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Chapter 56

Porphyria and its neurologic manifestations

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INTRODUCTION

Porphyrias are rare disorders of heme metabolism, each characterized by a defect in an enzyme required for the synthesis of heme. These disorders can produce disturbances of multiple organ systems, including the skin, liver, and central and peripheral nervous systems. The types of porphyria typically implicated in neurologic disease are acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria, which are all autosomal dominant inherited conditions. These are generally characterized by neuropsychiatric symptoms with mood disorder and/or psychosis, peripheral neuropathy (generally motor-predominant), gastrointestinal disturbances, and (in the case of variegate porphyria and sometimes hereditary coproporphyria) photosensitivity and other cutaneous manifestations. The best management of these disorders is through the prevention of acute attacks (e.g., avoidance of cytochrome P450-inducing agents and periods of fasting), but intravenous hematin and glucose should be considered in the context of an acute attack.

BACKGROUND

Neurologic manifestations of porphyria have been recognized for over a century, with cases reported as far back as 1890 (Ranking and Pardington, 1890), and many detailed descriptions of individual cases have been reported since then. There has been postulation of major historical figures having this disorder, including the British King George III as well as other members of royal families (Macalpine and Hunter, 1966). Early descriptions of the disorder, prior to intensive biochemical analysis, have reported on the characteristic reddish-purple discoloration of urine after prolonged exposure to light and air (which represents porphyrins in the specimen). Subsequent research has helped elucidate the biochemical processes of porphyrin formation and the defects along the heme biosynthetic pathway.

The porphyrias are disorders of heme metabolism, caused by a defect in an enzyme responsible for the synthesis of the heme molecule, which in turn is necessary for the production of hemoglobin, myoglobin, and cytochromes. Heme is an oxygen carrier, and is essential for aerobic respiration and adenosine triphosphate (ATP) production via the electron transport chain. Cytochrome production is necessary for metabolism of multiple drugs within the body, most notably through the cytochrome P450 system, and also mediates the removal of some toxic substances. Adequate heme formation is extremely important for the health of the individual, both in terms of energy production and metabolism, and abnormalities can have a profound impact. Heme formation occurs primarily in the bone marrow and in the liver, but synthesis does take place in all cells. Heme production in the liver is closely linked to a negative feedback mechanism regulated by the presence of heme, which has important treatment implications for porphyria. The production of heme is necessary for life, but partial defects in heme synthesis can be compatible with life, resulting in significant disease in some patients.

The heme biosynthetic pathway (Fig. 56.1) starts in the mitochondria, with the production of δ-aminolevulinic acid from glycine and succinyl-CoA, which is catalyzed by the pyridoxine-dependent enzyme δ-aminolevulinic acid synthase (ALAS). This is the rate-limiting step in heme production and is the site of feedback inhibition, with inhibition of ALAS by heme, the end product of this pathway. The next step occurs in the cytoplasm and is the formation of porphobilinogen (catalyzed by δ-aminolevulinate dehydratase), followed by the formation of hydroxymethylbilane (catalyzed by porphobilinogen deaminase), followed by the formation

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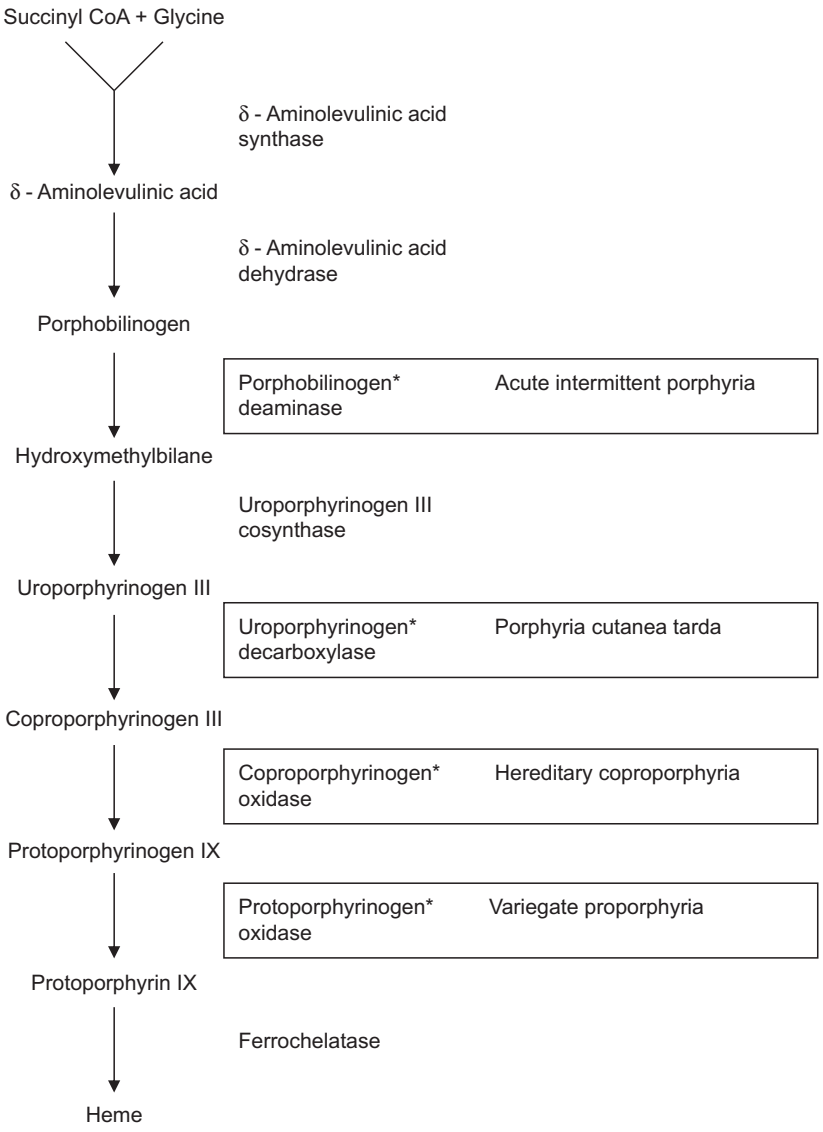

