Pathogenesis and treatment of acute intermittent porphyria: discussion paper[1]

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During the past 25 years much has been learnt about the biochemical and genetic aspects of the acute hepatic porphyrias (del C Batlle 1980, Goldberg & Moore 1980). Yet the management of a patient in an acute attack of the disease remains difficult and there is still uncertainty about the pathogenesis of the clinical features. Acute intermittent porphyria (AIP) is the commonest of the three types of acute hepatic porphyria in Britain (Figure 1). It is characterized by a partial deficiency of uroporphyrinogen 1-synthase (URO-S) (also known as porphobilinogen deaminase), which catalyses the third step in the haem biosynthetic pathway, and by the excessive excretion of delta-aminolaevulinic acid (ALA) and porphobilinogen (PBG) in the urine (Granick *et al.* 1972, Piepkorn *et al.* 1978). Transmitted as an autosomal dominant trait, only a minority of the affected individuals, probably fewer than one in three, will suffer from the disease. The acute attack is dominated by pain and neuropsychiatric symptoms, and the persistence of abdominal pain, despite treatment, can tax the therapeutic capabilities of the physician to the limit.

Clinical features

Abdominal pain is the initial symptom in more than 90% of the acute attacks. Location of the pain can vary from patient to patient and from attack to attack in the same patient. It frequently fails to conform to any particular neuroanatomical distribution as it can be localized to any part of the abdomen. Patients often describe the pain as 'nagging' and 'unremitting' although it can be colicky in nature. Vomiting and constipation, sometimes very severe, are common accompanying features. Back pain in the lumbar region is also a frequent complaint. Palpation of the abdomen characteristically reveals some degree of tenderness which is much less than would be expected for the severity of the pain. The episodes of abdominal pain usually settle spontaneously after a few days unless there is persistence of some precipitating factor. For some unfortunate patients, however, the pain can linger on for weeks or months without any satisfactory explanation.

Motor weakness is the other major feature of the acute attack in some 60% of the cases (Goldberg & Rimington 1962). Its progression is usually gradual, but occasionally flaccid paralysis of all extremities can occur rapidly, within a matter of days (Sorensen & With 1971). In addition, the patient often experiences pain in the limbs which is accompanied by muscle tenderness, yet the serum muscle enzymes remain normal. Abdominal pain and sinus tachycardia nearly always precede the paralytic manifestations, sometimes weeks before; and, conversely, slowing of the tachycardia signals recovery from the peripheral neuropathy (Ridley *et al.* 1968). Lower motor neurone involvement of the cranial nerves or isolated ptosis can rarely occur, but bulbar palsy and respiratory muscle paralysis are the most dreaded complications which have been responsible for the majority of fatal cases. Cerebral disturbance can trigger tonic-clonic seizures in the absence of other metabolic abnormalities. Occasionally involvement of the basal ganglia can cause abnormal movement disorders.

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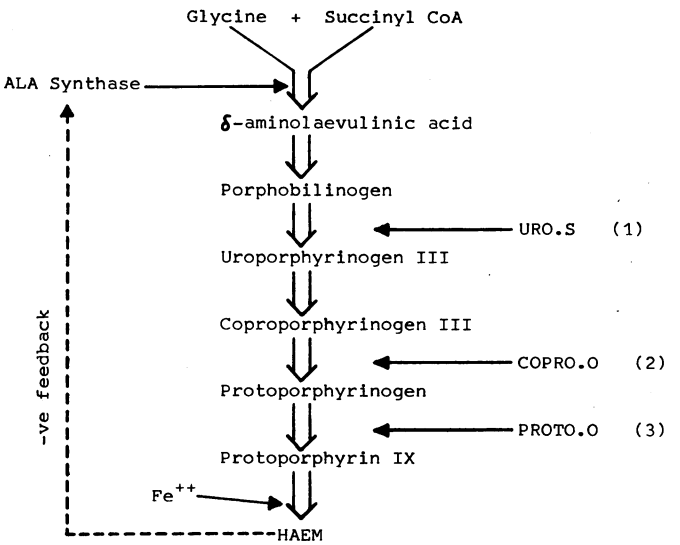

