Porphyria

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Glossary

genetic heterogeneity Several different mutations in the same gene are found in a genetic disorder.
porphyrin Compound with a chemical structure consisting of four pyrrole groups linked by methene bridges; the compound is pigmented and exhibits red fluorescence when exposed to ultraviolet light around 400 nm (Soret band).
porphyrinogen Reduced form of the porphyrin; not pigmented and does not exhibit fluorescence.
porphyrin precursors Early intermediates of the heme biosynthetic pathway (δ-aminolevulinic acid and porphobilinogen) from which pyrrole groups are formed.

Introduction

The first descriptions of the porphyrias appeared in the latter part of the nineteenth century. During the twentieth century, the individual porphyrias were identified and their biochemical and clinical features were defined. The porphyrias have been classified as hepatic or erythropoietic, depending on which tissue is the major site of expression of the biochemical abnormalities. Some are also classified as acute or inducible because they are associated with episodic attacks of neuropsychiatric dysfunction. In this article, the biochemical and clinical features of the eight types of porphyria are outlined. Two conditions that may be confused with the porphyrias, secondary porphyrinuria and pseudoporphyria, are also described.

Biochemical Abnormalities in Porphyrias

Porphyrins/porphyrinogens and porphyrin precursors are intermediates of the heme biosynthetic pathway, a critical metabolic process that involves eight enzymes. The first step in the pathway, which is the condensation of succinyl coenzyme A and glycine to form δ-aminolevulinic acid (ALA), is catalyzed by the mitochondrial enzyme ALA synthase and is rate limiting in the liver. The last step, in which ferrous iron is inserted into protoporphyrin to produce heme, also takes place in the mitochondria. Intermediate steps to form porphobilinogen (PBG) and porphyrinogens occur in the cytoplasm.

Deficient activity of an enzyme in the pathway causes a specific pattern of accumulation and excretion of porphyrins and porphyrin precursors (Table I). In the acute porphyrias, this is exacerbated during an attack due to a marked increase in hepatic ALA synthase activity. The pattern of biochemical abnormalities is used to diagnose porphyria in a patient with compatible clinical features. Demonstration of deficient enzyme activity in cells/tissue is also used in diagnosis, particularly in acute intermittent porphyria and the familial form of porphyria cutanea tarda.

The cloning and sequencing of cDNA and genomic DNA for enzymes of the pathway have made it possible to identify gene mutations that underlie the enzyme defects in the porphyrias. Genetic heterogeneity has been found in each. Thus, molecular analysis has not yet found widespread use in diagnosis, but it is helpful in identifying asymptomatic carriers of the gene defect in families in whom a mutation has been found and for evaluating individuals in geographic areas where a specific mutation has a high prevalence. There is not usually a clear relationship between specific gene mutations and the severity of clinical and biochemical manifestations, and expression of the disease is variable even among members of a family. Thus, other genetic and/or acquired factors are often critical to the phenotypic expression of the disorder.

Hepatic Porphyrias

Several porphyrias are classified as hepatic because the liver is the major site of expression of the biochemical abnormalities (Table I). Four of the hepatic porphyrias are also termed acute because there occur episodes of severe neuropsychiatric dysfunction that are separated by asymptomatic periods (Table II). The acute attacks are precipitated by ingestion of drugs, fasting, alcoholism, infection, and hormonal effects. The most common symptom is abdominal pain, which may be accompanied by hypertension and tachycardia as manifestations of autonomic nerve dysfunction. Peripheral neuropathy causes paralysis and respiratory compromise if the attack is severe. Psychiatric manifestations include hysteria, psychosis, and depression, which

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Table I Biochemical Abnormalities in the Porphyrias[a]

Type of porphyria	*Enzyme defect*	*Location/biosynthetic step*	*Major site of expression*	*Principal biochemical features*
ALA dehydrase deficiency	ALA dehydrase	Cytoplasm/2	Liver	↑ ALA in urine
Acute intermittent porphyria	PBG deaminase	Cytoplasm/3	Liver	↑ ALA and PBG in urine
Hereditary coproporphyria	Coproporphyrinogen oxidase	Mitochondria/6	Liver	↑ ALA, PBG, coproporphyrin in urine ↑ Coproporphyrin in feces
Variegate porphyria	Protoporphyrinogen oxidase	Mitochondria/7	Liver	↑ ALA, PBG, coproporphyrin in urine ↑ Protoporphyrin in feces
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Cytoplasm/5	Liver and bone marrow	↑ Uroporphyrin in urine Isocoproporphyrin in feces
Hepatoerythropoietic porphyria	Uroporphyrinogen decarboxylase	Cytoplasm/5	Liver	↑ Zn-protoporphyrin in red cells ↑ Uroporphyrin in urine Isocoproporphyrin in feces
Erythropoietic porphyria	Uroporphyrinogen III synthase	Cytoplasm/4	Bone marrow	↑ Uroporphyrin in red cells ↑ Uroporphyrin in urine
Erythropoietic protoporphyria	Ferrochelatase	Mitochondria/8	Bone marrow (liver variable)	↑ Protoporphyrin in red cells ↑ Protoporphyrin in feces

[a]Abbreviations: ALA, δ-aminolevulinic acid; PBG, porphobilinogen.

