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Review

Management of the acute porphyrias

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Three hepatic porphyrias – acute intermittent porphyria, hereditary coproporphyria and variegate porphyria – are characterized by episodic acute attacks that consist of various neuro-psychiatric symptoms and signs, such as abdominal pain, vomiting, constipation, hypertension and tachycardia associated with increased excretion of porphyrins and porphyrin precursors. Peripheral neuropathy is manifested as pain in the extremities, and it may progress to a severe motor neuropathy. Measurement of porphobilinogen in the urine gives a prompt diagnosis during acute attacks. Attacks are often induced by precipitating factors such as drugs, alcohol, infection, fasting or changes in sex-hormone balance, and they should be eliminated when a patient is treated during an attack. Heme, the end biosynthetic product, is the most effective therapy for restoration of porphyrin biosynthesis to normal, and it is usually infused at 3mg/kg daily for 4 days. Adequate calories are necessary and parenteral nutrition with carbohydrates may be necessary. Attacks may also require therapy for hypertension, pain and epileptic seizures. Strict avoidance of all precipitating factors may not be necessary in the asymptomatic phase.

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Pathogenetic mechanisms in the different porphyrias are variable, and no universal treatment is available (1). However, there are exceptions to this rule and three hepatic porphyrias – acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP) – are exceptions. Despite their different genetic backgrounds, they are characterized by similar episodic attacks and they can be treated identically. These attacks include various neuro-psychiatric symptoms associated with increased excretion of prophyrins and porphyrin precursors.

These three types of porphyria are inherited in an autosomal dominant fashion, but penetrance varies greatly. Only 10–20% of the patients experience acute attacks, whereas minor porphyric symptoms are more common (2). Attacks are potentially fatal and a 10% mortality has been suggested (3), although in recent series the prognosis has been better than this (2).

Endocrine factors are known to have major effects on porphyrin metabolism (1, 3). Acute attacks seldom appear before puberty, and onset is most commonly between the ages of 20 and 30 years. Porphyric symptoms may, however, appear at any age (4). Acute attacks are often precipitated by factors such as infection, alcohol, fasting, drugs and changes in sex-hormone balance (1,2). These factors induce heme biosynthesis, and they cause increased excretion of porphyrins and porphyrin precursors. It is still uncertain whether an acute attack results from a relative lack of heme or from toxic neuronal effects of accumulating intermediates, especially delta-aminolevulinic acid. The idea behind heme therapy is to replace the heme deficiency and via negative feedback to restore porphyrin biosynthesis to normal (5).

A fourth type of acute porphyria – delta-aminolevulinic acid dehydrase deficiency porphyria – is rare, and it differs from the classical acute porhyrias (6). This disease is autosomal recessive, and it may be manifested even in childhood. It is often associated with severe neurological symptoms.

Clinical features of an acute attack

An acute porphyric attack is a great mimic of abdominal crises (1, 4). The first symptoms of neuropathy include abdominal pain, vomiting and constipation that are associated with hypertension and tachycardia, as signs of increased sympathetic activity (Table 1). Peripheral neuropathy is mani-

Table 1. Symptoms and signs of an acute attack[1]

Abdominal pain	95%
Dark or red urine	90%
Tachycardia	85%
Abdominal tenderness	85%
Vomiting	80%
Constipation	80%
Extremity or/and back pain	70%
Hypertension (diastolic >100 mmHg)	55%
Pareses in extremities	50%
Minor behavioral changes	40%
Confusion and/or hallucinations	25%
Objective sensory loss	25%
Respiratory muscle paralysis	20%
Epileptic seizures	20%
Cranial nerve involvement	15%
Diarrhea	5%

[1] Adopted from Mustajoki and Koskelo with permission.

fested as pain in the extremities, and it may progress to a severe motor neuropathy. Cranial nerve palsies, epileptic seizures, respiratory insufficiency, abnormal sphincter function, hallucinations and mental changes may be present. Urine can be dark or even red in color because of increased amounts of porphobilin and porphyrins. Hyponatremia may be a consequence of vomiting or of inappropriate secretion of antidiuretic hormone. Patient mortality is attributable to respiratory paralysis or cardiac arrest.

Establishing a correct diagnosis is essential and measurement of porphobilinogen (PBG) in the urine gives prompt diagnosis during acute attacks (7). Some patients have persistently elevated amounts of urinary PBG, even in the asymptomatic phase (2). During acute attacks preexisting amounts of PBG are usually exceeded.

Treatment of an acute attack

Certain drugs – especially barbiturates, sulfonamides and preparations used for epileptic seizures – in addition to alcohol, infection, fasting or changes in sex-hormone balance can precipitate attacks; they should all be eliminated when a symptomatic patient is treated. More complete lists of potentially safe and unsafe drugs are given in other reviews (1, 8).

Heme, the end biosynthetic product, is usually infused at 3 mg/kg daily for 2–4 days, depending on the course of an attack (5, 9, 10). Treatment should be started promptly because the majority of patients benefit from quick remissions and short hospitalizations (11). After the administration of heme, biochemical remission, e.g., decreased urinary excretion of porphobilinogen in AIP patients and decreased fecal excretion of protoporphyrin and coproporphyrin in VP patients, lasts for a week and is usually enough to abolish porphyric symptoms if precipitating factors are eliminated (9).

