria. In protoporphyria, an adequate oxygen supply has been shown to be critical for the development of experimental phototoxicity in vivo. Singlet oxygen and other radicals may lead to lipid peroxidation and cross-linking of membrane proteins with acti- vation of late complement components. In the more severe dis- ease, congenital erythropoietic porphyria, egress of uroporphyrin I from circulating erythrocytes, which may be destroyed within capillaries, leads to gross accumulation of porphyrin in dermal tissue and juxtaposed epithelium. Exposure to light is known to promote photohaemolysis, indicating that light of the visible wavelength can penetrate the skin sufficiently to induce porphyrin photoactivation in situ. Induction of acute porphyric attacks Acute attacks of porphyria may be life-threatening illnesses that occur in genetically predisposed individuals who usually remain asymp- tomatic. The acute episodes develop on exposure to environmental or endogenous factors that place a demand for hepatic haem biosyn- thesis; this leads to the overproduction of porphyrin intermediates and pyrrole precursors. The most frequent precipitating factors are changes in reproductive steroid hormones either due to natural hor- mone cycles or the administration of exogenous gonadal steroids. Starvation, including that associated with surgical procedures and anaesthesia, intercurrent infections, and many xenobiotics, including alcohol as well as prescription drugs, over-the-counter agents, and chemicals present in health foods can precipitate acute porphyria. Boxes 12.5.1 and 12.5.2 list drugs that have been classified as unsafe in patients with porphyria, either because they have been shown to be porphyrinogenic in animals or in vitro studies, or have been associated with acute attacks in patients with porphyria. These tables are taken from the British National Formulary published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain. It is noteworthy that slight changes in the chemical structure can lead to marked differences in the ability of the drug to

induce attacks of porphyria. Inspection of contemporary national and international websites provides up-to-date information of immediate relevance and value, especially in relation to local pre- scribing practice (see ‘Further reading’). A clinically more useful list

12.5 The porphyrias 2039 is of safe drugs is provided in Box 12.5.3. For further information see the ‘Complete 2018 List of Safe Drugs in Acute Porphyrias’ (http:// www.drugs-porphyria.org/), which provides an updated current list with informative notes. Tolerance of alcohol varies greatly in patients with porphyria, many of whom appear to tolerate it in modest amounts. Alcohol is, however, best avoided, although at the same time it is wise not to implicate al- cohol in an acute attack unless other causes have been excluded. There is emerging evidence that cigarette smoking, which induces enzymes of the haem-rich cytochrome P450 system, is prevalent in patients who have frequent acute attacks of porphyria. The author recommends that persuasive advice to stop smoking is given when- ever possible. Acute attacks of porphyria occur in the four conditions known as the hepatic porphyrias and particularly occur for the first time in latent carriers who are aged between 15 and 40 years. Attacks have been recorded in children before puberty but are very rare and usu- ally occur during febrile illnesses or are precipitated by the use of porphyrinogenic drugs and over-the-counter remedies. Although the porphyrias occur in a latent state in men with a frequency that is equal to that in women, women who have acute porphyria out- number men by at least two to one. The recent description of Rev-erbα, a haem sensor involved in the coordination of metabolic pathways and circadian rhythms, as well as PGC-1α, a transcriptional coactivator involved in the regulation of ALAS1 expression, offers the hope that a better understanding of the mechanism by which environmental influences trigger acute porphyria in susceptible individuals will be forthcoming. Genetic variation in these pathways, particularly the cytochrome P450 system also may go some way to explain the immense variation that individuals show in their susceptibility to the attacks. Clinical features of acute porphyria The clinical manifestations of an acute attack are very diverse and the condition may be indistinguishable from many other disorders. The common neurovisceral symptoms of acute porphyric attacks are listed in Box 12.5.4 and, of these, abdominal pain is the most common presenting symptom. The pain itself may be difficult to identify since it is usually constant but poorly localized and usually not associated with tenderness. Beyond severe myalgic pains, some- times affecting anterior abdominal muscles, there may be an associ- ated colicky component and later ileus with abdominal distension, which may mimic a surgical emergency. Constipation is a charac- teristic symptom but diarrhoea with increased borborygmi can also occur. The patient is usually markedly distressed with anxiety and tachycardia. Marked arterial hypertension (not always previously noted), sometimes paroxysmal, is the rule Development of pain in the limbs is a frequent feature, particu- larly in the upper thighs and also in other somatic muscles of the chest, lumbar region, shoulders, and neck. Ultimately, muscle weak- ness and respiratory paralysis may occur. The patient, almost in- variably very anxious, becomes restless, frankly disturbed, or even deluded as in a toxic confusional state. Prominent mental disturb- ances are reported in patients with the posterior encephalopathy syndrome and cerebral vasculopathy that accompanies the parox- ysmal and severe systemic hypertension of untreated attacks. The inability of attending medical personnel to identify the cause of the pain and the distress associated with it often leads to alienation and an exaggeration of the complaints, which may be difficult to diag- nose. Should a suggestion of psychiatric illness (typically some type of somatic symptom disorder) be made by attending staff, this in- variably compounds the distress experienced by the patient. From every aspect, distressed patients with suspected porphyria should be treated attentively and every effort should be made to

accelerate the definitive diagnosis and treat accordingly It is a general rule that the mental features of porphyria subside rapidly as the biochemical disturbance resolves. Hypertension, sweating, and tremor together with tachycardia indicate marked sympathetic overactivity and cardiac arrhythmias may ensue. In about 10% of severe attacks, grand mal seizures de- velop, treatment of which may prolong the attack since many anti- convulsants are highly porphyrinogenic. With sustained attacks, there may be signs of a peripheral neuropathy that is related to axonal degeneration, principally affecting motor nerves. Peripheral neuropathy in its early stages may not affect the limb and tendon re- flexes, but with time these will be decreased or absent. In prolonged porphyric attacks, an ascending muscle weakness rapidly affecting the respiratory muscles and diaphragm, and with bulbar paralysis, may lead to ventilatory failure and death if life-saving cardiorespira- tory resuscitation and intensive care measures are delayed. In a full-blown attack, mental symptoms including anxiety, sleep- lessness, and depression are often prominent; the terrifying nature of the illness only aggravates distress in the patient. If the porphyric attack is sustained as a result of failed diagnosis or inadequate man- agement, progressive alienation, visual and auditory hallucinations, and frank paranoia with homicidal outbursts may occur. Such dis- turbances are difficult to contain within the environment of the busy acute hospital. Box 12.5.1 Classes of drug that are unsafe in acute porphyrias • Anabolic steroids • Antidepressants, monoamine oxidase inhibitors (contact the United Kingdom Porphyria Medicines Information Service (UKPMIS) for advice) • Antidepressants, tricyclic and related (contact UKPMIS for advice) • Barbiturates (includes primidone and thiopental) • Contraceptives, hormonal (for detailed advice contact UKPMIS or a porphyria specialist) • Hormone replacement therapy (for detailed advice contact UKPMIS or a porphyria specialist) • Imidazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure) • Non-nucleoside reverse transcriptase inhibitors (contact UKPMIS for advice) • Progestogens (for detailed advice contact UKPMIS or a porphyria specialist) • Protease inhibitors (contact UKPMIS for advice) • Sulphonamides (includes co-trimoxazole and sulfasalazine) • Sulphonylureas (glipizide and glimepiride are thought to be safe) • Taxanes (contact UKPMIS for advice) • Triazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure) For further information see UK Porphyria Welsh Medicines Information Service (2017): https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria.

section 12 Metabolic disorders 2040 Although seizures may be a presenting sign of the acute attack, they often occur in association with fulminant hyponatraemia re- sulting from the inappropriate secretion of antidiuretic hormone. Treatment of hyponatraemia in the acute attack poses special difficulties (see ‘Hyponatraemia and seizures’). Inappropriate use of hypotonic dextrose will aggravate hyponatraemia and seiz- ures and may induce fatal cerebral herniation due to severe brain oedema. Box 12.5.3 Drug classes thought to be safe in acute porphyrias • Antihistamines: cetirizine, chlorpheniramine, and cyclizine • Diuretics: acetazolamide, amiloride, bumetanide, cyclopenthiazide, and triamterene • Ergot derivatives: oxytocin is probably safe • Sulphonylureas: glipizide • Analgesics: morphine, diamorphine, codeine, dihydrocodeine, fen- tanyl, and pethidine. • Tranquillizers: chlorpromazine, and haloperidol • Local anaesthetics: bupivacaine and lignocaine can be used with caution • Antimicrobials: rifamycins have been used without ill effect in some patients Box 12.5.4 Clinical manifestations of acute porphyria • Abdominal pain • Vomiting • Constipation • Limb, head, neck, and chest pain • Muscle weakness • Sensory loss • Hypertension • Tachycardia • Convulsions • Respiratory paralysis • Fever • Psychiatric symptoms Box 12.5.2 Individual drugs unsafe in acute porphyrias • Aceclofenac •