Fig. 56.1. The metabolic pathway of hepatic heme synthesis. Deficiencies of the outlined enzymes are responsible for the clinical types of porphyria. PBG deaminase (uroporphyrinogen I synthase), coproporphyrinogen oxidase, and protoporphyrinogen oxidase are usually deficient on a genetic basis and are associated with acute attacks of neurologic disease. Uroporphyrinogen decarboxylase deficiency may exist on a genetic basis or occur secondarily to toxic (usually alcohol-induced) liver disease. Porphyria cutanea tarda is not associated primarily with neurologic disease. The enzymes marked with an asterisk may be routinely assayed in erythrocytes in reference laboratories. (Reproduced from: Windebank and Bonkovsky, 2005.)

of uroporphyrinogen III (catalyzed by uroporphyrinogen III cosynthase), followed by the formation of coproporphyrinogen (catalyzed by uroporphyrinogen decarboxylase). The next step, which occurs in the mitochondria, is the production of proptoporphyrinogen IX (catalyzed by coproporphyrinogen oxidase), followed by the formation of protoporphyrin IX (catalyzed by protoporphyrinogen oxidase), and ultimately the production of heme (catalyzed by ferrochelatase, and utilizing iron). There are some differences in heme production between liver and bone marrow, with the liver production being regulated by the presence of heme, which inhibits the activity of ALAS and decreases further production of heme. In contrast, in the bone marrow the formation of heme is driven by cellular response to erythropoietin (Puy et al., 2010).

There are eight specific types of porphyria, each resulting from a defect along the heme synthetic pathway; the only one of the heme biosynthetic enzymes for which deficiency is not associated with porphyria is ALA synthase. These defects lead to accumulation of toxic precursors within the body. Traditionally, these

disorders are separated out into the erythropoietic and the hepatic porphyrias, depending on the major site of enzymatic expression. Porphyrias can cause pathology of multiple organ systems, including neurologic (central and/or peripheral), dermatologic, and gastrointestinal. The erythropoietic porphyrias mainly manifest with skin findings without associated neurologic disease and will not be extensively discussed in this chapter. There are four main types of hepatic porphyria, acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, and porphyria cutanea tarda, all of which are implicated in neurologic disease except for porphyria cutanea tarda. The three hepatic porphyrias with potential neurologic manifestations are all autosomal dominant disorders and all present with acute attacks of illness. Another type of hepatic porphyria, caused by deficiency in δ-aminolevulinate dehydratase, can cause severe neurologic dysfunction but is extremely rare and will not feature in the following discussion.

CLINICAL PRESENTATION

Most porphyrias have an autosomal dominant inheritance pattern with incomplete penetrance. They affect approximately 0.5–10 per 100 000 people (Anderson et al., 2001). The prevalence within various populations can be difficult to accurately ascertain, given the frequency of asymptomatic cases, as will be described later. While there are multiple types of porphyria, not all cause neurologic dysfunction. Porphyria cutanea tarda, which is the most common type of porphyria, and erythropoietic protoporphyria typically have cutaneous manifestations and usually are not associated with clinical neurological disease. The types of porphyria which characteristically cause neurologic disease are acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria (all of which fall under the classification of acute porphyrias). Patients with these types of porphyrias have an approximately 50% reduction in the affected enzyme for their respective disorders. These porphyrias are characterized by relatively quiescent phases interspersed with attacks of the disease, often precipitated by drug or toxin exposure or hormonal changes, and occur more commonly in women. When the heme biosynthetic pathway is activated, there is a massive toxic buildup of heme precursors, which are toxic to the nervous system.