Two heme preparations are commercially available: heme arginate (Normosang, Leiras, Finland) in Europe and South Africa, and a lyophilized hematin (Panhematin, Abbot, USA) in the USA. No tolerance has been reported, despite repeated intravenous administrations. Repeated infusions may, however, cause thrombophlebitis and the drug should always be infused into large peripheral veins or via a central vein catheter. Heme arginate does not interfere with hemostasis (10).

Adequate calories are also necessary and parenteral nutrition with carbohydrates may be needed if the patient is vomiting and unable to eat. Attacks often require symptomatic therapy for hypertension, pain and epileptic seizures (Table 2).

Prevention of attacks

Strict avoidance of precipitating factors has been considered important during acute attacks (1, 3, 8), but it may not be necessary during the asymptomatic phase. According to our survey, the majority of patients tolerate many drugs, such as analgesics, cardiovascular and psychotropic drugs and local anesthetics, even though some of these have been implicated in precipitating attacks (2). Some drugs, e.g., sulfonamides, barbiturates, griseofulvin, phenytoin, carbamazepine and ethosuximide, which are frequently associated with acute attacks, should be avoided even in the asymptomatic phase of the disease (1, 8).

Other diseases should be treated appropriately, and so the possible merits and disadvantages of a given drug should to be evaluated for each patient individually. If porphyric symptoms appear, administration of a drug should be stopped immediately. Patients usually tolerate surgery and local anesthetics well (2). Moderate alcohol consump-

Table 2. Treatment of acute porphyric attack

1. Elimination of all precipitating factors
2. Specific therapy should be started without delay:
   Heme infusions 3 mg/kg daily for 2–4 days
   Mild attacks may be treated with excess glucose 500 g/day
3. Supply of adequate calories, parental nutrition if necessary
4. Pain: opiates, conveniently administrated with infusion pump
5. Hypertension: beta-adrenergic blocking agents
6. Hyponatremia: saline infusion, fluid restriction if signs of inappropriate antidiuretic hormone secretion
7. Epileptic seizures: diazepam, correction of hyponatremia
8. Psychosis: chlorpromazine
9. Motor neuropathy: physiotherapy, assisted ventilation if respiratory insufficiency

tion seldom causes serious problems, but heavy drinking is risky (2). Fasting or very low-caloric diets should be avoided.

Many women experience porphyric symptoms in association with the menstrual cycle (2, 8, 12). The earliest symptom is usually constipation during the premenstrual phase, which may progress to a fulminant attack. Porphyric symptoms abate after a few days of menstruation. Oral contraceptive pills and luteinizing hormone-releasing hormone (LHRH) analogues suppress endogenous sex hormone production, and these can be used to prevent cyclical attacks (12, 13). Most low-dose oestrogen-progesterone combination preparations are suitable, but responses may be individual and may depend on the nature and amount of oestrogen and progestagens they contain. The long-term administration of subcutaneous or nasal LHRH analogues induce menopause, and additional oestrogen administration may be beneficial. Weekly or biweekly prophylactic heme infusions may be effective if hormonal manipulations fail (5).

A minority of women have experienced porphyric symptoms during administration of oral contraceptive pills or pregnancy (1, 2). Although symptoms of porphyria are frequent in the premenstrual phase, they do not predict symptoms of porphyria during pregnancy (2). Sex hormone preparations such as oral contraceptive pills or drugs for menopausal symptoms can be used under supervision. Pregnancy should not be restricted because even women with previous acute attacks usually tolerate it well.

Skin symptoms of acute porphyrias

There is no specific treatment for skin disease in VP and HCP. The skin symptoms resemble those of porphyria cutanea tarda, being manifested as excessive fragility, blistering and scarring on sun exposed areas (14, 15). About half of VP patients experience skin symptoms that occur independently from acute attacks (16). In HCP skin symptoms occur usually in association with acute attacks (15).

Prognosis of acute porphyria

Acute attacks now have a better prognosis than previously, when they were a common cause of death (2). At present, most symptomatic patients experience only a few attacks during their life spans, although minor symptoms of porphyria are more common among patients who experience acute attacks. Some women with acute pophyria experience regularly cyclical symptoms of porphyria, and a few of these experience severe acute attacks, which may be difficult to prevent. A low rate of urinary excretion of porphobilinogen in remission may have prognostic value among adult AIP patients, because a low rate of excretion predicted freedom from acute attacks in a follow-up study (2).

Several factors may be responsible for the relatively benign course of acute porphyria. Increased awareness among physicians, and better diagnostic facilities allow early detection of the disease. Moreover, treatment has improved greatly. One reason for the less severe attacks is the detection of asymptomatic patients with acute porphyria in family studies. Precipitating factors can be avoided, and acute attacks can be treated early, preventing attacks from worsening.

Although patients with acute porphyria now live longer and lead relatively normal lives (2, 17), physicians should be aware of the higher risk of hepatocellular carcinoma, at least among AIP patients (18, 19, 20). In addition, chronic renal failure and hypertension are more prevalent in patients with the acute porphyrias (2, 21).

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