Alcohol • Amiodarone • Aprepitant • Artemether with lumefantrine • Bexarotene • Bosentan • Busulfan • Carbamazepine • Chloral hydrate (although evidence of hazard is uncertain, manufacturer advises avoid) • Chloramphenicol • Chloroform (small amounts in medicines probably safe) • Clemastine • Clindamycin • Cocaine • Danazol • Dapsone • Diltiazem • Disopyramide • Disulfiram • Ergometrine • Ergotamine • Erythromycin • Etamsylate • Ethosuximide • Etomidate • Flutamide • Fosaprepitant • Fosphenytoin • Griseofulvin • Hydralazine • Ifosfamide • Indapamide • Isometheptene mucate • Isoniazid (safety uncertain, contact UKPMIS for advice) • Ketamine • Mefenamic acid (safety uncertain, contact UKPMIS for advice) • Meprobamate • Methyldopa • Metolazone • Metyrapone • Mifepristone • Minoxidil (safety uncertain, contact UKPMIS for advice) • Mitotane • Nalidixic acid • Nitrazepam • Nitrofurantoin • Orphenadrine • Oxcarbazepine • Oxybutynin • Pentazocine • Pentoxifylline • Pergolide • Phenoxybenzamine • Phenytoin • Pivmecillinam • Pizotifen • Porfimer • Raloxifene • Rifabutin (safety uncertain, contact UKPMIS for advice) • Rifampicin • Riluzole • Risperidone • Spironolactone • Sulfinpyrazone • Tamoxifen • Temoporfin • Thiotepa • Tiagabine • Tibolone • Topiramate • Toremifene • Trimethoprim • Valproate • Verapamil • Xipamide

12.5 The porphyrias 2041 Acute attacks of porphyria appear to be more common in women as a result of changes in sex steroids: many women who have peri- odic attacks do so in the 1 or 2 days before the onset of menstrual bleeding, but sometimes attacks lasting a day or two may have their onset in the mid-menstrual phase soon after ovulation. The pattern may worsen as the menopause approaches, but severe attacks usually cease with the onset of oligomenorrhoea or amenorrhoea. Although it appears that progestogens are principally respon- sible for cyclical or periodic attacks in women and are more porphyrinogenic than oestrogens, pregnancy itself is not invari- ably associated with adverse outcomes in women at risk from acute attacks. Seizures and hypertension due to acute porphyria may be attributed erroneously to eclampsia. Drugs that provoke attacks, such as metoclopramide, may be used mistakenly to control gastro- intestinal symptoms in pregnancy and thus place the woman and her unborn infant at risk. Many mild attacks of porphyria resolve spontaneously within a few days, either as a result of withdrawal of the precipitating factor or because of natural hormonal rhythms. Prolonged attacks are usu- ally the consequence of multiple factors and delays in the institution of definitive therapy. The ensuing neurological injury, accompanied in severe attacks by bulbar and respiratory paralysis, may lead to prolonged or permanent disability. Experience shows that in many such cases inappropriate drugs have been given to counter the early manifestations of the condition (e.g. analgesics, psychotropic drugs and anticonvulsants), hence the initiating medical interventions ultimately prove to be critical determinants of outcome where the diagnosis is not suspected or, if known, has been perilously ignored. Diagnosis of acute attacks Diagnosis of the acute attack is often suspected from scrutiny of the past history, including episodes of photosensitivity with blistering lesions or intermittent discolouration of urine. The passage of frank wine-coloured or permanganate-coloured urine is unusual, but if present indicates a full-blown established attack. The family history is often informative, with a history of abdominal pain in first-degree family members, with or without photosensitivity skin eruptions. In all instances, it is the overproduction of haem precursors that characterizes the condition biochemically and this is the principal means by which a diagnosis can be made during an acute attack, confirmation of which requires the demonstration of increased por- phyrin precursors in the urine. Most commonly, increased excretion of the monopyrrole, porphobilinogen, is accompanied by increased excretion of urinary 5-aminolaevulinate, but porphobilinogen ex- cretion is not increased in the extremely rare aminolaevulinate dehydratase

deficiency or in the pseudoporphyria of lead poisoning. Without genetic characterization in a first-degree relative, ‘cold’ diagnosis can be very challenging when the biochemical abnor- malities have corrected themselves. Future developments in gen- etic diagnosis may well improve the interval diagnosis of acute porphyrias, but more work is needed before information from fo- cused sequencing of the responsible genes can be used appropriately to facilitate clinical diagnosis of these important conditions. Prognosis An early series showed that during the first acute attack of porphyria half the patients died. However, perhaps as a result of better hospital facilities to deal with severe or adverse outcomes, the mortality and effects of the disease in patients with acute attacks have improved. Reports from a single centre reported that about three-quarters of patients with acute intermittent porphyria or variegate porphyria were able to lead normal lives after an acute attack. Recurrent attacks of pain occurred only in a minority during a period of prolonged follow-up; these recurrent attacks were most likely to occur in the first 3 years. The development of national centres for the treatment of por- phyria, the early detection of genetic predisposition in at-risk first- degree relatives, and the dramatic reduction in prescriptions of porphyrinogenic drugs, such as barbiturates and sulphonamides, together with better treatment of acute attacks can undoubtedly contribute to improved outcome. Nonetheless, acute porphyria re- mains potentially life-threatening, and deaths or marked disability due to prolonged, mismanaged, or undiagnosed attacks are all too frequent. Complications Acute encephalopathy—posterior reversible encephalopathy syndrome (reversible posterior leucoencephalopathy syndrome) This syndrome has been reported in exceptionally ill patients with acute porphyria. Clinically, the patient is confused and complains of headache, visual phenomena, and field loss, often accompanied by generalized seizures. Ischaemia of the occipital cortex during acute attacks with severe hypertension has been associated, in several in- stances, with failed recognition of colours or of human faces (proso- pagnosia) and cortical blindness. Magnetic resonance imaging typically reveals bilateral symmet- rical and gyriform lesions in the cerebrum and cerebellar hemi- spheres due to oedema. The lesions are initially hyperintense on T2-weighted images and prominent in the posterior regions of the occiput and pons as well as parietal lobes. Should the patient make a neurological recovery with stabilization of blood pressure, the radiological changes are potentially reversible over a matter of 1 to 2 weeks. However, in some cases permanent neurological impair-ment including visual changes and seizures is the result. Though un- common, death may occur with progressive swelling due to cerebral oedema, compression of the brainstem, increased intracranial pres- sure, or intracerebral haemorrhage. Posterior reversible encephalopathy syndrome may recur in about 5 to 10% of cases. This happens most commonly in cases accom-panied by hypertension, and where sustained or paroxysmal sys- temic hypertension is difficult to control or escapes clinical attention. Other neurological complications Rapidly recurrent attacks of porphyria may be associated with se- vere motor neuropathy and sustained hypertension; postural hypo- tension may result from autonomic neuropathy. Cranial nerve palsies can occur in severe cases, typically affecting the facial and vagus nerves. Chronic kidney disease Chronic kidney disease is frequently associated with hypertension and a common long-term comorbidity of the acute porphyrias, but es- pecially acute intermittent porphyria. Nearly all patients with recur- rent acute attacks are or will be affected, as revealed in a large cohort

 of 415 patients with confirmed deficiency of hydroxymethylbilane synthase and acute intermittent porphyria. Chronic kidney dis- ease arose over 10 years in nearly 60% of the symptomatic patients, in whom an annual decline in the glomerular filtration rate of ap- proximately 1 ml/min per 1.73 m2 was documented; proteinuria

was rarely observed. Renal histology showed a chronic tubulointerstitial nephropathy associated with a fibrous intimal hyperplasia and focal cortical atrophy. The effects of quasi-pathological amounts of por- phyrin precursors were examined and the investigators suggested that endoplasmic reticulum stress, apoptosis, and epithelial changes reflected injury to proximal tubular cells. Chronic kidney disease associated with acute porphyria should be considered in the presence of chronic tubulointerstitial nephropathy or focal cortical atrophy with severe proliferative arteriosclerosis. Hepatic carcinoma There are multiple reports of primary liver carcinoma in the three most frequent acute porphyrias: acute intermittent porphyria, varie- gate porphyria, and hereditary coproporphyria. Histological reports indicate that most of these tumours are hepatocellular carcinomas, but cholangiocarcinomas are also found. Annual incidences of 0.16 to 0.35% are reported in cohorts of patients followed. Tumours are associated with age over 50 years and undoubtedly more frequent in patient cohorts from Sweden and Norway, suggesting the presence of additional genetic factors due to at least one high-prevalence, cosegregating modifying factor. No consistent environmental co- factor (drug, hepatitis virus, or other features) has been identified. Specificity in relation to the acute porphyrias may not be ab- solute: the author has recently cared for an unusual patient, a 62- year-old man with congenital erythropoietic porphyria and with no other frank toxicity, iron storage, or hepatitis infection: a cryptic but ultimately fatal hepatocellular carcinoma developed at the time of splenectomy. Regular radiological surveillance of the liver, typically by ultra- sonography, is appropriate for older patients suffering from acute porphyria. Individual acute porphyrias These are, in a descending order of frequency: acute intermit- tent porphyria, variegate porphyria, hereditary coproporphyria, and Doss' porphyria (5-aminolaevulinate dehydratase deficiency). The first three of these disorders occur in at-risk heterozygotes for a single mutant allele in the cognate gene as autosomal dominant traits; 5-aminolaevulinate dehydratase deficiency is inherited as a very rare autosomal recessive trait. Acute intermittent porphyria This, the most frequent of the acute porphyrias, is caused by muta- tions in the porphobilinogen deaminase gene that maps to human chromosome 11q23 in which well over 200 mutations have been identified. Several widespread mutations have been identified in cer- tain populations, but most are reported in only one or two pedigrees. Two isozymes of the human porphobilinogen deaminase enzyme occur in the tissues: an erythroid mRNA variant and a nonerythroid transcript that encodes 17 additional amino acid residues in its N- terminus, leading to synthesis of a housekeeping ubiquitous isozyme and an erythroid-specific isozyme. Most mutations cause a decrease in the abundance as well as the activity of the porphobilinogen deaminase enzyme in all tissues. A few mutations associated with lack of the detectable protein product from the mutant allele are as- sociated with reduction of the housekeeping isozyme but normal enzymatic activity of the erythroid-specific isozyme. Thus, in such patients, hepatic porphobilinogen deaminase activity may be re- duced to approximately half normal values while the activity of the easily accessed red cell enzyme is within the normal range. A few mutations lead to the synthesis of a catalytically impaired but stable porphobilinogen deaminase protein from the cognate mutant allele, but these are a minority. Molecular analysis of the porphobilinogen deaminase gene in patients with acute intermit- tent porphyria has been very valuable in establishing diagnosis of latent heterozygotes at risk in the affected family, for the provision of appropriate counselling, and for the introduction of preventative strategies (see 'Latency or genetic penetrance'). Acute intermittent porphyria is characterized solely by acute porphyric attacks and cutaneous photosensitivity does not occur. In most instances, the patients do not notice any change in their urine, but when the urine is allowed to stand, the increased excretion of pyrroles leads to the formation of coloured oxidation products of porphobilinogen