Acute intermittent porphyria (AIP) results from a partial defect of porphobilinogen deaminase, which is the third enzyme in the heme biosynthetic pathway, caused by a mutation in the hydroxymethylbilane synthase gene. While this is an autosomal dominant disorder it is classically not fully penetrant, and it is estimated that less than 10% of people who carry this mutation become symptomatic throughout their life (Sassa, 2006). Attacks of AIP typically produce severe and acute abdominal pain in association with neuropsychiatric symptoms. Patients will often also have a motor predominant neuropathy with proximal and distal components (such as is seen in acute inflammatory demyelinating polyneuropathy (AIDP) or chronic inflammatory demyelinating polyneuropathy (CIDP)), though prominently axonal. Autonomic involvement is also common. This is the most common type of acute hepatic porphyria, occurring most frequently in Scandinavia, Britain, and Ireland, though it can occur in any ethnic group (Albers and Fink, 2004). It is common in Sweden, with a prevalence of 1 in 10 000, though its rate of clinical penetrance can be variable. The W198X mutation is the most common within that population due to a founder effect, though many other mutations in the porphobilinogen deaminase gene have been described (Floderus et al., 2002). A large retrospective study of 356 AIP gene carriers from Sweden (Bylesjo et al., 2009) showed that just under half had clinical manifestations (42%), with attacks occurring more frequently and more severely in women. Some 89% of the patients in this study had the W198X mutation. They noted that half of the patients using medications were using agents that were considered unsafe in porphyria, most commonly medications for hypertension. Andersson et al. (2000) found a higher rate of clinical penetrance with the W198X and R173W mutations, as well as greater number and duration of attacks when compared with the R167W mutation.

Hereditary coproporphyria is also an autosomal dominant disorder, characterized by a defect in coproporphyrinogen oxidase, which can produce attacks of gastrointestinal and neuropsychiatric symptoms and signs and less commonly, skin changes. The presentation is very similar to AIP but is typically milder. Brodie et al. (1977) reviewed 111 cases of patients with hereditary coproporphyria and found that 23% had neurologic involvement, 23% had psychiatric symptoms, 29% had photosensitivity, and 80% had abdominal pain. He notes a relative increase in female gender compared to males in both acute attacks and latent cases. Similar to the other porphyrias described, drug use was felt to be a specific precipitant in 54% of the attacks. In a study by Kühnel et al. (2000) of hereditary coproporphyria attacks, the most frequent symptoms were abdominal pain (89%), neurologic (33%), and psychiatric (28%).

Variegate porphyria results from a defect in protoporphyrinogen oxidase and is also an autosomal dominant disease. Attacks are generally less severe and less frequent than in AIP. Variegate porphyria is much less common than AIP and the prevalence in Europe is approximately 0.5 per 100 000 (Elder et al., 1997). This form of porphyria is more common in the white South African population due to a founder effect, which

appears to derive from a Dutch settler in South Africa (Dean, 1971). Hift and Meissner (2005) described 112 porphyric attacks in South Africa (25 with variegate porphyria and 87 with AIP) and found that the relative risk of an acute AIP attack compared to a variegate porphyria attack was 14.3, the median age of first attack was higher in patients with variegate porphyria than in AIP (30 versus 23.5 years old), the gender ratio was equal, and exposure to drugs was a common precipitant of variegate porphyria attacks (16 of the 25 attacks). Von und zu Fraunberg et al. (2002) evaluated the outcomes of 103 Finnish patients diagnosed with variegate porphyria and found that only 52% had clinical symptoms and 27% had acute attacks. They found that the specific mutation was important for prognosis, noting that patients with the I12T mutation, one of the three most common mutations causing variegate porphyria in Finland, had no photosensitivity and only 8% of this group had acute attacks.

Skin manifestations do not occur in acute intermittent porphyria but gastrointestinal and neuropsychiatric manifestations are prominent. Skin changes are much more common in variegate porphyria and can sometimes occur in hereditary coproporphyria. From a gastrointestinal and neuropsychiatric perspective, however, the attacks are very similar in these three types of porphyria. These attacks typically present with gastrointestinal distress with severe pain, though generally there are no objective signs of an "acute abdomen." Psychiatric and central nervous system manifestations can occur. Neuropsychiatric symptoms can vary markedly in severity from mild changes in affect, such as anxiety, but can also include psychosis and hallucinations. Seizure activity can also occur in a minority of patients, though management can be complicated by the limitations on safe medications in porphyria (Bylesjo et al., 1996).

Autonomic features, including tachycardia, constipation, and hypertension, are common. In general, peripheral neurologic manifestations occur later, within a few days or so of symptom onset. Peripheral neuropathy is typically motor predominant and asymmetric; it can involve proximal and distal muscles as well as cranial nerves. It can clinically resemble AIDP but with more abdominal pain and psychiatric symptoms. Sensory manifestations are often less evident or overlooked given the severity of the motor and autonomic changes, though various types of pain are commonly reported. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported in patients with porphyric attacks (Chogle et al., 1980; Muraoka et al., 1995) and should be considered as possible contributing factor to changes in cognition and/or seizure activity.