Figure 1. Haem biosynthetic pathway showing the enzymes whose lowered activities result in the three types of acute porphyria: (1) acute intermittent; (2) hereditary coproporphyria; (3) variegate porphyria. (URO.S, uroporphyrinogen 1-synthase; COPRO.O, coproporphyrinogen oxidase; PROTO.O, protoporphyrinogen oxidase)

Inappropriate anti-diuretic hormone secretion (Hellman *et al.* 1962) and other hormonal disturbances (Perlroth *et al.* 1967, Waxman *et al.* 1969) have been explained on the basis of hypothalamic-pituitary dysfunction. Furthermore, a variety of psychiatric manifestations, especially depression, and an organic brain syndrome have been reported in association with the acute hepatic porphyrias (Wetterberg 1967). The electroencephalogram is often abnormal during an acute attack, and in some patients this persists during remission (Stein & Tschudy 1970). The abnormality usually appears as a generalized slowing of the tracings, but focal disturbances may be seen. In the presence of clinically established neuropathy, peripheral nerve conduction studies have demonstrated changes consistent with axonal injury predominantly involving the motor nerves (Ridley 1969, Albers *et al.* 1978). Surprisingly, Mustajoki & Seppatainen (1975) have claimed to have found both motor and sensory conduction abnormalities in latent asymptomatic cases. Histological examination of the peripheral and autonomic nerves obtained at autopsy from patients dying of an acute attack have shown evidence of both demyelination (Gibson & Goldberg 1956) and axonal degeneration (Cavanagh & Mellick 1965, Ridley 1969). A striking feature, however, is the discrepancy between the clinical severity of the neuropathy and the relatively mild histological changes.

Pathogenesis of the clinical features

Until now, the interrelationship between the biochemical disorder of haem synthesis and the pathogenesis of the clinical features has remained conjectural. Nevertheless, the symptomatology of the acute attack has been explained on the basis of a generalized neuropathy (Goldberg 1959).

One of the early pertinent observations made radiologically and confirmed at laparotomy in patients suffering from an acute attack was the presence of marked bowel spasm often interspersed with areas of gut dilatation. This gave rise to the neurogenic theory, proposed in the 1950s, suggesting that the abdominal pain might be due to an autonomic dysfunction causing incoordination of gut innervation (Berlin & Cotton 1950). Other clinical features attributable to an autonomic neuropathy include inappropriate tachycardia, labile

hypertension, which paradoxically can be associated with postural hypotension, excessive sweating, cutaneous vasoconstriction and urinary disturbances, such as retention or frequency of micturition. Of note, Schley *et al.* (1970) reported that some patients appear to excrete large amounts of urinary catecholamines during an acute attack that can reach the high levels seen with a phaeochromocytoma. Unfortunately, no account was given of the severity of pain experienced in relation to the timing of catecholamine measurements. Reports have indicated that ganglion-blocking drugs and phenothiazine derivatives, with their anticholinergic and α-adrenergic blocking effects, are effective in alleviating the abdominal pain of acute porphyria (Melby *et al.* 1956). Similar claims have been made for using β-adrenergic blockers, such as propranolol given in large doses (Beattie *et al.* 1973, Douer *et al.* 1978). At present it is not possible to draw any firm conclusion as to the role of cholinergic or adrenergic neurotransmission in the pathogenesis of the pain.