(loosely called porphobilin), which may lead to obvious discoloration (Fig. 12.5.2). During the increased excretion of porphyrin precursors, water-soluble porphyrins, formed as a re- sult of nonenzymatic photochemical reactions, induce a pink discol- ouration. During severe acute attacks, copious excretion of pyrrole precursors, including porphobilin, may occasionally give the urine a striking appearance resembling blackcurrant juice or strong solu- tions of potassium permanganate. Latency or genetic penetrance The incidence and severity of acute attacks in acute intermittent por- phyria and variegate porphyria are generally greater than in heredi- tary coproporphyria. Various estimates indicate between 1 in 10 to 1 in 5 of heterozygotes experience acute attacks of porphyria during their lifetime; a study in France indicated penetrance of 23%. Recent large-scale studies using genomic/exomic sequencing data in white Fig. 12.5.2 Urine from a patient with acute intermittent porphyria around the time of an acute attack (left); control urine (right). A positive reaction with Ehrlich's diazo reagent is shown in the patient's urine following the addition of 50 µl urine to 1 ml of 2% acidic dimethyl benzaldehyde. Subsequent tests showed that the pink diazo adduct was insoluble in chloroform and other organic solvents indicating the presence of excess porphobilinogen. (Urobilinogen in excess may give a positive reaction with the diazo reagent but the product is readily extracted into organic solvents.)

12.5 The porphyrias 2043 persons identified nonsynonymous and two consensus splice-site pathogenic variants for a combined prevalence of approximately 0.00056. Since the estimated prevalence of acute attacks is approxi- mately 0.000005, and the estimated frequency of clinical pathogenic variants is approximately 0.00056, the penetrance of acute intermit- tent porphyria appears to be as low as 1% of all heterozygotes. Since the disease is monogenic, very low penetrance points to the exist- ence of modifying factors (environmental or genetic) that either pre- dispose heterozygotes to the acute attack or suppress expression of the disease. More recent research into acute intermittent porphyria from France has reconsidered the concept of autosomal dominant in- heritance with incomplete penetrance. This work examined the prevalence, penetrance, and heritability in affected pedigrees with 602 overt patients, 1968 first-degree relatives, and control samples from the general population. The pathogenicity of the 42 missense variants identified was assessed in silico, and also systematically in vitro by measuring residual enzyme activity of recombinant mutant hydroxymethylbilane synthases. The minimal estimated prevalence of acute intermittent porphyria in the general population was 1 in 1299. Thus, 50 000 subjects would be expected to carry the gen- etic trait in France, allowing penetrance to be estimated at 22.9% in affected families but in only 0.5 to 1% of the general population. Intrafamily studies showed correlations to be strong overall and modulated by kinship and the area in which the person was living, immediately pointing to a combination of interacting and strong influences of genetic and environmental modifiers on the expres- sivity of the trait in pedigrees. Null alleles were associated with a more severe phenotype and a higher penetrance than for other mu- tant alleles. The authors concludes that the striking difference in the penetrance of the mutant hydroxymethylbilane synthases between the general population and the French families affected by porphyria indicates that the inheritance does not follow the classical autosomal dominant model: expression of disease is modulated by strong en- vironmental and genetic factors that are independent of the 'causal' HMBS gene. In practice, increasing use of molecular diagnostic methods for screening at-risk families, institution of appropriate avoidance, and the careful dissemination of information to family members and their medical advisers will further reduce the likelihood of dis- ease in latent gene carriers. Latent carriers of acute intermittent porphyria have a high frequency of hypertension and, although this should be treated, the potential for inducing

attacks is in- creased by the uninformed prescription of antihypertensive drugs. Some patients appear to have depression and other chronic mental symptoms, and at least one survey has reported an increased prevalence of acute intermittent porphyria in patients attending long-stay psychiatric facilities, which again puts them at risk from the ill-considered use of porphyrinogenic neuroleptic and other psychoactive drugs. Variegate porphyria Variegate porphyria is particularly frequent among white South African people and other ethnic groups within that country. The condition is associated with typical acute attacks of porphyria as well as skin manifestations (the van Rooten skin). Acute attacks of porphyria occur very much as in acute intermittent porphyria. In a series of patients, more than one-half presented with skin lesions alone, one-fifth had acute neurovisceral disease, and a similar pro- portion had acute attacks as well as cutaneous disease. Cutaneous photosensitivity resembles that seen in porphyria cutanea tarda and hereditary coproporphyria (see ‘Hereditary coproporphyria’) with fragility, milia, hyperpigmentation, and hairi- ness of light-exposed skin. During acute sunlight exposure, vesicles and even large bullas may form. Microscopic examination of the affected skin shows deposits of immunoglobulin and hyaline ma- terial (that stains positively with periodic acid–Schiff reagent) in the dermal capillaries with proliferation of the basal lamina. As with porphyria cutanea tarda, ingestion of reproductive steroids (e.g. the oral contraceptive pill) may induce the cutaneous manifestations of variegate porphyria in otherwise latent heterozygotes. A few severely affected patients with variegate porphyria have inherited mutations of the protoporphyrinogen oxidase gene (that maps to chromosome 1q22–q23) from each parent, leading to homozygous ‘dominant’ variegate porphyria. These individuals pre- sent in childhood with a severe phenotype associated with marked photosensitivity and a neurological syndrome as described briefly in ‘Protoporphyrinogen oxidase’. Hereditary coproporphyria This condition is an infrequent and often mild form of acute por- phyria which may be associated with cutaneous manifestations. It is due to mutations in the coproporphyrinogen III oxidase gene that maps to chromosome 3q12 and is transmitted as an autosomal dom- inant trait of low penetrance. The condition usually presents with acute attacks of abdominal pain, as with the other acute porphyrias, and about 30% of patients develop cutaneous photosensitivity. As with some other porphyrias, several children presenting with marked photosensitivity in childhood have been shown to have in- herited a mutant allele of the coproporphyrinogen III oxidase gene from each parent giving rise to so-called homozygous dominant her- editary coproporphyria. Particular mutations in the gene are usually restricted to individually infected pedigrees. As with the other acute porphyrias, molecular analysis of the coproporphyrinogen III oxi- dase gene may be of value in identifying at-risk heterozygotes for genetic counselling and provision of appropriate advice about the prevention and management of symptomatic disease. 5-Aminolaevulinate dehydratase deficiency
(Doss’ porphyria) Only a few affected homozygotes for this recessive condition have been identified. Molecular analysis of the cognate gene has revealed the presence of compound heterozygosity and homozygosity for point mutations in the gene which map to chromosome 9q34. As with the porphobilinogen deaminase gene, there are two promoter regions and alternative noncoding exons that allow for the synthesis of housekeeping and erythroid-specific transcripts. Less than 10 cases of this porphyria have been reported, but it seems likely from the individual case histories of those identified that the disease will be under-recognized as the cause of acute abdominal crises, usually presenting shortly after puberty and associated with neurological symptoms, including respiratory paralysis. The condition resembles acute lead poisoning. The urine contains an excess of 5-aminolaevulinate but the excretion of porphobilinogen and tetrapyrrolic haem precursors is normal. Heterozygotes for aminolaevulinate dehydratase deficiency have been