The classic description of the reddish discoloration of urine may be helpful diagnostically during an attack; however, initially the urine will appear normal and it is only after prolonged observation with oxidation of porphyrin precursors that this color change can be observed; hence it can easily be missed in the hospital setting. In general, if an individual survives an attack there is good resolution of most symptoms with a more delayed, and sometimes incomplete, improvement of neuropathic weakness. Jeans et al. (1996) reviewed survival for patients hospitalized for AIP attacks from 1940 to 1988 and found the standardized mortality ratio for these patients to be 3.2, compared to age-matched hypothetical controls using census data, and noted that most deaths were due to an acute attack.

Several atypical manifestations have been described, including presentation with bilateral radial neuropathies (King et al., 2002) and subarachnoid hemorrhage due to transient hypertension from porphyria (van Heyningen and Simms, 2008). Andersson et al. (2002) described a patient with porphyria who had varying attacks over the years, including isolated weakness without gastrointestinal symptoms. Greenspan and Block (1981) reported on two patients with AIP whose diagnosis occurred in the context of respiratory insufficiency.

Psychiatric manifestations may be common in porphyria patients as a group. Tishler et al. (1985) screened 3867 psychiatry inpatients for intermittent acute porphyria and found eight patients who met criteria for this diagnosis, with a 0.21% positivity rate, noting that this is higher than expected for the general population. Millward et al. (2005) evaluated 90 patients with porphyria and felt that anxiety was a "relatively stable personality trait," with 46% of their group self-reporting some problem with anxiety and/or depression. Another long-term concern is the potential risk of carcinogenesis. Kauppinen and Mustajoki (1988) reviewed case histories of 82 deceased Finnish patients with acute hepatic porphyria and found that the cause of death in seven was hepatocellular carcinoma, noting that this risk was much higher than that of the general population. This finding of risk of hepatocellular carcinoma in acute hepatic porphyria was also reported by Andant et al. (2000), who recommended periodic screening in these patients.

RISK FACTORS FOR ATTACKS

Attacks in porphyria can be induced by a number of different factors. While it is clear that in many cases the precipitant of a specific attack cannot be identified, known factors in the induction of attacks include hormonal factors, nutritional factors, alcohol, and the use of drugs which induce the heme production pathway, thus leading to an overabundance of toxic heme precursors. The main risk factor for the development of attacks is the use of drugs which stimulate heme production, in particular those which require metabolism throughout

the cytochrome P450 system leading to excess production of heme precursors and inducing an attack.

Because of the increased incidence of acute porphyric attacks in women, as well as the rarity of symptom onset prior to puberty, the role of sex hormones has been reviewed. The hormones estrogen, progesterone, and testosterone all cause increased ALA synthase activity (Windebank, 2003). One study found that 12 out of 50 women with AIP using oral contraceptives reported that oral contraceptives precipitated AIP attacks, and it precipitated the first attack in nine of those 12. In addition, of 22 women using hormone replacement therapy after menopause, no AIP attacks were induced (Andersson et al., 2003). Another group reviewed female patients with either AIP or variegate porphyria and recurrent menstrual-associated attacks who were treated with gonadotropin-releasing hormone (GnRH) agonists; they were also given low-dose estradiol and usually progesterone. Attacks were fewer and less severe in most of these women, though in some the estradiol and progesterone induced attacks (Innala et al., 2010). Treatment with a luteinizing hormone-releasing hormone agonist was found to reduce perimenstrual AIP attacks in women (Anderson et al., 1984).

Lip et al. (1991), through a questionnaire given to patients with AIP, found no difference in proportions of patients with latent or active disease who were smokers or nonsmokers, but did identify that of patients with active disease, smokers were more likely to have had more than one attack than nonsmokers. This was attributed to stimulation of the P450 system by elements of cigarette smoke and also to altered balance of steroid hormones in smokers. Alcohol use can induce a porphyric attack through inhibition of uroporphyrinogen decarboxylase and thus further accumulation of porphyrin precursors. In addition, decreased glucose to the liver can result in upregulation of ALA synthase activity, which can lead to an attack (Windebank, 2003). High carbohydrate diets cause reduction in porphobilinogen (PBG) excretion (Welland et al., 1964).

MECHANISMS OF NERVOUS SYSTEM DYSFUNCTION

The actual mechanisms of damage to nervous system tissue in porphyria are poorly understood and may be varied. The central and the peripheral nervous systems are both affected by porphyria. Because of the structural similarities of aminolevulinic acid (ALA) and γ-aminobutyric acid (GABA), it has been postulated that its accumulation may impair normal GABA function in the nervous system, leading to some of the central nervous system manifestations (Windebank, 2003). Other possible mechanisms described include direct toxicity of the heme metabolites to nervous system tissue, direct effects of inadequate heme synthesis in the brain, secondary effects on brain heme synthesis from defective hepatic heme synthesis, and biochemical pathways leading to elevated synthesis of 5-hydroxytryptamine (Sassa, 2006). It has been suggested that the development of SIADH in some of these patients may be due to a direct toxic effect of the CNS by porphyrin precursors (Desaga et al., 1985).

