CONTINUING MEDICAL EDUCATION

PORPHYRIAS

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Porphyrias are metabolic disorders of porphyrin biosynthesis and excretion and their cutaneous lesions act as a mirror of their systemic nature. They are mainly hereditary, but may be acquired. Characteristic clinical features are accompanied by specific patterns of porphyrin over-production, accumulation and excretion, each pattern defining a particular form of porphyria.

HISTORICAL

In 1874, Schultz and Baumstark[1] were the first to report a case of porphyria under the name of "Pemphigus leprosus." Gunther[2] did not discover congenital porphyria, though he clarified the confusing clinical patterns of various types of porphyrias as early as 1912 and 1925.[3] In 1937, Waldenstrom[4] introduced the title porphyria cutanea tarda (PCT). Schmid et al[5] in 1954, divided the porphyrias into two groups depending upon whether the main pathology was in the bone marrow or the liver. Thus, Gunther's disease was renamed congenital erythropoietic porphyria (CEP) and porphyria cutanea tarda (PCT) became just one of several kinds of hepatic porphyrias. Porphyria may justly be called as a Royal malady. Ida Maccalpine and her colleagues[6] have detected the presence of porphyrias in royal members of the Houses of Stuart, Hanover and Prussia. The illness of King George III has been traced to porphyria.

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Porphyrins are mainly synthesized in bone marrow and liver. Stages of porphyrin synthesis are shown in figure 1.

Normally, the body is most economical with the porphyrins that it forms and only traces of them are excreted in the urine and stools. In porphyria, however, there is mostly increased formation and excretion of porphyrins or some of its precursors.

Normal quantitative values of porphyrins in urine, stools and red blood cells of Punjabis (Indians)[8-15] compared with those of Whites (given in brackets)[16] are given in table 1.

Table I. Normal quantitative values of porphyrins in urine, stools and RBCs of Punjabis (Indians) compared with those of Whites (given in brackets) (Goldberg, 1966)

Urinary	
Coproporphyrins	12.93-117.85 (0-280) ug/24 hrs.
Uroporphyrins	0-22.71 (0-40) ug/24 hrs.
Porphobilinogen	0.11-1.67 (0-0.5) mg/24 hrs.
d-Aminolevulinic acid	0.27-3.82 (0-5.0) mg/24 hrs.
Faecal	
Coproporphyrins	0.28-3.52 (0-50) ug/g dry weight
Protoporphyrin	1.05-14.91 (0-115) ug/g dry weight
"X"	0.05-5.42 (0-20) ug/g dry weight
Red blood cells	
Coproporphyrins	0-4.99 (0-4) ug/100 ml cells
Protoporphyrin	2.26-83.9 (0-30) ug/100 ml cells

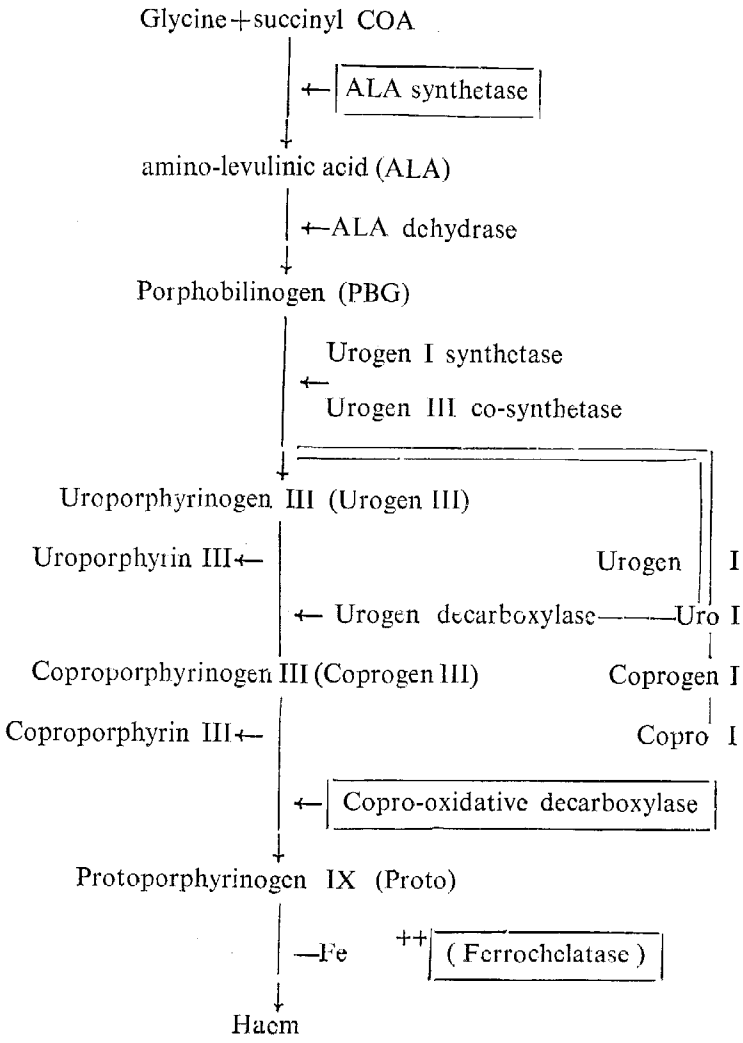

Fig. 1. Simplified scheme of the main features of the porphyrin biosynthetic pathway. Enzymes shown in boxes are intra-mitochondrial, others lie in cell sap. Pathway indicated in double line with series I isomers, normally insignificant, is greatly increased in Gunther's disease and PCT (Dr. I. A. Magnus).

