Therapeutics Reviews

Acute Intermittent Porphyria: Pathophysiology and Treatment

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Acute intermittent porphyria is caused by an inherent error of porphyrin metabolism characterized by a deficiency of porphobilinogen deaminase and increased activity of delta-aminolevulinic acid synthase, key enzymes necessary for the biosynthesis of heme. During an attack patients may have abdominal pain, vomiting, muscle weakness, constipation and neuropsychiatric symptoms. In the majority of individuals the disease remains clinically latent throughout life. Various drugs and chemicals, hormones and nutritional factors predispose to clinical attacks, probably by inducing hepatic delta-aminolevulinic acid synthase. Avoidance of these substances is important in preventing attacks. Screening of family members to detect genetic carriers permits precautionary measures. Management of attacks includes symptomatic therapy, high carbohydrate intake and intravenous administration of hematin.
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OUTLINE

Acute intermittent porphyria (AIP) is a hereditary disorder characterized by an abnormality in the pathway of heme biosynthesis, resulting in an overproduction of precursors of heme. The genetic defect is inherited as an autosomal dominant trait. Although the exact prevalence is not known, the frequency of clinical disease or acute attacks of porphyria is higher in females than in males. Attacks most commonly occur between the ages of 20 to 50 years and are virtually never seen before puberty.

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Fundamental Defect

Heme is synthesized primarily in the liver and the bone marrow by a complex pathway that involves a series of enzymatic reactions (Figure 1).[1–3] Starting with succinyl CoA and glycine, the first step is the formation of delta-aminolevulinic acid (ALA). This reaction, catalyzed by the mitochondrial enzyme delta-aminolevulinic acid synthase (ALA synthase), is the rate-limiting step in the pathway. Under basal conditions, the activity of hepatic ALA synthase is low. Certain drugs and chemicals, however, can induce enzyme activity to levels 50 to 100 times above the baseline.[4–6] An increased demand for heme can also induce hepatic ALA synthase. Heme, the end product of the pathway, represses hepatic ALA synthase through a negative feedback effect as shown in Figure 1. The activity of ALA synthase is known to be limiting for overall heme synthesis in the liver. It is not clear if this is also the case in the bone marrow or in most other organs.

Another key enzyme in the pathway is porphobilinogen deaminase (PBG deaminase), which has frequently been referred to as uroporphyrinogen I synthetase. Recent evidence indicates that PBG deaminase does not produce uroporphyrinogen directly, but forms a straight-chain tetrapyrrole, hydroxymethylbilane, which then undergoes cyclization to produce uroporphyrinogen I.[7] In acute intermittent porphyria, PBG deaminase activity is approximately 50% of that seen in normal individuals. A deficiency of PBG deaminase activity, even to 50% of normal, in itself is not sufficient to cause overpro-

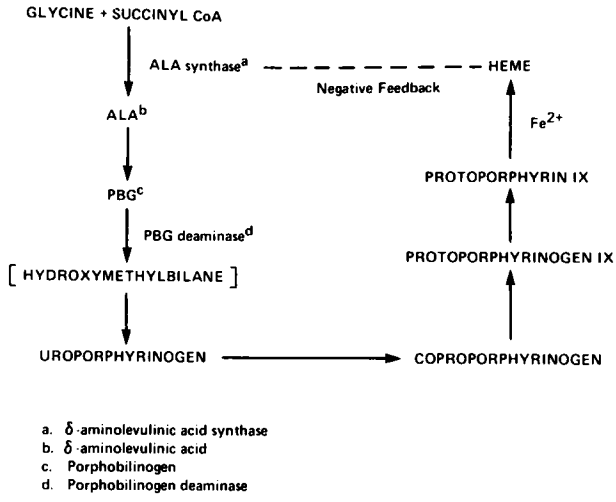

Figure 1. Heme biosynthetic pathway.

duction or overexcretion of the porphyrin precursors. Also required is an increase in ALA synthase activity, coupled with a loss of ALA and porphobilinogen (PBG) from hepatocytes and perhaps other cells. The disease in the majority (about 90%) of AIP remains clinically latent, and patients seldom excrete excessive quantities of porphyrin precursors, even though deficiency of PBG deaminase is present. It is likely that in latent carriers, hepatic ALA synthase activity is normal. Drugs, chemicals and factors that exacerbate AIP appear to act by inducing ALA synthase, the rate-controlling enzyme for hepatic heme synthesis. In AIP, overproduction of ALA and PBG occur in the liver, not in the bone marrow.