Disturbances of the haem biosynthetic pathway could impair the functioning of the nervous system in several ways. First, the elevated plasma concentrations of ALA and PBG originating from the liver or other organs could interfere with neurotransmission or affect other cellular functions of the nerve cells. Other monopyrrolic compounds like haemopyrrole-lactam, capable of depressing ALA-S activity in rat liver, are present in increased amounts in the urine of patients with acute intermittent porphyria; but, no correlation was found between these elevated urinary concentrations and the clinical activity of the disease (Graham *et al.* 1979). It is of interest that Irvine (1974) should point out that these substances, also found to be neurotoxic in mice, are excreted in the urine of a high proportion of patients suffering from a variety of psychiatric disorders, the reason for which remains obscure. Second, the neuropsychiatric manifestations could be due to the depletion of important co-factors which, although not directly related to haem synthesis, might be a consequence of the inherited enzymic defect. For example, tissue depletion of pyridoxal phosphate necessary for ALA-S activity (Cavanagh & Ridley 1967), and defective mitochondrial oxidation of NADH (Labbe 1967, Bonkowsky *et al.* 1975) have been suspected. Third, should there be a deficiency of URO-S activity in the cells of the nervous system as already demonstrated in other tissues, such as the liver, erythrocytes, cultured fibroblasts and amniotic cells (Sassa *et al.* 1975), then the intracellular accumulation of ALA, PBG or other monopyrroles could possibly cause a functional impairment or even exert a cytotoxic effect. Lastly, the enzymatic deficiency could restrict the availability of haem compounds necessary for certain oxidation reactions and for energy production.

Neurobiochemistry

Although a broad relationship exists between the neurological dysfunction and increased urinary concentrations of ALA and PBG, the pathogenetic role of these compounds remains controversial. In contrast to the non-acute types of porphyrias (i.e. cutaneous hepatic porphyria, erythropoietic protoporphyria and congenital porphyria), in which neurological dysfunction does not become manifest, excessive excretion of ALA and PBG is characteristic of the acute porphyrias. Interestingly, a similar type of neuropathy occurs in lead poisoning (Dagg *et al.* 1964) and hereditary tyrosinaemia (Gentz *et al.* 1969) in which ALA levels are grossly elevated.

Central to the ALA-neurotoxicity hypothesis is the unsettled question as to whether a significant amount of ALA crosses the blood-brain barrier to affect the nervous system. Percy & Shanley (1977) concluded that the blood-brain barrier was relatively impermeable to ALA after finding low concentrations of this compound in the CSF of four patients with acute attacks of variegate porphyria. They had previously reported that in rats, pre-treated with phenobarbitone, the brain concentrations of the porphyrin precursors reached a maximal 4–8% of the blood levels (Shanley *et al.* 1975). On the other hand, McGillion *et al.* (1974, 1975) showed that ALA could pass the blood-brain barrier at plasma concentrations known to occur in the acute attack of porphyria. Becker and his associates (1974) also provided evidence that slices of brain preparations could concentrate ALA.

It has not been possible to demonstrate conclusively any major neurotoxic effects of ALA: while abnormal behavioural changes were induced in rodents given high doses of ALA (McGillion *et al.* 1973, Shanley *et al.* 1975), Watson *et al.* (1978) reported that neither ALA nor PBG caused any change in the behavioural pattern or blood pressure of nephrectomized rats. Goldberg *et al.* (1955) and Marcus *et al.* (1970) observed no neurological abnormality in animals with allyl isopropyl-acetamide-induced experimental porphyria in which high levels of ALA are produced endogenously. Oral and parenteral administration of ALA and PBG have failed to induce an acute attack of porphyria in man (Dowdle *et al.* 1968, Meyer *et al.* 1972). These negative findings are not surprising, since the plasma concentrations of ALA and PBG attained are relatively low and transient, approaching nowhere near the levels in the porphyric states. Tishler *et al.* (1982) have recently shown that solid-phase sorbents, such as coconut-derived activated charcoal, are extremely effective in removing ALA, PBG and formed porphyrins. The possible use of these agents in haemoperfusion might provide a means for settling the issue of whether elevated concentrations of monopyrroles in plasma cause the acute attack.