King and Bragdon (1991) described a patient with porphyria, hallucinations, and seizures with brain lesions on MRI, which resolved along with her symptoms after treatment, and felt there was likely a vascular etiology. Aggarwal et al. (1994) described a patient with porphyric encephalopathy with MRI findings of diffuse predominantly gyriform cortical enhancement in both cerebral hemispheres; the findings resolved over time as the patient clinically improved. Kupferschmidt et al. (1995) described two patients with porphyria who developed cortical blindness, both with bilateral occipital lobe lesions which were felt to be consistent with vasospasm-induced ischemic lesions, though it has been suggested (Sze, 1996) that these may have represented findings of hypertensive encephalopathy. Central nervous system pathologic findings, similar to those of the peripheral nervous system, are not specific for porphyria and data are limited. In the 1950s, Gibson and Goldberg examined brains of patients with porphyrias and found evidence of axonal loss and perivascular demyelination in the cerebellum and white matter (Gibson and Goldberg, 1956).

The mechanism of the damage to the peripheral nervous system is not well understood, but axonal degeneration appears to predominate over segmental demyelination (Fig. 56.2). The enzyme defect causes a deficiency in the production of heme containing proteins for oxygen transport, electron transport, and the cytochrome P450 system. These abnormalities may disrupt axonal transport leading to axonal degeneration. The first autopsy case of porphyria was an acute polyneuritis following sulfophonal administration, in which Wallerian degeneration was described (Erbsloh, 1903).

In 1945, Denny-Brown and Sciarra (1945) reported segmental demyelination in porphyric nerve, suggesting that the primary source of pathology was in the myelin, but teased nerve fiber preparations were not done. Anzil and Dozic (1978) evaluated a sural nerve biopsy of a patient with porphyric neuropathy, by both light and electron microscopy, and found damage to both myelin and axons, and noted both myelin ovoids and mild evidence of segmental demyelination on teased fiber preparations. Felitsyn et al. (2008) exposed Schwann cells and sensory neurons in culture to δ-aminolevulinate and found that this was associated with lower levels of myelin-associated proteins and lipids.