Diagnosis

Evaluation for AIP should include measurement of PBG in urine and PBG deaminase in erythrocytes. The Watson-Schwartz test[8] is widely used for qualitative determination of PBG in urine. The drawbacks with qualitative tests presently available are low sensitivity and lack of specificity. False positive or negative results may occur for a variety of reasons. Urinary PBG should be determined quantitatively[9] when AIP is suspected. During an attack, patients excrete excessive quantities of PBG in urine; with clinical improvement, this usually decreases. In the differential diagnosis of acute symptoms that may be due to acute porphyria, it is important to measure urinary porphobilinogen and to demonstrate by qualitative and preferably quantitative methods increases in urinary PBG concentrations.

Porphobilinogen deaminase is most conveniently measured in erythrocytes.[10, 11] Although in AIP the mean enzyme activity is approximately 50% of normal, a wide range in PBG deaminase activity has been observed, with overlap between normal and disease ranges.[1, 2, 12, 13] Activity of PBG deaminase in patients with AIP may fall within the normal range, and more often, within an indeterminate range between normal and disease values.[13] Assay of the deaminase, therefore, totally fails in some cases to diagnose the condition.

Measurement of PBG deaminase in erythrocytes is useful for detecting clinically latent gene carriers in families of patients with known AIP.[12] Because most persons with clinically latent disease have normal urinary PBG excretion, the enzyme assay is more useful for diagnosis. In cases where PBG deaminase activity falls into a range that is nondiagnostic, repeat assays, quantitative determinations of urinary PBG and family genetic analysis are helpful in diagnosis.[12, 13]

Clinical Manifestations

Acute intermittent porphyria mimics a variety of other disorders and is therefore difficult to diagnose on the basis of signs and symptoms alone. The clinical pattern is quite variable. Although the disease is characterized by exacerbations and remissions, a great many patients remain asymptomatic throughout their lifetime. The most common symptoms include abdominal pain, nausea, vomiting, constipation, back pain, muscle weakness, tachycardia, hypertension and a variety of neuropsychiatric symptoms.[1, 2, 6, 14, 15] Abdominal pain is the principal symptom in approximately 85% or more of the attacks. Pain may be localized or general, is often colicky and may simulate appendicitis or biliary colic. Pain in the back and extremities is common and may last from days to months. Motor neuropathy usually affects the upper extremities more severely and may progress to quadriplegia, dysphagia and respiratory paralysis. Impairment of the autonomic nervous system may also occur and result in paralytic ileus. Tachycardia is frequently observed during an acute attack. Hyponatremia may be a complication and has been attributed to the syndrome of inappropriate secretion of antidiuretic hormone.[16, 17] Hypomagnesemia has also been reported and may be severe enough to cause tetany.[17, 18] Neuropsychiatric symptoms frequently observed include hysteria, depression, agitation, delirium, psychoses and seizures.[14]

Pathology

Postmortem studies on patients with acute intermittent porphyria indicate that pathologic changes may involve multiple areas in the central, peripheral and autonomic nervous systems. Both demyelination and axonal degeneration of peripheral and autonomic nerves have been reported in the literature.[6, 19, 20] Ten Eyck and associates[21] demonstrated patchy demyelination with extensive degeneration of neurons. Autopsy studies by Tschudy et al[6] revealed large areas of chromatolysis, vacuolization and degeneration of neurons in the supraoptic nucleus of

the hypothalamus. The mechanism of central nervous system involvement underlying the disease is not known. Several theories have been suggested to explain the chemical mechanism underlying an acute attack. It is possible that neurologic disturbances are caused by either a lack of heme in the nervous system or a toxic effect from excessive amounts of porphyrin precursors and their metabolites. Several investigators have demonstrated that delta-aminolevulinic acid and porphobilinogen, although not normally present in the cerebrospinal fluid, are detectable during acute episodes of porphyria.[6, 22, 23] It is conceivable that certain changes occur in the blood-brain barrier during an attack, thereby allowing prophyrin precursors to gain entry into the central nervous system. It is also likely that because of higher plasma concentrations, porphyrin precursor concentrations in the cerebrospinal fluid become detectable without any change in the blood-brain barrier.