ALA has been shown to affect neuromuscular function in a variety of ways in different types of *in vitro* preparations (Dichter *et al.* 1977, Loots *et al.* 1975, Cutler *et al.* 1978, 1980). But the concentrations of ALA required in these experiments are several times higher than those occurring in the cerebrospinal fluid of patients with porphyria or lead poisoning. ALA, structurally similar to the neurotransmitter gamma amino-butyric acid (GABA), has been shown to have GABA-agonist effects *in vivo* and *in vitro* (Nicholl 1976, Brennan & Cantrill 1979). The clinical relevance of this observation remains open to question as sodium valproate, an anti-convulsant drug with potent GABA-agonist properties, has been considered to be safe for use in porphyric patients by some investigators (Biagini *et al.* 1979, Houston *et al.* 1977) but condemned as outright porphyrinogenic by others (Doss *et al.* 1981).

Haem deficiency

Impaired haem biosynthesis within the nerve cells can cause a deficiency of essential haemoproteins such as the microsomal cytochromes required for the mixed-function mono-oxygenase system or the mitochondrial cytochromes necessary for oxidative phosphorylation. Control of the initial and rate-limiting enzyme ALA-S is effected by haem via feedback repression and inhibition both at transcriptional and translational levels. Partial blockade of the haem biosynthetic pathway has been shown experimentally to cause an impairment of drug-mediated induction of cytochrome P450 (Smith & De Matteis 1980). It is therefore of interest that the addition of haematin to rat brain preparations resulted in a marked increase in its mono-oxygenase function (Omiecinski *et al.* 1979). If the neuropathy of acute porphyria were due to impaired intraneuronal haem biosynthesis, then the factor precipitating an acute attack ought to modify neuronal haem biosynthesis. Yet two independent studies failed to demonstrate the induction of rat brain ALA-S after fasting the animals or by injecting intraperitoneally porphyrinogenic materials like alcohol, allyl-isopropyl-acetamide or phenobarbitone (Paterniti *et al.* 1978, Percy & Shanley 1979).

Prophylaxis

Preventive measures have a major role to play in the management of acute porphyria. The majority of individuals with the porphyric trait are asymptomatic and well unless they are exposed to some precipitating factor, the most important being certain drugs, steroidal hormones, alcohol and fasting. Accurate detection of the latent case is now possible with the measurement of ALA-S and URO-S activities in peripheral blood cells (McColl *et al.* 1982). Sole reliance upon urinalysis is of limited value as increased excretion of ALA and PBG is present in only about one-third of latent cases. Following identification of the heterozygous individual, advice must be given about possible risk factors to be avoided. Moreover, a list

of suspected porphyrinogenic drugs (Moore 1980) should be given to each patient who is also instructed to inform any medical attendant that he has acute porphyria.

Management of the acute attack

In dealing with an acute attack the first step is to remove or correct any potential porphyrinogenic factor, such as drugs or infection. Management is then directed at controlling pain, ensuring a good fluid and nutritional intake, providing appropriate physiotherapeutic measures, and last but not least, maintaining the patient's morale and alleviating fear.

Correction of any fluid or electrolyte imbalance is important. Supplementary carbohydrates in the form of glucose or laevulose, given orally, by nasogastric tube or parenterally, appear to modify an attack, both clinically and biochemically. It has been our experience that the timely use of supplementary feeding aborts the onset of the paralytic phase.

Muscle weakness and limb paralysis require appropriate physiotherapy and splinting to prevent contractures or overstretching of tendons. Active physiotherapy should be started as early as possible and continued until full recovery. With the onset of muscle paresis, pulmonary function must be carefully monitored to detect incipient respiratory embarrassment. The Wright peak flow rate meter provides a simple, but useful, means of monitoring the patient's ventilation sequentially. At the earliest signs of respiratory embarrassment, at times heralded by dysphonia, intermittent positive pressure ventilation should be considered; indeed, full recovery can take place following such assistance for several months.