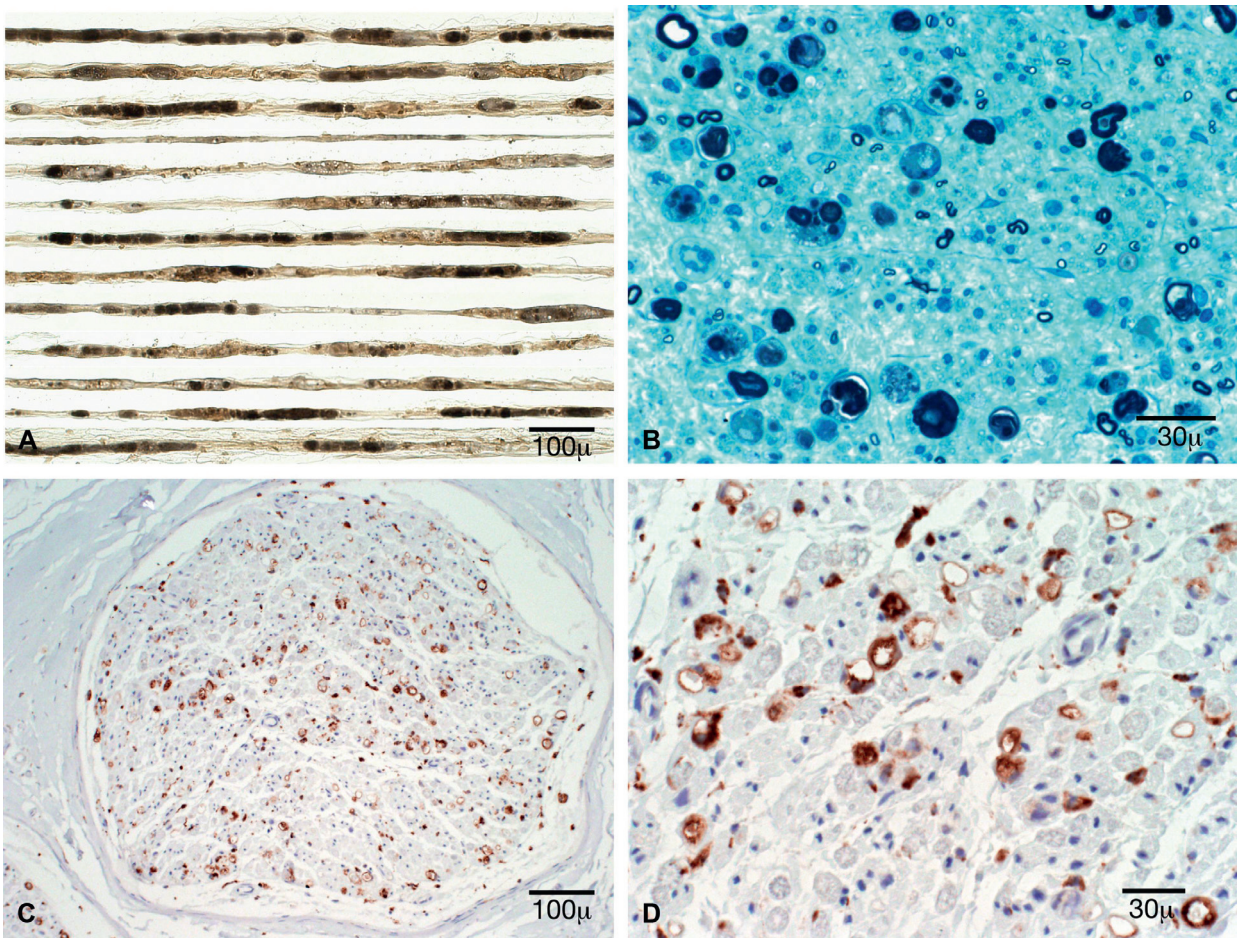

Fig. 56.2. Sural nerve biopsy showing fulminant axonal degeneration from a 33-year-old woman with 2 years of episodic abdominal pain, nausea, and vomiting, with acute onset of lower limb pain and weakness, vomiting, and anxiety. Urine porphobilinogen levels were elevated. (**A**) Teased nerve fiber preparations showing all myelinated fibers undergoing early axonal degeneration at the same stage (implying a common insult). (**B**) Semithin epoxy section stained with methylene blue showing most myelinated nerve fibers are degenerating. (**C**) Low and (**D**) high power of CD68 immunostain that reacts with macrophages. There are frequent macrophages at sites of axonal degeneration. These findings show the widespread acute axonal degeneration that can occur in an attack of acute porphyria.

Most pathologic and electrophysiologic studies suggest that the axon and not the myelin is the main target of porphyric neuropathy. Albers et al. (1978) reported on the electrophysiologic features of 11 patients with acute quadriparesis from AIP and found that eight had low amplitude compound action potentials with preserved conduction velocities, as well as fibrillations on electromyography consistent with a primarily axonal process. Cavanagh and Mellick (1965) performed detailed autopsy studies of nerve, muscle, spinal root, and cord of four patients with AIP and found no evidence of a primary demyelinating process but rather found evidence of an axonal process with motor fibers affected more significantly than sensory fibers. Thorner et al. (1981) described a patient with acute neuropathy from variegate porphyria for whom autopsy material was available, showing evidence of a primary axonopathy with a dying-back phenomenon. Yamada et al. (1984) studied an autopsy case of a patient with acute porphyria and also found evidence consistent with a primary process of axonal degeneration with loss of axons and myelin in the peripheral nervous system and central chromatolysis of anterior horn cells in the spinal cord. Furthermore, they performed biochemical analyses on the sciatic nerve and reported increased ALA-S activity and decreased uroporphyrinogen I synthetase and ferrochelatase activities. These findings of primary axonal pathology are most in keeping with the classic electrophysiologic features described.

Lin et al. (2008) performed excitability measurements of peripheral motor axons in AIP subjects and found different responses to hyperpolarizing currents compared

to controls. Their belief is that AIP neurotoxicity causes a decreased hyperpolarizing activated conductance in axons of patients without neuropathy and that membrane depolarization from decreased sodium/potassium pump activity results in porphyric neuropathy.

DIAGNOSIS

The diagnosis of porphyria can be challenging unless a high clinical suspicion is present. The presence of a family history of similar symptoms can be extremely helpful, but often this is not present. A history of discolored urine can also be helpful. In the context of an acute attack of porphyria, the diagnosis is often less complicated than when a patient presents after an attack has occurred but in an asymptomatic state.

The primary tool for diagnosis is measurement of porphyrin levels in urine, stool, and blood; these are most useful in the acutely symptomatic state as excretion of porphyrins is highest under that condition. In an acute attack of acute intermittent porphyria, there is elevated urinary excretion of aminolevulinic acid (ALA), porphobilinogen (PBG), uroporphyrin, and coproporphyrin; erythrocyte PBG deaminase may be normal or decreased. In the asymptomatic phase, in between attacks of acute intermittent porphyria, there can be decreased erythrocyte PBG deaminase or the value can be normal, urine excretion of the aforementioned compounds is generally normal or mildly elevated In hereditary coproporphyria, urine coproporphyrin, ALA, uroporphyrin and PBG levels are increased during an attack, and fecal coproporphyrin in particular can be quite increased during attacks; coproporphyrin is usually increased in urine and feces in between attacks as well. Variegate porphyria usually has increased levels of urine and fecal porphyrins during an attack, but generally urine porphyrin levels are normal in the latent phase of disease, aside from the possibility of increased coproporphyrin.

It should be remembered that there are other causes of increased porphyrin levels aside from porphyria, as these can be elevated in patients taking medications that induce the cytochrome P450 system, but these levels should normalize after discontinuation of the suspected offending drug (Windebank, 2003).

DNA testing is available for AIP, hereditary coproporphyria, and variegate porphyria and should be considered after initial screening tests are performed. There are many different mutations described in the respective genes for these disorders (Puy et al., 1997; Rosipal et al., 1999; Whatley et al., 1999), requiring careful screening. This testing is usually employed after suggestive findings on the testing previously described, or when an affected family member is identified and asymptomatic individuals want to be screened.