Precipitating Factors

Acute intermittent porphyria may remain clinically latent for indefinite periods of time. The deficiency of the enzyme PBG deaminase does not necessarily lead to an attack, suggesting that superimposed factors come into play in precipitating an episode. Factors that are known to exacerbate AIP include a wide variety of chemicals and drugs,[1, 6, 15, 24–34] drastic changes in diet,[31, 35] starvation, bacterial and viral infections, certain endogenous hormones, onset of puberty, menstruation and pregnancy.

Drugs are frequently the cause of acute attacks of porphyria. Approximately 68% of the heme synthesized in the liver is used for the synthesis of cytochrome P-450, a microsomal enzyme that catalyzes mixed-function oxidations.[2] Drugs and chemicals that are potent inducers of cytochrome P-450 are known to exacerbate AIP. An increase in the requirement for cytochrome P-450 leads to an increased demand for heme. This may partially deplete the regulatory heme pool and lead to induction of ALA synthase, so that the increased demand for heme can be met. It is not clear whether the induction of ALA synthase is mediated by increased synthesis of new enzyme or a stimulation of enzyme activity. Both methanisms may be operative,[5] and it may also occur by other mechanisms. A drug or chemical may decrease the concentration of hepatic heme by either inhibiting the synthesis of heme or by accelerating its destruction. It is also possible that certain drugs may act directly on ALA synthase independent of changes in heme concentration. Drugs that induce cytochrome P-450 or ALA synthase or cause destruction of hepatic heme are best avoided if possible.

All barbiturates, whether alone or in combination with other drugs, are notorious for causing exacerbations of AIP and therefore must be avoided.[15, 24, 26, 27] Sulfonamides and their derivatives have been implicated in causing serious, even fatal, attacks of porphyria[26, 27, 30] Griseofulvin is a potent inducer of delta-aminolevulinic acid synthase and may induce an acute attack.[27, 30–32] The effect of many drugs on porphyria remains unknown. Drugs have been screened for their porphyrinogenic potential using either animal models or tissue cultures with chick embryo liver cell preparations. One must be cautious in extrapolating data from animals or tissue cultures to the clinical setting because of interspecies differences in metabolism. For example, rifampin is a potent enzyme inducer in man, although this effect is not seen in the rat.[33, 34] Furthermore, patients with AIP respond differently to identical porphyrinogenic agents. Many agents do not consistently lead to an attack. For this reason all drugs should be carefully evaluated and merits weighed against risks with their use. Patients must be informed about the potential dangers of drugs and helped to recognize an impending attack. Tables 1 and 2 are a compilation of drugs reported to be safe or unsafe for use in acute intermittent porphyria. Table 3 includes drugs reported as both safe and unsafe, and over which there is still a great deal of controversy. The data have been extracted from reports in the worldwide literature, and references are cited should readers require more extensive information.

Drastic reduction in caloric intake is also known to precipitate acute clinical symptoms of porphyria. In a study by Welland and associates,[35] a 60–80% reduction in daily intake in patients with AIP led to significant increases in urinary ALA and PBG excretion. Isocaloric substitution of fat for protein alone or for protein and carbohydrate had a similar effect. Addition of carbohydrate to the diet was associated with decreases in excretion of ALA and PBG. A reciprocal relationship was demonstrated between carbohydrate and/or protein intake and porphyrin precursor excretion in AIP. A specific link between sex hormones and the heme pathway at the enzyme level was first reported by Granick.[51] In chick embryo liver cell cultures it was demonstrated that estrone, estradiol, progesterone and testosterone stimulated excess porphyrin production. Further studies have revealed that many C_{19} and C_{21} steroids of the 5-beta-hydroxy configuration can stimulate porphyrin synthesis. This was related to the induction of ALA synthase.[52]

Management

Prophylaxis is of utmost importance in preventing an attack of AIP. The patient must be informed about factors that may induce clinical symptoms. Severe reductions in caloric intake should be avoided. All drugs known to exacerbate the disease and all potent inducers of cytochrome P-450 should be avoided if possible.