reported in at

section 12 Metabolic disorders 2044 least one lead worker in whom peripheral neuropathy was ascribed to simple lead poisoning, but it may have resulted from the suscep- tibility of the residual 5-aminolaevulinate dehydratase to inhibition by environmental lead. Unusual genetic variants of the acute porphyrias (homozygotes or compound heterozygotes) In the last 20 years, very rare homozygous forms of porphyria have been recognized where the presence of two mutant alleles of the causative gene are responsible for severe clinical disease. Most in- dividuals affected prove to be compound heterozygotes for two mu- tant alleles of the cognate gene; true homozygotes are most likely to occur only in consanguineous pedigrees. Porphobilinogen deaminase (hydroxymethylbilane synthase) Bialleic mutations in the third enzyme in the haem biosynthetic pathway led, in one well-studied pedigree, to an unusual neurological syndrome with impaired cerebellar function and slowly progressive white matter disease with hypomyelination. There was also truncal muscle weakness and wasting, notably associated with ptosis, a clin- ical sign compatible with mitochondrial disease. Biochemical tests revealed excessive urinary porphobilinogen, 5-aminolaevulinate, porphobilinogen, and uroporphyrin. Furthermore hepta-, hexa-, penta-, and coproporphyrins I were highly increased in urine and typical of patients with acute porphyria during a metabolic crisis. The author suggests that these features indeed indicate a mitochon- drial defect, probably due to impaired oxidative phosphorylation related to the haem deficiency in critical cytochrome components of the electron transport chain, such as cytochrome c. Supportive evidence is provided by defective mitochondrial energetics in the brain and skeletal muscle of mice generated as homozygous mutants for the porphobilinogen deaminase locus, and by a patient having consistently elevated plasma lactate concentrations and metabolic acidosis. Intermittent hypoglycaemia was found in one patient who died at the age of 20 years due to cardiorespiratory failure; their sibling had died suddenly at 9 years of age of unknown causes. Despite greatly reduced hydroxymethylbilane synthase activity in these two sib- lings due to compound heterozygosity for adjacent base transitions in the same codon in exon 10 of the PBG deaminase gene, neither had any evidence of metabolic decompensation or the neurovisceral manifestations of an acute porphyric attack; neither of the biological parents had ever suffered acute porphyria. Coproporphyrinogen oxidase This is a very rare syndrome principally dominated by haemato- logical (erythroid) features of haemolytic anaemia accompanied by hepatosplenomegaly and marked photosensitivity. The patients thereby resemble those suffering from congenital erythropoietic porphyria (Gunther’s disease) due to biallelic mutations that induce marked deficiency of uroporphyrinogen III cosynthase. This presen- tation is associated with expression of a missense mutation, p.K404E, in either homozygous or compound heterozygous form with a dis- abling splice-site mutation in the COX gene. The hallmark of this disorder is the incomplete decarboxylation of the tetracarboxylic coproporphyrinogen III to yield excess tricarboxylic intermediate harderoporphyrin rather than the principal product of wild type coproporphyrinogen III oxidase, the dicarboxylic isomer and immediate haem precursor, protoporphyrinogen IX. These patients do not develop acute neurovisceral symptoms of acute porphyria. Protoporphyrinogen oxidase Patients harbouring biallelic mutations of protoporphyrinogen oxidase present in infancy or childhood with a severe phenotype associated with disfiguring photosensitivity accompanied by soft tissue mutilation, evidence of digital bone loss (osteolysis), and impaired cognitive development. Peripheral skeletal abnormal- ities include medially deviated and shortened fifth digits, known as clinodactyly, and slight growth retardation. A mild distal sensory neuropathy has been reported. There is later development of gen- eralized

seizures, usually during adolescence or early adulthood. Cranial magnetic resonance imaging reveals a leucodystrophy with hypomyelination of long tracts. Biochemical investigation reveals striking elevation of red cell and plasma protoporphyrin which is predominantly zinc-chelated, a feature of homozygous hepatic porphyrias. None of the patients so far reported has devel- oped attacks of acute porphyria. Ferrochelatase Although homozygous ferrochelatase deficiency (protoporphyria) is not strictly related to an acute porphyria, patients who are com- pound homozygotes or true homozygotes have a severe photosensi- tivity syndrome that is more frequently complicated by accelerated cholestatic liver disease and pigment cirrhosis. However, the pos- ition is etymologically complex, since generally only those who in- herit a mutation on one FECH allele and a polymorphism in trans on the other allele, which is common in general European popula- tion and diminishes expression of the ferrochelatase, develop clin- ical manifestations. Such patients are not conventional compound heterozygotes since the polymorphism is common in the apparently healthy population (c.11% of Europeans). However, rare individuals with biallelic inheritance of disabling FECH mutations appear to be especially predisposed to the development of cholestatic liver dis- ease with cirrhosis that aggravates the photosensitivity and leads to a potentially fatal outcome unless liver transplantation is undertaken. Individual cutaneous porphyrias Congenital erythropoietic porphyria Congenital erythropoietic porphyria (Gunther’s disease) is a classic but very rare syndrome now known to have an astonishing range of presentation from severe haemolytic anaemia in utero or severe photosensitivity presenting soon after birth (with excess porphyrins staining the teeth and urine) to mild late-onset forms presenting with skin lesions in adult life. Most patients have a mild to severe haemolysis with increased reticulocytosis, circulating normoblasts, decreased serum haptoglobin, and increased unconjugated bilirubin concentrations. Inclusion bodies are often seen in marrow, erythroid cells, and circulating normoblasts. Splenomegaly develops in child- hood, thereby causing pancytopenia as a result of hypersplenism; this accelerates the haemolysis and leads to compensatory erythro- poiesis in the bone marrow. Under these circumstances, splenec- tomy may help to control the condition. The classic skin manifestations are of severe blistering lesions on sunlight-exposed skin, particularly of the hands and face, with the

 formation of vesicles and bullae that may become infected. There are pigmentary changes with greatly increased skin fragility. Healing of the lesions with or without consequential infection often leads to cutaneous deformities with loss of digits, scarring of the eyelids, nose, lips, ears, and scalp, and occasionally blindness due to corneal scarring (Fig. 12.5.3). Examination of the teeth shows erythrodontia and deformities, and exposure to ultraviolet light may reveal striking dental fluorescence. The condition is associated with osteoporosis (a) (b)
Fig. 12.5.3 Congenital erythroid porphyria (Gunther’s disease). (a) Pinnae and hand showing porphyrin deposits and tissue destruction due to photonecrosis. (b) Splenomegaly. (c) Successive urine samples before and after splenectomy showing progressive postoperative reduction in porphyrinuria (uroporphyrin I and coproporphyrin I).

 and resorption of long bones as a result of gross expansion of the erythroid bone marrow. Mutations in the uroporphyrinogen III synthase gene that maps to chromosome 10q25.3–q26.3 have been shown to be respon- sible for this disease and thus may assist in the prenatal diagnosis of mothers who have previously given birth to an affected infant and are harbouring an at-risk pregnancy. Constitutive activation of the haem biosynthetic pathway in erythroid cells leads to persistent overproduction of uroporphyrinogen I and coproporphyrinogen

I as by-products of the defective synthesis of uroporphyrinogen III, the sole precursor of protoporphyrin IX and haem. These reduced and colourless metabolites become oxidized to the fluorescent tissue and urinary porphyrins associated with the passage of pink urine that characterizes this often devastating disease. Several infants and children with congenital erythropoietic por- phyria have been successfully treated by haematopoietic stem cell transplantation (HSCT) and this remains a convincing option for treatment of this very severe and otherwise life-shortening in- born error of haem metabolism. Splenectomy is often required in early childhood to reduce transfusion requirements and improve cytopenias (Fig. 12.5.3). It has recently been identified that an ap- proved antifungal agent, ciclopirox, binds allosterically to and stabilizes several naturally occurring uroporphyrinogen III syn- thase human mutants and restores their activity. This may lead to an innovative treatment for this severe and destructive disease, which currently lacks molecular therapy. Porphyria cutanea tarda This disease is the most common of the cutaneous porphyrias and, unlike other hepatic porphyrias, is never associated with acute porphyric crises. It is characterized by skin blistering which is re- lated to sunlight exposure. Aetiology Toxic cutaneous porphyria may result from environmental exposure to dioxin or to hexachlorobenzene, particularly after industrial accidents such as that which occurred in Turkey in the 1960s. Occasional cases have been reported after exposure to other halo- genated phenols, but under these circumstances it appears simply to be an environmental toxic syndrome which is separate from the sporadic porphyria cutanea tarda that is precipitated by other spe- cific environmental factors including increased hepatic storage iron, excess ethanol consumption, administration of oestrogens, hepatitis C virus infection, human immunodeficiency virus infection, and (possibly) nutritional deficiencies including antioxidants such as vitamin C. Most individuals who develop sporadic porphyria cutanea tarda prove to have increased iron stores in association with the presence of one or more mutant alleles for the HFE gene that also predispose to the development of hereditary adult haemochromatosis. Many patients also consume excess alcohol and smoke. There is a clear as- sociation with renal impairment in which the development of the disease can be explained by the presence of iron overload (as a result of defective iron utilization with or without routine iron supplemen- tation, particularly in patients on haemodialysis) and failure to ex- crete excess plasma porphyrins that do not readily diffuse through the peritoneal cavity or haemodialysis membranes. In sporadic porphyria cutanea tarda, there is a partial defi- ciency of uroporphyrinogen III decarboxylase activity in the liver and no family history of the condition. The sequencing of the human uroporphyrinogen decarboxylase gene that maps to human chromosome 1p34 has not provided any evidence of mutations to account for the tissue-specific enzyme deficiency, and no isoforms of the enzyme have yet been identified, hence the molecular patho- genesis of sporadic porphyria cutanea tarda remains unknown, but it is clear that iron and other environmental influences inactivate the hepatic enzyme. The relationship between regulators of iron homeo- stasis and the demand for haem biosynthesis in the hepatocytes of affected individuals is not understood, but it appears likely from studies in experimental animals that genetic variation in the ex- pression and activity of cytochrome isozymes such as P450 IA2 may be critical for disease expression. Irreversible inhibition of hepatic (c) Pre-operative Day of surgery Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 1 2 3 4 5 6 7 8 9 10 11 Fig. 12.5.3 Continued