The differential for this disorder can be broad and includes acute inflammatory demyelinating polyradiculoneuropathy (AIDP, Guillain–Barré syndrome), which can appear similar to a porphyric attack. AIDP is characterized by an ascending, motor-predominant polyradiculoneuropathy, sometimes with associated sensory and autonomic symptoms and signs. This disorder can be associated with gastrointestinal symptoms, such as diarrhea. However, important differentiating characteristics include the lack of central nervous system manifestations, such as seizures or psychiatric symptoms in AIDP, as well as primary demyelinating features on nerve conduction studies, as opposed to the axonal pattern seen in porphyria. A variant of Guillain–Barré syndrome, acute motor axonal neuropathy (AMAN), can present with axonal features on EMG but again should not have central nervous system symptoms or findings. Porphyria should be at least considered in patients who have multiple episodes of acute to subacute weakness that have previously been labeled as Guillain–Barré syndrome.

There are many other motor-predominant neuropathies, including multifocal motor neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome, but these should be ruled out due to their generally slower time course.

Other considerations for acute motor-predominant neuropathies should include infectious and inflammatory conditions such as Lyme disease, West Nile virus, enterovirus and herpesvirus-mediated polyradiculoneuropathies, and vasculitic neuropathies. Differentiation should be aided by attaining good exposure histories and appropriate serologies and CSF analyses. The association of an attack of weakness with either hormonal factors or medication use may be of help. Lead poisoning, which can produce both severe motor neuropathy as well as abdominal pain, should be considered in patients with risk for exposure, either occupationally or through hobbies, and certainly should be considered in children with a porphyria-like clinical presentation. In suspicious cases, blood lead levels should be obtained. As always in the case of acute weakness, one must always consider the possibility of acute presentations of neuromuscular junction disorders such as myasthenia gravis or of myopathies (such as toxic myopathies).

One must also be careful not to overinterpret less classic features seen in porphyria and attribute them to other disease processes. As previously noted, there are reports of patients with brain lesions in the context of an acute porphyric attack. Bylesjo et al. (2004) reported on the frequency of white matter T2 hyperintense lesions in patients with AIP. He found four of 16 AIP carriers (two with prior AIP attacks and two

without) had such white matter lesions; however, he noted that all of these patients had CSF analysis which did not show oligoclonal bands, distinguishing these from multiple-sclerosis type patients. He also found that seven of these 16 patients had a hemoglobin A1c level over 6.0, suggesting chronically elevated blood sugars.

TREATMENT

The most important management strategy in patients with porphyria is prevention of acute attacks. Activation of the cytochrome P450 system uses up heme in the production of cytochromes, and the reduced heme supply reduces the inhibition on δ-aminolevulinic acid, thereby upregulating the heme production cycle, and in the case of porphyria, increases the production of toxic intermediates. Any medications that induce the cytochrome P450 system have the potential to induce an attack of porphyria. The use of alcohol can induce attacks as can many other pharmacologic agents, and any medication used in a patient with porphyria should be selected with care. While evaluation of the safety of any drug should be evaluated individually between a patient and his/her health care professional, there are useful guides available, including an online database provided through the American Porphyria Foundation's website (http://www.porphyriafoundation.com/drug-database). It is important to note that there may be a time lag for assessing the safety of newer medications for patients with porphyria, so caution must always be employed in treatment decisions. Prolonged fasting should be avoided. In addition, care needs to be taken in prescribing hormone therapy.

Once a porphyric attack is established, understanding of the biochemical pathways is helpful in determining treatment. From a biochemical perspective, heme serves as an inhibitor of ALAS in the liver and so artificially introducing heme can suppress the biosynthetic pathway of heme and thus reduce the amount of toxic metabolites produced in a patient with porphyria, which makes it an attractive option for the management of an acute porphyric attack.

For management of the underlying disorder, intravenous hematin should be given with a daily dose of 2–5 mg/kg given for 3–14 days. Mustajoki and Nordmann (1993) treated 51 acute porphyric attacks (in 22 patients with AIP and two with variegate porphyria) with heme arginate at either 250 mg or 3 mg/kg infusions for 4 days in almost all cases, with good clinical response in all patients, and with a mean duration of pain 2.5 days after the first infusion (which in nearly three-quarters of cases was given within 24 hours of admission). Potential side-effects of hematin administration include renal failure, phlebitis, and coagulopathy (Morris et al., 1981). Nutritional supplementation is also crucial as the lack of sufficient glucose can increase the ALA synthase activity and thus increase porphyrin accumulation, worsening the attack. Intravenous glucose supplementation is advised with a recommendation of 3–500 g intravenously per 24 hours (Bonkovsky, 1990; Windebank, 2003).