In general, physicians should be extremely conservative in prescribing drugs for patients with acute porphyria. If a person with a known underlying genetic defect requires a drug that has not been tested, however, it is ethical to administer the agent cau-

Table 1. Porphyrinogenic Drugs

Drug(s)	Reference(s)
Alpha methyldopa	26, 27
Amphetamines	27
Aminopyrine	26, 27
Antipyrine	26, 27
Barbiturates	15, 24, 26, 27, 30
Basulfan	30
Carbamazepine	26, 27, 30, 36
Chlorambucil	30
Chloroform	26
Chlorpropamide	30, 37, 38
Cimetidine	26
Clonidine	39
Cyclophosphamide	30
Cycloserine	40
Dimenhydrinate	27
Ergot preparations	24, 27
Erythromycin	27
Ethchlorvynol	30
Eucalyptol	6
Furosemide	27
Glutethimide	27, 30
Gold preparations	41
Griseofulvin	27, 30, 31, 32
Hydantoins (phenytoin, ethotoin, mephenytoin)	15, 26, 27, 30, 36, 42
Lidocaine and derivatives	43
Meprobamate	42
Methoxyflurane	44
Metoclopramide	45
Oral contraceptives	26, 27, 29, 30
Oxazolidinediones	26, 29
Para-aminosalicylic acid	40
Pargyline	30, 39
Pentazocine	29, 38, 44
Phenylbutazone	29, 30, 37
Primidone	27, 46
Progesterone	27, 29, 30, 37
Pyrazinamide	40
Spironolactone	29, 30
Steroids	26, 29
Succinimides	26, 29, 30, 40
Sulfonamides	26, 27, 30
Sulfonylureas	26, 27, 30, 40
Theophylline	29, 30, 38
Tranylcypromine	30
Valproate	26, 27, 36, 38, 47

tiously and with close observation, including serial measurements of urinary excretion of ALA and PBG.

Another important feature is screening family members for detecting carriers of AIP, so that precautionary measures can be taken to prevent an attack. Evaluation should include quantitative determinations of urinary PBG and erythrocyte PBG deaminase.[1, 2, 13]

Treatment of the Acute Attack

Supportive care is necessary to control the acute

Table 2. Safe Drugs

Drug(s)	Reference(s)
Acetazolamide	30
Adrenaline	26
Aminoglycosides	27
Aspirin	26, 27, 29, 30
Bromides	26, 30
Beta blockers	27, 29, 30
Cephalosporins	26, 27
Chloral hydrate	6, 26, 27, 29, 30
Chlorpheniramine	27, 30
Chlorpromazine	26, 27, 29, 30
Codeine	24, 26, 27, 30
Colchicine	26
Diazoxide	30
Digitalis	27, 29, 30
Diphenhydramine	6, 27, 30
Dicumarol	30
Droperidol	29, 30
Ethambutol	40
Ether	27, 29, 30
Fentanyl	43
Guanethidine	26, 27, 29, 30
Heparin	26
Ibuprofen	26
Indomethacin	26
Insulin	26, 30
Isoniazid	40
Lithium	26
Meperidine	24
Methadone	24
Methenamine mandelate	27
Methylphenidate	30
Morphine group	24, 43
Naproxen	26
Neostigmine	27, 29, 30
Nitrous oxide	27, 29, 30, 44
Nortriptyline	27
Pancuronium	43
Penicillins	27, 29, 30
Penicillamine	26
Pethidine	43
Prednisolone	26
Primaquine	27
Procaine and derivatives	26, 38, 43, 44
Prochlorperazine	27
Promethazine	26, 27, 30, 40
Propantheline bromide	26
Propoxyphene	26, 29, 30, 40
Propranolol	26, 29, 30
Prostigmine	26, 27, 30
Quinine	27
Reserpine	27, 30
Streptomycin	6, 27, 30, 40
Succinylcholine	29, 30
Thiazides	26, 27
Thiouracil	27
Thyroxine	27
Trifluoperazine	26, 27
Tubocurarine	26
Vitamins A–K	27, 30