12.5 The porphyrias 2047 Fig. 12.5.4 Porphyria cutanea tarda in a 60-year-old heterozygote for the HFE p.C282Y mutation. This man, a taxi driver, had noticed irritation after exposure of his hands to light transmitted through the windscreen. He had noticed fragility and blistering combined with pigmentary changes typical of this disorder. After treatment by controlled phlebotomy his skin

complaint has regressed. uroporphyrinogen decarboxylase may also explain the occurrence of toxic porphyria cutanea tarda after exposure to halogenated hy- drocarbons, metabolites of which cause experimental uroporphyria in animals. Less than one-quarter of patients who have porphyria cutanea tarda show a familial susceptibility to the condition, when muta- tions in one allele of the human uroporphyrinogen decarboxylase gene lead to catalytic deficiency of the enzyme in all cells, including erythrocytes. In most instances, the genetic defect leads to par- tial reduction of the enzyme protein encoded by the mutant allele. Studies of pedigrees affected by familial porphyria cutanea tarda indicate that expressivity of the trait is very low; less than 10% of heterozygotes develop clinical disease. Conversely, a very few pa- tients present with a syndrome that closely resembles congenital erythropoietic porphyria with marked blistering skin lesions, excess hair growth, and cutaneous scarring in association with the excre- tion of pink or red urine. These individuals represent a homozy- gous form of uroporphyrinogen decarboxylase deficiency, termed hepatoerythropoietic porphyria, associated with a variety of muta- tions in the uroporphyrinogen III decarboxylase gene. In hepatoerythropoietic porphyria, the activity of uro porphyrinogen decarboxylase is markedly deficient, although re- sidual activity remains to preserve essential haem biosynthesis in the erythron and liver. Most patients ultimately develop spleno- megaly with accelerated haemolysis closely resembling con- genital erythropoietic porphyria. Molecular analysis of the human uroporphyrinogen decarboxylase gene may assist the prenatal diag- nosis of at-risk pregnancies in women who have already given birth to an affected infant. Clinical features The clinical features of porphyria cutanea tarda of whatever form are very characteristic and are confined to light-exposed skin (Fig. 12.5.4). Usually, the only signs are of erosions resulting from minor trauma in skin, with increased fragility as a result of light ex- posure, typically on the dorsum of the hands. Other changes include the development of large subepidermal bullae after exposure to light, which may burst leaving ulcerated lesions that are slow to heal. Increased pigmentation, often accompanied by areas of decreased pigmentation, is a common feature combined with increased hair growth, particularly on the face. Patients with porphyria cutanea tarda do not always notice the photosensitivity and rarely experience marked pain unless exposed to brilliant sunlight. Occasionally, there is evidence of dermal injury and loss of nails, damage to the conjunctivae, and hair loss. Careful examination of the affected areas shows small depigmented cuta- neous scars and the formation of milia. If bacterial infection occurs and there is repeated exposure to sunlight, then severe and per- manent scarring may result. Typically, porphyria cutanea tarda occurs in middle-aged men with a history of alcohol use and in women after institution of oestrogen replacement therapy; in young persons, infection with hepatitis C or the immunodeficiency virus may precipitate dis- ease expression. Frank signs of hepatomegaly or iron overload are rare in porphyria cutanea tarda but have been noted; as with adult haemochromatosis, there is a significantly increased frequency of hepatocellular carcinoma. Occasionally patients with porphyria cutanea tarda may notice an increase in urine excretion of formed porphyrins which, especially after concentration overnight, may resemble the colour of tea or cola. The stool and urine contain large quantities of coproporphyrins and uroporphyrins that fluoresce intensely on exposure to long-wavelength ultraviolet light when placed in a suitable vessel for its transmission (namely silica rather than standard glass). Similarly, examination of liver biopsy specimens under ultraviolet light reveals bright red/orange fluorescence; microscopic examination may also show coincidental hepatitis with or without excess deposits of stain- able tissue iron reflecting the increased iron storage of this disease. In sporadic porphyria cutanea tarda, increased storage iron is re- flected by the modest elevations of serum ferritin that often occur in association with the presence of one or more copies of the C282Y allele of the HFE gene that maps to human chromosome 6 and which is

associated with adult haemochromatosis. Treatment Sunlight exposure should be avoided as much as possible and sun- block creams used until the porphyrin abnormality is corrected. Care is needed to protect fragile skin from mechanical injury and from infection. Patients should be advised to moderate or stop their intake of alcohol and avoid the use of iron tonics and sex hormones, especially oestrogens. Screening should be undertaken for chronic infection with human immunodeficiency virus and hepatitis viruses, especially hepatitis C. Management should also include imaging or biopsy of the liver if serum liver-related tests are abnormal, as well as measurement of serum α-fetoprotein since there is a risk of hepatocellular carcinoma in this disease. Most patients with porphyria cutanea tarda respond to iron de- pletion by phlebotomy and initial iron status should be determined by measuring serum ferritin concentrations. Weekly or fortnightly removal of 500 ml of blood will usually correct the abnormal urine and plasma porphyrin profile within a few months, but maintenance phlebotomy will be required, usually amounting to the removal of 2 to 4 units of blood at intervals each year. Successful therapy re- duces the urinary excretion of porphyrins to normal. Patients with

section 12 Metabolic disorders 2048 porphyria complicating renal failure should be treated with recom- binant human erythropoietin and depleted of iron by gentle phle- botomy or parenteral desferrioxamine if necessary. The cutaneous manifestations of porphyria cutanea tarda respond rapidly to low-dose chloroquine treatment, which should be con- sidered in patients with persistent symptoms or at the outset before iron storage has been fully corrected. This action of chloroquine was discovered empirically, but the agent forms complexes with uroporphyrin deposits and promotes their external cellular disposal, promoting excretion of uroporphyrin from the liver and inducing marked but transient porphyrinuria. Although chloroquine usually provides rapid relief from the cutaneous disease and photosensi- tivity, it does not correct the underlying metabolic defect in the liver and its long-term use is not recommended unless the other pro- vocative factors in porphyria cutanea tarda have been removed. The usual effective dose of chloroquine is 100 to 200 mg given once or twice weekly; larger doses are associated with marked hepatic tox- icity in porphyria cutanea tarda. The drug is reported to have no therapeutic effect on other photosensitive porphyrias. (Erythropoietic) protoporphyria and X-linked protoporphyria Protoporphyria is caused by the overproduction of the immediate precursor of haem, protoporphyrin IX, principally in the bone marrow. It causes an unusual cutaneous photosensitivity syndrome that presents in infancy and is a neglected cause of fatal hepatobiliary disease in about 5% of those affected. Genetics Protoporphyria is inherited as a recessive condition but often generation-to-generation transmission of the disease has been ob- served. An original ingenious postulate of an autosomal three-allele mode of transmission has been further refined by the remarkable identification of causal mutations at three distinct chromosomal loci—the ferrochelatase gene (FECH on chromosome 18q21.31), the erythroid 5-aminolaevuliate synthase gene (ALAS2, which maps to Xp11.21), and the caseinolytic mitochondrial matrix peptidase chaperone subunit gene (CLPX, localized on chromo- some 15q21.32). Inheritance of mutations in the coding region of the ferrochelatase gene that partially inactivate the enzyme are coinherited in the trans isomer with a low-expression allele (FECH IVS3–48T>C) that occurs at polymorphic frequency (c.10%) in the population, which gives rise to apparent dominant transmission in some families. Parent-to-offspring transmission of protoporphyria occurs in less than 10% of cases, but in all instances of the disease there is a marked deficiency of the enzyme ferrochelatase (substan- tially <50% of control values). The asymptomatic carrier parent only shows mild ferrochelatase deficiency with occasional fluorescent red cells that are even visible on examining the unstained blood film by conventional