Table II Clinical Features in the Porphyrias

Type of porphyria	*Usual inheritance*[a]	*Usual onset of disease*	*Photocutaneous lesions*	*Neuropsychiatric symptoms*	*Chronic liver disease*	*Hepatoma*
ALA dehydrase deficiency	AR	Childhood	−	+	−	−
Acute intermittent porphyria	AD	Early adulthood	−	+	−	+
Hereditary coproporphyria	AD	Early adulthood	+	+	−	+
Variegate porphyria	AD	Early adulthood	+	+	−	+
Porphyria cutanea tarda	AD (familial type)	Adulthood	+	−	+	+
Hepatoerythropoietic porphyria	AR	Childhood	+	−	+	−
Erythropoietic porphyria	AR	Infancy	+	−	−	−
Erythropoietic protoporphyria	Triallelic	Childhood	+	+ (cholestatic crisis)	+	−

[a]Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

sometimes persist after the attack has subsided. Seizures also occur and present a difficult problem because most antiepileptic drugs can exacerbate the attack.

During an acute attack, urinary excretion of the porphyrin precursors ALA and PBG increases markedly. Clinical and basic studies indicate that ALA may cause the neurological dysfunction. An alternate possibility is that heme deficiency in nerve tissue is the cause. Finally, both (and other) factors may underlie the attack.

Therapy of the acute attack consists of stopping the precipitating factor, carefully managing fluid and electrolyte status, and providing adequate caloric intake that is high in carbohydrates. Intravenous administration of hematin (ferriheme hydroxide) has become standard, because this may promptly ameliorate biochemical and clinical manifestations. During asymptomatic periods, patients should not take drugs that precipitate attacks, should avoid fasting and excess intake of alcohol, and should have infections treated promptly.

In four of the hepatic porphyrias, photocutaneous lesions occur (Table II). Skin fragility develops as a consequence of the photoactive properties of porphyrins deposited in skin tissue and/or circulating in dermal blood vessels. This causes blisters to form after minor trauma to sun-exposed areas. Erosions, scarring, pigment changes, and small white papules called milia subsequently develop. Sclerodermoid changes of the skin may occur in long-standing untreated disease.

In porphyria cutanea tarda, hepatic iron overload is frequent, and there is an increased prevalence of mutations in the HFE gene, which is associated with hereditary hemochromatosis. Patients also have a higher rate of chronic hepatitis C. In long-standing untreated porphyria cutanea tarda, there is an increased incidence of hepatocellular carcinoma. This is also found in the acute porphyrias, particularly acute intermittent porphyria, the reason for which is unclear.

The photocutaneous lesions in porphyria cutanea tarda are managed by phlebotomy to deplete excess hepatic iron, as uroporphyrin formation decreases concomitantly. Removal of 4–8 liters of blood usually resolves the clinical and biochemical abnormalities. Chloroquine or related compounds are used if phlebotomy is not tolerated. Once in remission, most patients with porphyria cutanea tarda remain free of photocutaneous lesions provided that they avoid taking iron-containing compounds and remain abstinent from alcohol. Photocutaneous lesions in variegate porphyria and hereditary coproporphyria do not respond to phlebotomy, however.

Erythropoietic Porphyrias

In two porphyrias, erythropoietic protoporphyria (EPP) and erythropoietic porphyria, the bone marrow is the major site of expression of the biochemical abnormalities. The major clinical manifestation in EPP is lifelong photosensitivity. In contrast to the other porphyrias, photosensitivity occurs acutely during sun exposure. Erythema and edema of the skin develop but blisters and erosions are rare. Chronic skin changes involve thickening and lichenification of the skin on the nose and dorsal aspects of the hands. Oral administration of β-carotene reduces photosensitivity in many patients. In some cases, the only effective management is use of opaque sunscreens or avoidance of sun exposure, even through window glass.

Hepatobiliary disease is another feature of EPP, and in approximately 5% of individuals, the occurrence of structural damage to the liver may cause liver failure and necessitate liver transplantation. Liver damage is due to the toxic effect of protoporphyrin on liver function and structure, particularly when there is progressive accumulation of protoporphyrin in the liver due to impaired excretion of protoporphyrin in bile. Therapies for this condition involve interruption of the enterohepatic circulation of protoporphyrin by using cholestyramine or activated charcoal and decreasing the excess production of protoporphyrin and improving liver function through the intravenous administration of hematin. However, when liver damage is advanced, liver transplantation is the only effective treatment. Unfortunately, disease frequently recurs in the graft because excessive production of protoporphyrin in the bone marrow is not significantly changed by liver transplantation.

Erythropoietic porphyria is a recessive disorder that usually has onset in infancy. A few cases of adult onset have been reported. Skin lesions are similar to those in porphyria cutanea tarda. As patients age, there may be progressive destruction of the fingertips, ears, and nose. Hemolytic anemia and splenomegaly are common. Therapy is generally supportive, consisting of protection from sun exposure and prompt treatment of skin infections. Red blood cell transfusion and intravenous administration of hematin are used to decrease the production of porphyrin. Splenectomy effects remission of disease in some patients.

Secondary Porphyrinuria and Pseudoporphyria

Several diseases are associated with an increase in the urinary excretion of porphyrin, particularly coproporphyrin excretion, which is termed secondary porphyrinuria. These diseases include various types of anemia and malignancy, hepatobiliary diseases, diabetes, and infections. Some patients have abdominal pain and other symptoms of acute porphyria. However, with the exception of lead poisoning and hereditary tyrosinemia, urinary excretion of ALA and PBG is normal. The patients also do not develop photocutaneous lesions like those with the porphyrias. Thus, the secondary porphyrinurias can usually be distinguished from the porphyrias.

Pseudoporphyria is a condition in which there are skin lesions similar to those in porphyria cutanea tarda, but serum and urine porphyrin levels are normal or only minimally elevated. This occurs in renal failure, from use of medications such as nonsteroidal antiinflammatory drugs and tetracycline, and from ultraviolet A exposure. Treatment consists of discontinuing the causative factor and protection from the sun.

Further Reading

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