Table 3. Drugs Listed as both Safe and Unsafe

Drug(s)	Reference(s)
Amitryptiline	26, 27
Androgens	48
Chloramphenicol	26, 29, 30
Chlordiazepoxide	26, 27, 29, 30, 42
Chloroquine	26, 27, 29, 37
Clonazepam	36, 47
Diazepam	26, 29, 30
Estrogens	26, 27, 29, 30, 49
Ethanol	26, 27, 29, 30
Fentanyl	29
Halothane	29, 44
Hydralazine	26, 30, 39
Imipramine	25, 26, 29, 30, 38, 42
Ketamine	26, 27, 29, 30, 44, 50
Nitrofurantoin	29, 30
Oxazepam	26, 29
Paraldehyde	26, 30
Pethidine	29
Probenecid	26, 30
Progesterone	26, 27, 29, 30, 49
Pyrimethamine	26, 27
Rifampin	29, 30, 33, 34
Tetracycline	6, 26, 27, 29, 30

symptoms and prevent complications. Hypertension and tachycardia can be adequately controlled with beta blockers. One patient who was suffering from severe hypertension and tachycardia during an attack was treated with propranolol.[53] A total of dose of 284 mg of propranolol was administered intravenously over a period of 18 hours. The acute symptoms subsided, and there was a concomitant decrease of porphyrin precursors in the urine. Administration of large doses of propranolol, however, is a dangerous practice and requires careful monitoring for hypotension and bradycardia. Bonkowsky and Tschudy[54] reported a case in which two doses of propranolol 10 mg administered intravenously six hours apart was followed by life-threatening hypotension and bradycardia. Menawat et al[55] treated 20 patients during acute attacks with propranolol administered orally in dosages ranging from 20–200 mg/day. The hypertension and tachycardia were adequately controlled within 10 to 15 days of therapy.

Atenolol may be a suitable alternative to propranolol. To date, however, there are no published reports of its use in porphyria. Pain can be adequately controlled with codeine, meperidine or morphine if necessary. Chlorpromazine is a suitable antiemetic and in addition, serves to control the anxiety, neurosis and psychosis frequently observed during an attack. Promazine and trifluoperazine are also of value in management of psychosis. Choosing a drug is a problem when seizures complicate the picture because anticonvulsants are known to exacerbate an attack. All anticonvulsant agents listed under the category of unsafe drugs are best avoided if possible. Numerous reports seem to indicate that bromide may be a useful alternative.[36, 47, 56] Careful monitoring of serum levels is necessary to avoid the many adverse toxic effects associated with bromide.

Carbohydrates are widely used in the treatment of acute attacks of AIP. Investigations on the effects of carbohydrates on porphyria followed the early findings that a high carbohydrate intake could prevent experimental porphyria.[46] Welland and associates[35] demonstrated that a high carbohydrate intake lowered urinary porphyrin precursors in AIP. Further studies revealed that carbohydrates could block the induction of certain enzymes, which was referred to as the glucose effect.[28] Tschudy et al[57] reported that in experimental animal models, large amounts of carbohydrates could prevent porphyria by blocking the induction of ALA synthase. Glucose feeding is known to repress activity of ALA synthase, although the mechanism for this repression has not been clarified.[28] In a study by Giger and Meyer,[58] an inhibitory effect of glucose on drug-mediated induction of ALA synthase was demonstrated in cultured hepatocytes. The glucose effect was dose-dependent and occurred in the complete absence of extrahepatic factors such as serum and hormones, implying a direct effect on hepatocytes and not necessarily mediated through hormonal or other metabolic changes. Glycerol[59] is reported to be as effective as glucose in lowering porphyrin precursor excretion. During the acute attack, 300 to 500 g of glucose are administered per day, either orally or intravenously. Response is variable and may range from a dramatic recovery to no effect at all.