Depression, often accompanied by marked emotional lability, commonly occurs during the acute attack. With good nursing care, it does not usually require any specific therapy, provided pain relief is adequate. In some cases, however, other psychiatric manifestations such as hypomania or an acute organic brain syndrome may necessitate the use of psychotropic agents like chlorpromazine. Phenothiazine drugs also constitute a useful analgesic adjunct, but troublesome postural hypotension can complicate treatment, especially when combined with β-adrenergic blockers or large doses of narcotic analgesics.

Anticonvulsant therapy is not indicated if convulsive seizures are short-lived and infrequent, but prolonged seizures are best treated with intravenous diazepam. As none of the currently available oral anticonvulsant drugs is absolutely safe in porphyria, they should all be avoided whenever possible. In the past, however, we have successfully used sodium valproate to control epilepsy, whereas other workers have recommended oral bromide or clonazepam (Larson *et al.* 1978, Bonkowsky *et al.* 1980).

Recently, intravenous haematin infusion has been claimed as a major therapeutic advance (Bonkowsky *et al.* 1971, Dhar *et al.* 1975). It is aimed at restoring effective repression of ALA synthase to reduce the excessive production of ALA and PBG. Unfortunately, in our experience, haematin therapy has not been consistent in improving the clinical state of the patients in the severe acute attack, although there is definite biochemical improvement (McColl *et al.* 1981). Not only do the irritant and thrombogenic effects of the haematin preparation preclude its repeated use, but it can also cause acute renal failure.

Over the years claims have been made for the effectiveness of other remedies in shortening the acute attack but, because of the unavailability of patients in sufficient numbers, few if any of these treatments have been properly evaluated. For instance, whereas Cavanagh & Ridley (1967) argued the case for providing supplementary pyridoxal phosphate to replenish the tissue levels of this co-factor for ALA-S, Becker & Kramer (1977) suggested that giving sodium benzoate orally may divert glycine, necessary for ALA synthesis into the hippurate pathway. A preliminary report also encouraged the use of large doses of folic acid as a means of 'boosting' URO-S activity during the acute attacks (Wider de Xifra *et al.* 1980). Although chlorpromazine and other phenothiazine derivatives are useful for their antiemetic and sedative properties, the evidence that these drugs act primarily on the pyrrolic disturbance

for their beneficial effect is not convincing. In much the same way, β-adrenergic blockers can satisfactorily control the hypertension and tachycardia occurring in the more severe acute attacks, but whether large doses of propranolol *per se*, e.g. 1 gram daily, can modify the disease process is yet to be confirmed (Douer *et al.* 1978).

Pain control

Many patients seem to control their abdominal pain with simple analgesics, such as paracetamol, aspirin or dihydrocodeine, provided the attack subsides within a few days. When the pain becomes more severe, however, it may need stronger narcotic analgesics, like pethidine or morphine. In a prolonged attack, the patient's response to pain changes from the 'acute pain situation' with typical sympathomimetic accompaniments, to a 'chronic pain situation' during which the patient may not look particularly distressed while complaining bitterly of severe pain. Once a 'chronic pain situation' sets in, even large doses of narcotic analgesics are often incapable of controlling the abdominal pain. Failure to provide adequate symptomatic pain relief in other acute and chronic painful conditions is still a widespread occurrence in clinical practice, and with acute porphyria this can be a particular problem.

We have been treating a group of eight patients with AIP who have had frequent attacks of the disease, often lasting for several months. Pain control in three such patients could not be achieved in spite of large doses of narcotic analgesics administered by slow intravenous infusion. Interestingly, parenteral administration of naloxone, the specific opiate-receptor antagonist, immediately after the pethidine or morphine infusions, appeared to confer some symptomatic benefit to the pain, contrary to what was to be expected. Our preliminary data suggest that there might well be an abnormal opiate-receptor response in such patients having recurrent episodes of acute porphyria.

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