ultraviolet light transmission microscopy. A few patients, usually with clinically severe protoporphyria, have biallelic mutations in ferrochelatase—true recessive protoporphyria—and these may be predisposed to the severe cholestatic liver disease described in several pedigrees. Since ferrochelatase, an iron-sulphur cluster protein located on the inner mitochondrial membrane, is responsible for the final step of haem biosynthesis in the inner mitochondrial membrane, where it catalyses the insertion of ferrous iron into the protoporphyrin IX macrocycle, partial deficiency of this enzyme will give rise to the compensatory increase in protoporphyrin abundance and hence the consequential photodynamic effects of protoporphyria. These findings are reflected in a large series of 226 patients with a clinical and biochemical diagnosis of protoporphyria from the United States of America. This demonstrated an equal sex distri- bution and mean age of 37 years. A ferrochelatase mutation and the common low-expression mutation was detected (presumed in trans) in 186 (82.3%) and only one patient had two FECH mutations. Twenty-two patients had X-linked protoporphyria (9.7%; 10 male and 12 female). Of note, nine patients (4.0%) had symptomatic and biochemical evidence of protoporphyria but no detectable mutation in the FECH or ALAS2 genes (see following subsections). CLPX gene-related protoporphyria Several patients with clinical and biochemical protoporphyria but lacking FECH or ALAS2 mutations have been shown to harbour heterozygous mutations in an unusual AAA+ (ATPases associated with diverse cellular activities) protease, caseinolytic mitochondrial matrix peptidase chaperone subunit (ClpXP), of the Clp protease complex that regulates ALAS2 activity among other mitochondrial proteins. The gene CLPX encodes a chaperone subunit that confers ATP-dependent specificity of the Clp protease complex, which acts as an unfolding enzyme that regulates ALAS1 and ALAS2 proteins. Another action of the protein is to facilitate incorporation of the essential pyridoxal 5′-phosphate cofactor into 5-aminolaevulinate synthase. Detailed studies in several experimental systems of the first mu- tant ClpXP protein in a family with protoporphyria but no muta- tions in either FECH or ALAS2 genes convincingly showed that the mutation would disrupt the ATP binding domain of the protein but leave the activating and stabilizing chaperone function towards the ALAS pyridoxal cofactor intact. The predicted net effect would be activation of the ALAS2 enzyme in erythroid cells and in effect protoporphyrin substrate overdrive at the next rate-limiting step in the pathway, ferrochelatase. These are early findings and more com- prehensive genetic studies are needed fully to explore the role of ClpX mutations in erythropoietic protoporphyria. X-linked protoporphyria X-linked protoporphyria is due to inheritance of gain-of-function variants of ALAS2 enzyme in which erythroid precursor cells over- produce 5-aminolaevulinate and accounts for 5 to 10% of patients with a diagnosis of protoporphyria. While this disorder also demon- strates generation-to-generation transmission and may erroneously be considered as a dominant trait of variable penetrance, the ALAS2 gene on the short arm of the X chromosome undergoes gene-dosage compensation by lyonization. Females with the trait may be asymp- tomatic and—as somatic mosaics—show greater variability of clin- ical expression than affected males within their pedigree. Diagnosis The detection of markedly increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin is the most sen- sitive biochemical diagnostic test for this disease. Identification of pathogenic gain-of-function variants affecting the last exon of ALAS2, the gene encoding erythroid-specific 5-aminolaevulinate synthase 2, confirms the diagnosis. These mutations have proved

 to be sequence variants in exon 11 and in other coding and spli- cing regions. Thorough expression studies of the cognate isozyme show consistently enhanced catalytic activity for the formation of aminolaevulinate, which in the pathological milieu of erythroid

precursor cells in protoporphyria presumably leads to a relative, secondary bottleneck at the level of ferrochelatase with the conse- quential constitutive overproduction of protoporphyrin IX. Clinical features and pathology Skin disease Protoporphyria characteristically presents with severe burning pain and cutaneous irritation on exposure to visible light and is usually obvious in infancy or early childhood. Erythema and diffuse oe- dema may follow marked light exposure, but vesicles, blistering, and altered skin fragility are most unusual. After several years, increased pigmentation and thickening of the skin (lichenification) occur, es- pecially over the knuckles. A typical feature is of shallow scarring in the malar regions of the cheeks and at the angle of the lips, where scarring is termed ragades. Overt scarring is unusual. There are no changes in urine colour. Protoporphyria is often the subject of de- layed diagnosis because of the marked disparity between the severity of the symptoms and the development of physical signs in the skin. The cutaneous pathology results from photoactivation of red cell- and plasma-derived protoporphyrin IX in skin capillaries (Figs. 12.5.4 and 12.5.5). Protoporphyrin IX is a hydrophobic mol- ecule that dissolves in cell membranes; it has a photoactivation spec- trum in the Soret region with subsidiary activation by green and yellow light. Photoinjury is associated with complement activation and release of vasoactive factors; there is intracellular epidermal oedema accompanied by acute inflammatory changes and extrava- sated red cells. Deposits of hyaline material are found in superficial capillaries with thickening of the basement membranes. Haematological and liver disease Mild hypochromic microcytic changes with mild anaemia are usually the only manifestations of disturbed haem biosynthesis and iron metabolism in the bone marrow, although examin- ation of the marrow may reveal occasional sideroblasts with intramitochondrial iron deposits. Haemolysis is usually clinically insignificant until severe cholestatic hepatic disease occurs, when splenomegaly and hypersplenism aggravate haemolysis. The photosensitivity worsens under these circumstances and there is upper abdominal pain with splenic enlargement, jaundice, and ex- treme photosensitivity as concentrations of free protoporphyrin in the plasma rise (Fig. 12.5.6). A vicious cycle of decompensation is established with either fulminant hepatic failure associated with cholestasis due to protoporphyrin deposits within biliary radicals, or the development of cirrhosis. Without treatment (hepatic trans- plantation) the prognosis is dismal. Protoporphyria is normally associated with trivial abnormalities of serum liver-related tests but in a few patients micronodular cirrhosis with pigment deposition occurs. Examination of the liver under po- larized light shows birefringent crystals with a characteristic Maltese- cross appearance, and examination under long-wave ultraviolet light reveals bright fluorescence. Gallstones containing precipitated protoporphyrin occur frequently, but cholestasis results principally from intracellular and canalicular precipitation of protoporphyrin. Deteriorating hepatic disease is heralded by generalized abdominal pain, splenic enlargement, worsening jaundice, and haemolysis. Treatment Interruption of the enterohepatic circulation of protoporphyrin with charcoal or polymeric cationic resins, such as cholestyramine, may arrest the early downhill course by binding protoporphyrin or promoting hepatic bile acid secretion. However, once established, hepatic decompensation and accelerating photosensitivity is rapid. Haematopoietic stem cell transplantation or bone marrow transplantation Studies in mice and in a few human patients with protoporphyria confirm that the disease can be arrested, and in practical terms Fig. 12.5.5 Fluorescence microscopy of an unstained blood film from a patient with erythropoietic protoporphyria. Note the fluorescence of increased free protoporphyrin within individual young erythrocytes and reticulocytes. Fig. 12.5.6 Examination of human plasma under long-wave ultraviolet light. Plasma on the left was obtained from a patient with protoporphyrin hepatopathy and greatly increased photosensitivity. On the right is plasma obtained from a healthy subject. Maximum fluorescence was obtained by exposure to visible light in the violet and green–

yellow spectral regions, corresponding to the absorbance bands of protoporphyrin. Note the bright red fluorescence due to the presence of high concentrations of free protoporphyrin.

section 12 Metabolic disorders 2050 completely corrected by HSCT or bone marrow transplantation. Carried out sufficiently early, HSCT allows at least partial recovery of the damaged or failing protoporphyric liver and is the ideal pro- cedure in patients who are at high risk of fatal liver disease: por- phyrin biochemistry is corrected and photosensitivity is no longer present, liver-related tests and imaging can be restored to healthy values. Theoretically, the definitive therapy of protoporphyria will re- quire restoration of erythroid cell ferrochelatase activity in bone marrow. There is a single report of successful marrow transplant- ation in protoporphyria with coincidental myeloid leukaemia. This procedure cured the symptomatic protoporphyria. In future, either bone marrow transplantation or erythroid progenitor gene therapy will be used to correct this disease in patients with life-threatening liver sequelae. Ancillary treatment by blood transfusion or red cell exchange transfusion will reduce the immediate source of plasma and red cell protoporphyrin, and in the immediate preoperative period plasmapheresis may also reduce phototoxicity.
Liver transplantation Established severe protoporphyrin hepatotoxicity remains an in- dication for liver transplantation, but even successful treatment is likely to be complicated by recurrence of the disease in the engrafted liver, with the pace at which the liver deteriorates being difficult to predict. For these reasons, some patients will be considered for serial hepatic and marrow transplantation/HSCT. There is evidence that splenectomy may reduce the haemolytic component of end- stage protoporphyria, hence consideration should be given to the simultaneous removal of the enlarged spleen at the time of the liver transplantation. In some patients with end-stage liver disease due to proto porphyria, a bizarre neurological syndrome has been identified. Axonal neuropathies requiring mechanical ventilation and cranial nerve palsies have been reported in the perioperative period. Under these circumstances, coproporphyrin and uroporphyrins appear in the urine and may account for a blistering photosensitivity in end- stage protoporphyric liver disease.
Operative treatment in patients with protoporphyria can be very dangerous as a result of phototoxic injury to visceral tissues and mucous membranes exposed to brilliant vertical lighting in the operating theatre. Surgical lights are best attenuated by the use of filters that reduce spectral power output below 530 nm; such precau- tions should be used throughout the perioperative period to reduce overall phototoxicity in the clinical environment. Management of photosensitivity
Photosensitivity is managed by avoiding excessive light exposure, remembering that visible light of exciting green and violet wave- lengths traverses ordinary window glass. Effective sunscreen prepar- ations may assist management, especially in young children at risk. For many years, β-carotene has been given to patients with protoporphyria: it may absorb light energy at the appropriate wave- lengths and also serve as a free-radical quenching agent. The prep- aration Lumitene at a dosage of 120 to 180 mg/day is normally used. This causes orange staining of the skin due to carotenaemia, but is otherwise well tolerated and may improve tolerance to sunlight when plasma carotene concentrations between 10 and 15 µmol/ litre are achieved. A recent review of 20 studies of concluded that β-carotene had only small or marginal objective benefit for the light- induced symptoms of protoporphyria. Melanin, in the form of eumelanin, quenches ultraviolet light and scavenges free radicals; it also acts as a neutral density filter that re- duces all wavelengths of light. Moreover, melanogenesis may pro- vide a major antioxidant drive. Increasing melanin formation in the epidermis by narrow-band phototherapy has been shown to im- prove phototoxic symptoms in five patients with protoporphyria, whose tolerance of a standardized source of high-radiance xenon light improved progressively over 120 days. While the narrow-band