Hematin has been investigated in the treatment of attacks of AIP.[60–67] Intravenous infusion has been found to be effective in reduction of the plasma as well as urinary concentrations of ALA and PBG. The effect has been more dramatic and clinical response to hematin has been more consistent than that seen with carbohydrates. In a number of trials, patients who were unresponsive to glucose responded to hematin. The optimum dose is not known. Dosages of 3–4 mg/kg body weight were selected somewhat arbitrarily and were found to be effective.[61, 63, 65] It is not known whether smaller doses could also be effective clinically. Within 48 hours of administration, plasma concentration of porphyrin precursors decreased by 60–100% of prehematin values. Several days after the infusions were discontinued, the level gradually increased again to reach 50–100% of prehematin values, indicating that hematin-induced repression of ALA synthase was transient. Clinical response to the hematin varied with the severity of the attack. In many cases, patients refractory to glucose therapy showed a striking improvement clinically.[61, 63] As many as 20–50% of patients showed temporary improvement with relapse within 2 to 14 days. In 15–20% there was no apparent benefit from hematin.

Hematin, an exogenous source of heme, is prepared as a lyophilized powder from hemin that is crystallized from human red cells, sterilized and made pyrogen free prior to administration. The solution is administered over 15 to 20 minutes through the tubing of a free-flowing saline infusion. Injections are given at 12- to 24-hour intervals for 3 to 5 days. Intravenously administered hematin is bound to albumin and hemopexin in the plasma.[68, 69] The mean concentration of circulating hemopexin, a beta-globulin, is only 77 mg/100 ml.[70] When the hemopexin pool is saturated, hematin binds to albumin from where it is slowly released as free hemopexin becomes available.[71, 72] The heme-hemopexin complex is transferred to the liver where hematin is released and represses hepatic delta-aminolevulinic acid synthase.[63, 72, 73] The clearance of hematin from serum is biexponential, with a half-life for the first component ranging from 4.5 to 10.6 hours and for the second component 28 to 54 hours.[63] Fifty percent to 70% of an administered dose is converted to bilirubin in the liver.[74, 75] Exogenously administered hematin ultimately appears in the bile as free hematin or bilirubin.

Few complications have been reported when hematin was administered in recommended doses. Dhar et al[76] reported a case of transitory renal failure following rapid administration of 1,000 mg in a patient with acute porphyria. The picture was consistent with acute tubular necrosis, which resolved after hematin was discontinued. It was theorized that this adverse effect resulted from significant amounts of circulating free hematin. Coagulopathy manifested by markedly prolonged prothrombin time, partial thromboplastin time and thrombocytopenia has been reported.[77] Thrombophlebitis has been reported at the site of infusion.[63]

Summary

Acute intermittent porphyria is a hereditary disorder characterized by the deficiency of porphobilinogen deaminase, an enzyme necessary for the biosynthesis of heme. This results in over production, accumulation and excessive excretion of porphyrin precursors, notably delta-aminolevulinic acid and porphobilinogen. The disease is characterized by exacerbations and remissions. Many patients remain asymptomatic until a precipitating factor activates the disease to provoke an attack. Many drugs have been notorious in causing attacks.

During an acute attack the patient may experience abdominal pain, nausea, constipation, muscle weakness and neuropsychiatric symptoms. Treatment involves two therapeautic approaches: use of a high-carbohydrate diet and the administration of intravenous hematin.

One of the ultimate goals in acute intermittent porphyria is prevention of an attack by avoidance of known precipitating factors. It is important for clinicians to be familiar with drugs and other factors that have been known to cause acute attacks of porphyria. The patient should be counseled and warned about potential danger of drugs so that acute, life-threatening attacks of the disease can be prevented.

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