While hematin is considered the standard of care, there are also limited reports of liver transplantation essentially rendering patients free of acute exacerbations (Seth et al., 2007). Soonawalla et al. (2004) described a 19-year-old patient with AIP and frequent exacerbations who underwent an orthotopic liver transplant, with no recurrent attacks over the 1.5 year period of follow-up. Stojeba et al. (2004) described a 46-year-old man with variegate porphyria and liver failure (with chronic alcohol abuse), who had a successful liver transplantation with no porphyria relapse over 3 months and normal uroprotoporphyrinogen and fecal protoporphyrin levels.

The importance of choosing medications that will not activate the heme biosynthetic pathway in patients with porphyria requires vigilance on the part of the treating physician. This adds a layer of complexity to the treatment of symptoms once a porphyric attack has occurred, as one must be careful not to cause pharmacologic worsening. Seizures in the context of a porphyric attack pose particular challenges. Bylesjo et al. (1996) carried out an epidemiologic study in which 10 of 268 AIP patients in Sweden reported having had seizures – six with tonic-clonic seizures and four with partial seizures with secondary generalization. Review of patient records indicated that six of these patients had a seizure in the context of an acute porphyric attack, with an estimate of a lifetime prevalence of 2.2% of patients with AIP-induced seizures.

Seizures are difficult to treat as phenytoin, phenobarbital, clonazepam, and valproic acid all have the potential to worsen a porphyric attack, though individual reports exist supporting the safety and efficacy of clonazepam. Bromides have been used with success in an attempt to avoid other enzyme-inducing antiepileptic drugs (Magnussen et al., 1975). Hahn et al. (1997) used a cell culture model of chicken embryo liver cells and induced a partial block in heme synthesis to simulate changes seen in porphyria, treated them with varying doses of vigabatrin, gabapentin, felbamate, lamotrigine, tiagabine, and phenobarbital, and found that vigabatrin and gabapentin did not lead to increased porphyrin accumulation while the other agents led to increased porphyrin production.

Taylor (1981) has reported on the use of intravenous magnesium for seizures in AIP. Zaatreh (2005) described a patient with AIP and status epilepticus, who was successfully treated acutely with a combination

of intravenous magnesium and oral levetiracetam, and was maintained thereafter on oral gabapentin and levetiracetam without side-effects. Another case (Bhatia et al., 2008) of a 12-year-old boy with AIP and status epilepticus reported resolution with intravenous propofol (in addition to continuation of the gabapentin and levetiracetam he was on at the time of the episode of status epilepticus). Another patient with AIP was given propofol induction twice for anesthesia with no disease exacerbation (Mitterschiffthaler et al., 1988). Weir and Hodkinson (1988) described a patient with variegate porphyria for whom propofol induction was used, with a subsequent increase in urinary porphyrins, but no associated clinical symptoms. One case report (Asirvatham et al., 1998) adds a note of caution as they describe a patient treated with propofol for a cardiac procedure, who had prolonged impaired consciousness and elevated urinary porphyrins, suspected to be a case of previously asymptomatic coproporphyria.

Tatum and Zachariah (1995) described good seizure control using gabapentin in two patients with AIP, without induction of acute attacks. Krauss et al. (1995) reported on a patient with porphyria cutanea tarda with complex partial seizures, who became seizure free on gabapentin monotherapy (1800 mg/day) without recurrent manifestations of porphyria. Zadra et al. (1998) reported on a female patient with AIP who had both partial and generalized seizures, who had porphyric attacks with the use of phenytoin, carbamazepine, and valproic acid, but who remained seizure-free and attack-free on monotherapy with gabapentin. Another report (Paul and Meencke, 2004) of a patient with hereditary coproporphyria treated with levetiracetam reported no porphyric exacerbations.

There are also individual reports of patients with types of porphyria without neurologic manifestations who have coexisting seizure disorders, commenting on drug efficacy and safety in this context. Bilo et al. (2006) reported on a patient with idiopathic generalized epilepsy and porphyria cutanea tarda with full seizure control and no induction of porphyric attacks on levetiracetam monotherapy. There is also a report of a patient with porphyria cutanea tarda with partial seizures, who had good seizure control with oxcarbazepine without elevation of liver function tests, and it was suggested that with the lower hepatic enzyme induction of oxcarbazepine (as opposed to carbamazepine) may render this agent a safer alternative (Gaida-Hommernick et al., 2001).

CONCLUSIONS

Porphyrias are disorders of the heme biosynthetic pathway. A limited number of these can cause significant neurologic deficit (AIP, hereditary coproporphyria, variegate porphyria) with autonomic symptoms, motor-predominant peripheral neuropathy, gastrointestinal distress, and sometimes cutaneous manifestations. An accurate diagnosis can be made through routine testing for overproduction of porphyrins during an acute attack, but this may be more difficult during a quiescent phase of disease. The most important factor for making the correct diagnosis is a high index of suspicion and awareness of the diversity of clinical manifestations. DNA testing is also available for the diagnosis. Treatment, based upon knowledge of the biochemical pathways of porphyria, can be very effective for management of acute attacks, including hematin as well as glucose supplementation and prohibition of drugs that may worsen an attack. For long-term management, careful modification of risk factors, in particular the avoidance of drugs that stimulate the heme biosynthetic pathway is crucial.

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