phototherapy requires careful exposure protocols and is reserved for specialist centres, the benefit gained provides proof of concept for the exploration of other means to stimulate melanin synthesis. Administration of a depot preparation of afamelanotide, an α- melanocyte-stimulating hormone analogue, has been explored in clinical trials in patients with protoporphyria in Europe and the United States of America. Compared to placebo, subcutaneous implants of the drug given every 60 days increased the patients' hours of direct exposure to sunlight, greatly reduced the number of phototoxic reactions, and the patients' quality of life improved. Adverse events were mostly mild, serious adverse events were not considered to be related to the afamelanotide, and it has received marketing approval as Scenesse for this indication in the European Union since 2014. Treatment of an acute porphyric attack It is essential to establish that the symptoms complained of are caused by an acute attack of porphyria. Of key importance is the careful la- boratory analysis of urine and blood early in the course of the illness. This demonstrates elevated concentrations of porphyrins and haem precursors typified by elevated urinary 5-aminolaevulinate and porphobilinogen, which should be high in an attack of acute por- phyria. The urine sample should be freshly taken from the patient and protected from light before analysis to avoid nonenzymatic conversion of the porphyrin precursors to porphyrins and hence misdiagnosis.
Immediate management An immediate and fastidious review of avoidable factors that would precipitate or aggravate an attack is mandatory. The precipitating factors are usually drugs, alcohol, exogenous or endogenous hor- monal changes, fasting (including that due to dieting), or recent surgical procedures. More than 100 drugs may induce attacks of porphyria (Boxes 12.5.1 and 12.5.2). Particular care should be taken to exclude agents that are obtained over the counter as tonics or herbal remedies. Any agent that might be implicated should be stopped immediately. Abdominal pain and distress, together with anxiety, require prompt treatment; opiates which are safe in porphyria may be useful, although they often exacerbate constipation. Opiates may be com- bined with phenothiazine tranquillizers such as chlorpromazine, which may usefully potentiate their action. Since starvation induces attacks of porphyria and haem biosyn- thesis may be suppressed by the ingestion of carbohydrate, it is advised that patients with minor attacks should eat regular meals containing carbohydrate in a complex form such as starch for its

 slow release. One-half to two-thirds of the energy intake should be derived from ingested carbohydrate. The management of an acute attack should involve repeated moni- toring for the development of hyponatraemia, which may be very se- vere as a result of inappropriate secretion of antidiuretic hormone. In the past, intravenous glucose or fructose solutions have been ad- vocated as a means to suppress haem biosynthesis in the liver. Great caution is needed in the use of these agents, either as 5 or 20% solu- tions, since they exacerbate hyponatraemia and may cause fatal cere- bral oedema. In the author's view, if the patient is sufficiently unwell not to be able to control the attack with oral carbohydrate-rich food, parenteral preparations of haem such as haem arginate, rather than glucose or other sugar solutions, should be administered. Haem therapy Haem arginate is administered by a short intravenous infusion in porphyric crises of sufficient severity to merit hospital admission or those associated with limiting pain or metabolic disturbance. Haem arginate supplied by Orphan Europe (see 'Sources of information) is provided as a stable 25 mg/ml concentrate and should be adminis- tered at a dosage of 3 mg/kg body weight (to a maximum dose of 250 mg) once daily for up to 4 days. It should be given in 100 ml physio- logical saline infused into a large vein over at least 30 min. Haem arginate, like all preparations of haem, tends to polymerize and is unstable, hence the administration should be completed within 1 h after diluting the concentrate, the shelf-life of which

is about 2 years. In the United States of America, haemin appears to be a compar- able preparation for suppressing hepatic haem synthesis and cor- recting the metabolic disturbance of the acute attack. Haem arginate and a preparation of haem albumin are apparently somewhat more stable than haemin, which tends to produce phlebitis or interfere with the action of coagulant proteins. Recovery from an acute attack depends on the degree of damage to the nervous system and may occur within 1 or 2 days if haem therapy is introduced at the outset. Certain proof of clinical benefit of haem treatment is lacking, but there is sufficient evidence of its benefit for it to be approved in 19 countries, including the United Kingdom. Haem arginate has a rapid effect on the excretion of aminolaevulinate and porphobilinogen in acute porphyria, and retrospective studies suggest that outcomes are better than that in patients previously documented before the use of the agent. Moreover, the results of a double-blind study com- paring placebo and haem therapy showed a trend in favour of haem arginate in terms of duration of hospital stay and the requirement for pain relief, although the differences did not quite reach statistical significance in the limited study of 12 patients. On the balance of probabilities, however, the evidence for a beneficial effect of haem arginate therapy, particularly at the onset of a porphyric attack, is compelling. Haem therapy should be used in any patient with significant hyponatraemia, incipient neuropathy, seizures, or bulbar paralysis, and in any patient with severe symptoms, particularly of abdominal pain. It must be recognized that patients with established neuropathy may take many months or even years to recover from an attack and, if it is to be effective, haem therapy should be introduced early. Occasional patients, usually women, are seen in whom repeated acute attacks occur irrespective of the use of one or two courses of haem arginate. The reason for this is unknown, but it is pos- sible that haem arginate therapy induces tachyphylaxis as a result of exaggerated oscillation of haem catabolism by the induction of haem oxygenase in the liver. Tin protoporphyrin, an inhibitor of haem oxygenase, has been considered in this circumstance. This agent is only available in specialist centres and, because it contains toxic heavy metal and itself may induce photosensitivity, is currently not recommended for routine use. Hypersensitivity reactions to haem arginate are rare and the drug has been used during attacks in pregnant women without injury to either the mother or the child. Haem contains 10% by weight of iron and the maximum daily dose of haem arginate would contain only 23 mg of elemental iron; the development of iron storage disease is unlikely, except in very rare instances where an acutely ill patient receives numerous infu- sions of haematin over prolonged periods. However, patients who have received regular haem arginate infusions over more than 10 years have developed iron accumulation, with increased serum ferritin concentrations and magnetic resonance signals indicating iron accumulation in the liver, spleen, and bone marrow. Such iron accumulation has been associated with histological evidence of hep- atic fibrosis and emphasizes the need for careful evaluation of the relative harm and benefits of treating refractory disease by haem arginate or liver transplantation.

Carbohydrate loading Where haem therapy is not available, parenteral carbohydrate loading is the only alternative treatment for an acute attack; 2 litres of a 20% weight per volume glucose solution is recommended over a 24-h period, administered through a central venous catheter. There are risks from giving such therapy as outlined previously and in the author’s opinion the treatment has been superseded by the introduc- tion of stable preparations of haem. Management of complications of acute porphyric attacks Hypertension Hypertension is frequent in porphyric attacks and may be very se- vere as a result of sympathetic overactivity; during the attack, sinus tachycardia is frequent. β-Blockers are effective in the control of the hypertension and labetalol and propranolol are safe; they also relieve the sinus tachycardia. Hyponatraemia and seizures Hyponatraemia may be very severe and in acute porphyria pro- gresses on a daily basis during the

course of the acute attack in most patients. The rapid onset of severe hyponatraemia clearly contributes to confusion and other mental symptoms associated with a porphyric attack. Prompt treatment by fluid restriction and appropriate careful use of hypertonic saline is needed (see Chapter 22.2.1). The place- ment of a patient with porphyric abdominal pain on a surgical ward, with the almost inevitable administration of an intravenous infusion of 5% dextrose, may contribute to death as a result of cerebral oe- dema or the complications of rapid-onset hyponatraemia. Grand mal seizures in acute porphyric attacks pose a par- ticular problem for management; they are often precipitated by the hyponatraemia that frequently complicates an acute attack. Clearly, from every aspect, prevention is the optimal course of action and appropriate management of the electrolytic abnormality is an

section 12 Metabolic disorders 2052 essential element of treatment. Even in an era of greater awareness, fits and status epilepticus occur and pose special difficulties. Seizures have been treated successfully with parenteral diazepam or the re- lated benzodiazepine, temazepam. Carbamazepine, lorazepam, and midazolam are probably (but not definitely) safe in acute por- phyria. Clonazepam and valproate have each been used for seizure prevention; the generally outmoded therapy of bromide may also have a role. Acetazolamide, which has been used as a minor agent in seizure prophylaxis, has been used safely in acute porphyria, but many first-line drugs such as carbamazepine, sodium valproate, phenytoin, and chloral hydrate have been classified as unsafe or are frankly porphyrinogenic. Primidone and phenobarbitone are abso- lutely forbidden. Further problems arise in the management of acutely disturbed patients who are not responsive to the safe but outdated phenothia- zine, chlorpromazine. Thioridazine is classed as unsafe, but paren- teral haloperidol was used with good effect in a few patients with uncontrollable or life-threatening manic aggression and paranoid disturbance during their acute attack. In all instances, prescription of any agent to a patient who has had or is having an acute porphyric crisis must involve consultation with a reliable pharmacopoeia with individual drugs categorized for safety (see Boxes 12.5.1–12.5.3). Cimetidine The ability of most drugs to initiate attacks of porphyria appears in many instances to be related to their effects on the induction of haem biosynthesis in the liver and specifically for the formation of the relevant P450 xenobiotic-metabolizing isoforms. One key isoform involved in the induction of porphyria is inhibited, at least in vitro, by the H2 antagonist cimetidine. It has been reported that cimetidine at 400 to 800 mg daily is sufficient to inhibit induction of this P450 isozyme in adult humans. Cimetidine has been ad- ministered with occasional success as a means to inhibit or control spontaneous porphyric crises and as a last resort it might be con- sidered in patients with life-threatening and otherwise uncontrol- lable disease. Prevention and management of recurrent acute porphyric attacks Hormonal interventions Young women with cyclical porphyric attacks may benefit tem- porarily from hormonal intervention by the use of gonadotropin- releasing hormone analogues such as goserelin or buserelin. These agents inhibit androgen, oestrogen, and progestogen production and as a result they induce menopausal-like symptoms and depres- sion, as well as rapid decreases in trabecular bone density. Doses sufficient to suppress luteinizing and follicle-stimulating hormone concentrations in serum are required. Prolonged use for more than a few months is not recommended, but buserelin may be used intranasally and may be more convenient. To avoid the worst aspects of hypogonadism in women, low-dose oestrogen therapy under ap- propriate gynaecological supervision may be coadministered once cyclical porphyric attacks have come under control. Given the risk of accelerated skeletal demineralization and osteoporosis, it is prudent, especially in women, to monitor bone mineralization density in pa- tients receiving

gonadotrophin-releasing hormone analogues and to use appropriate bone conserving therapy as advised. Acute perimenstrual attacks can be controlled by the prompt ad- ministration of haem arginate for 1 to 2 days at the predicted time of susceptibility. Liver transplantation The combination of recurrent life-threatening porphyric attacks and poor venous access for administration of therapeutic haem prepar- ations, or unresponsiveness to haem treatment, has led to the use of liver transplantation in a few young women with this disease. This approach can be successful, although it should be reserved for those who are able to cooperate with the peri- and postoperative surgical regimens. Scrupulous attention to removing all definable risk fac- tors, including smoking, is clearly necessary before such measures are considered. The first successful transplant was carried out in 2002 in a young woman with severe frequent neurovisceral attacks which were cured by the procedure. A subsequent retrospective review of 10 patients (9 women) aged 18 to 50 years reported that clinical and biochem- ical remission occurred in all patients, with urinary porphyrin precursors returning to the healthy reference range within 72 h of surgery. In a few cases, patients with renal failure requiring haemo- dialysis and associated hypertension have undergone simultaneous liver and kidney transplantation. Gene therapies Complementing, liver-directed gene therapy Gene delivery of porphobilinogen deaminase (hydroxymethylbilane synthase) to hepatocytes using a recombinant adeno-associated virus vector serotype 5 (rAAV2/5-PBG) in a murine model of acute intermittent porphyria prevented acute porphyric attacks after chal- lenge of the animals with barbiturate. In a subsequent human phase I, open label, dose-escalation, multicentre clinical trial, administra- tion of rAAV2/5-PBGD to patients with severe acute intermittent porphyria was safe, but metabolic correction was not achieved at the doses tested although two out of eight patients were able to stop haemin infusions. However, securing long-term correction of the liver would require permanent transduction of the entire organ and this challenge has yet to be overcome with the recombinant adeno- associated viral system. RNA interference Short-interfering RNA molecules (siRNAs) are able to modulate gene expression. Experiments conducted in mice that model acute inter- mittent porphyria have explored an investigational RNA interference agent (givosiran) that specifically targets hepatic ALAS1 gene expres- sion: it was able to prevent and curtail the biochemical abnormalities and paralysis associated with barbiturate challenge in affected animals. Givosiran is currently undergoing late-phase clinical development for the treatment of acute hepatic porphyria: monthly subcutaneous ad- ministration suppresses pathologically induced liver ALAS1 activity in a sustained manner, thereby decreasing aminolaevulinate and porphobilinogen to near normal concentrations in plasma and urine. At the time of writing, givosiran has been granted ‘Breakthrough Therapy’ designation by the Food and Drug Administration in the United States of America and PRIME designation by the European Medicines Agency; it has also been granted orphan drug designations in both the United States of America and the European Union for the

 treatment of acute porphyria. Its safety and efficacy are under investi- gation in the ENVISION phase III clinical trial and an ongoing phase I/II study. The outcomes of these studies have yet to be formally evalu- ated by the regulatory authorities, but interim updates indicate that annualized rates of acute porphyric attacks and of haemin use are both reduced by over 90%, with no significant safety concerns excepting an anaphylactic reaction in a single patient. Given the striking efficacy and relatively sustained and salutary effects of givosiran in patients with severe recurrent acute porphyria under- going clinical trials, it seems likely that those who are able to gain access to this innovative RNA interference therapy will no longer be looking to liver transplantation or repeated use of haem infusions to control their disease. At the time of

writing (2019), long-term safety data and reim- bursement stratagems for this are incompletely worked out; however, it seems very likely that the recommended management of all but the most mild or occasional disease will include siRNA therapy. Sources of information Drugs, drug interactions, and safe prescribing British National Formulary, British Medical Association, Tavistock Square, London WC1H 9JP. United Kingdom and Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN. The Drug Database for Acute Porphyria: http://www.drugs-porphyria.org/. The United Kingdom Drug Information Pharmacists Group: http://www.ukdipg.org.uk. The Welsh Medicines Information Centre (WMIC) provides ad- vice on drug safety in acute porphyria. The Cardiff safe drug list is available via their website. Contact is by telephone: +44 (0)29 2074 3877 or fax: +44 (0)29 2074 3879. Haem arginate (Normosang) is supplied in the United Kingdom by Orphan Europe (UK) Limited: 200 Brook Drive, Green Park, Reading, Berkshire, RG2 6UB, UK. http://www.orphan-europe. com. Telephone: +44 (0)1491 414 333. Medical Information e-mail: infoUK@orphan-europe.com; stock availability: krobinson@ orphan-europe.com Advice about management of acute porphyria National Acute Porphyria Service—Cardiff & Vale University Health Board and Kings College Hospital London are designated by the Advisory Group for National Specialised Services, NHS England, to provide a national service for patients with active acute porphyria (acute intermittent porphyria, variegate porphyria, her- editary coproporphyria). Two further Regional Porphyria Centres provide services (in Salford and Leeds) for patients who have recently had a new acute attack or with recurrent acute attacks. They provide clinical advice and support to healthcare professionals within the patient's own hospital. 24-h emergency telephone: 029 2074 7747. Patient associations The British Porphyria Association, 136, Devonshire Road, Durham City, DH1 2BL, UK. http://www.porphyria.org.uk; email: helpline@ porphyria.org.uk The American Porphyria and Canadian Porphyria Foundations may be accessed via the Internet websites. Warning jewellery: it is often valuable in patients with acute porphyrias for them to have a wrist bracelet or neck pendant that provides information about diagnosis in medical emergencies. Details in the United Kingdom can be obtained from The MedicAlert Foundation, 12 Bridge Wharf, 156 Caledonian Road, London N1 9UU. Telephone: +44 (0)207 833 3034. FURTHER READING Anderson KE, et al. (2004). Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Scriver CR, et al. (eds) The metabolic and molecular bases of inherited disease, 8th edi- tion, vol. 2, pp. 2991–3062. McGraw-Hill, New York. http://www. ommbid.com. Balwani M, et al. (2017). Clinical, biochemical, and genetic characteriza- tion of North American patients with erythropoietic protoporphyria and X-linked protoporphyria. JAMA Dermatol, 153, 789–96. Balwani M, et al. (2017). Acute hepatic porphyrias: recommenda- tions for evaluation and long-term management. Hepatology, 66, 1314–22. Bylesjö I, Wikberg A, Andersson C (2009). Clinical aspects of acute intermittent porphyria in northern Sweden: a population-based study. Scand J Clin Lab Invest, 69, 612–18. Chiabrando D, Mercurio S, Tolosano E (2014). Heme and erythropoi- esis: more than a structural role. Haematologica, 99, 973–83. Collins P, Ferguson J (1995). Narrow-band UVB (TL-01) photo- therapy: an effective preventative treatment for the photdermatoses. Br J Dermatol, 132, 956–63. Cox TM (2007). The porphyrias. In: Lomas D (ed) Horizons in medi- cine, vol. 19, pp. 67–83. Royal College of Physicians, London. Elder G, et al. (2013). The incidence of inherited porphyrias in Europe. J Inherit Metab Disease, 36, 849–57. Elder GH, Smith SG, Smyth SJ (1990). Laboratory investigation of the porphyrias. Ann Clin Biochem, 27, 395–412. Fontanellas A, Ávila MA, Berraondo P (2016). Emerging therapies for acute intermittent porphyria. Expert Rev Mol Med, 18, e17. Gorchein A (1997). Drug treatment in acute porphyrias. Br J Clin Pharmacol, 44, 427–34. Handshin C, et al. (2005). Nutritional regulation of hepatic heme syn- thesis and porphyria through PGC-1α. Cell, 122, 505–15. Holme SA, et al. (2006). Erythropoietic

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