Review of Indian Literature

1956 First report from India dates back to 1956, when Taneja and Seth[38] from Delhi described congenital erythropoietic porphyria in two brothers.

1958 Chaudhary et al[17] reported two cases of congenital erythropoietic porphyria from Calcutta.

1960 Dhirwani 18 reported two cases of acute hepatic porphyria.

1961 Mandal[19] reported one case of congenital erythropoietic porphyria from Calcutta.

1962 Chatterjee and Chatterjee[20] reported two cases of congenital erythropoietic porphyria from Calcutta.

1962 Chatterjee and Chatterjee[21] reported one case of porphyria cutanea tarda from Calcutta.

1963 Bhargawa[22] reported one case of porphyria cutanea tarda from Bikaner.

1963 Subhedar and Markand[23] reported one case of acute intermittent porphyria.

1964 Handa[39] reported three cases of congenital erythropoietic porphyria in one family from Punjab.

1965 Choube and Chorghade[24] reported seven cases of acute intermittent porphyria from Nagpur.

1970 Harjeet Singh and Nachhattar Singh[25] reported one case of acute intermittent porphyria from Punjab.

1970 Bhargawa and Gupta[26] reported six cases of acute intermittent porphyria from Bikaner and a further study of their families but this study lacks the support of detailed porphyrin analysis.

1972 Verma and Krishanbir Singh[27] reported a case of congenital erythropoietic porphyria from Haryana.

1972 Ghosh[28] reported a case of congenital erythropoietic porphyria with scleromalacia perforans from Calcutta.

1974 Bhutani et al[40] reported autopsy findings in a case of congenital erythropoietic porphyria from Delhi.

1975 Handa et al[61] reported a case of variegate porphyria from Punjab.

1976 Hajini et al[29] reported a case of congenital erythropoietic porphyria from Kashmir.

1977 Insaf and Khan[30] reported a case of erythropoietic uroporphyria from Aligarh.

1980 Mehta and Agrawal[31] reported two cases of a relatively benign variant of congenital erythropoietic porphyria.

1984 Mittal and Gautam[33] reported one case of acute intermittent porphyria from Delhi.

1984 Sharma et al[33] reported a case of congenital erythropoietic porphyria from Nagpur.

The author, in addition has observed six cases of CEP and six cases of PCT along with one case of AIP at Patiala, in addition to the reported data **(Unpublished data)**

BIOCHEMICAL ABNORMALITIES

Congenital erythropoietic porphyria (CEP)

The underlying enzyme defect in CEP is a deficiency of uroporphyrinogen III co-synthetase relative to uroporphyrinogen I synthetase. This leads to the formation of a greater proportion of uroporphyrinogen I, while the overall production of porphyrinogen III is normal or may even be increased. Uroporphyrinogen I, cannot be used for haem synthesis and is deposited in the tissues and converted to uroporphyrin I, partly excreted in the urine and partly converted to coproporphyrinogen I and coproporphyrin I for excretion mainly but not entirely in the faeces.

Erythropoietic protoporphyria-erythrohepatic protoporphyria (EPP)

The defect in EPP responsible for increased synthesis of ALA synthetase is not known with certainty. It is probably due to deficient synthesis from protoporphyrin of haem required for a specific haem protein important in the feedback mechanism. This may affect both the liver and bone marrow. The excess protoporphyrin in the liver is partially excreted in the faeces through bile and partly transferred via the plasma to the circulating red cells which take up protoporphyrins passively, thus augmenting the protoporphyrins accumulation because of the defect in erythropoietic tissue.

The hepatic porphyrias

Current concept of pathogenesis of hepatic porphyrias is increased production of ALA in the liver.

Symptomatic cutaneous hepatic porphyria (PCT)

There is increased endogenous production of ALA by the liver, possibly due to a partial block in haem synthesis. At present it is not clear why the acute attack and porphobilinogenuria do not occur in PCT.

Bantu porphyria

The urine contains excessive quantities of porphyrins and occasionally, increased amounts of porphobilinogen and delta-amino-laevulinic acid, but the faecal porphyrins are not significantly increased.[34]

Turkish porphyria

Uroporphyrin I and coproporphyrin III are excreted in the stools and urine, but the urine contains no porphobilinogen. The bone marrow porphyrins are not increased.

Variegate porphyria (VP)

There is increased excretion of urinary ALA and PBG. There is excessive excretion of porphyrin peptide conjugates or "X" porphyrins in variegate porphyria.[35, 36]

Acute intermittent porphyria (AIP)

The increased porphyrin precursor excretion results from high levels of ALA synthetase.

Cutaneous photosensitivity may be associated with increased porphyrin levels in the skin, erythrocytes and/or plasma. Oxidised fluorescent porphyrins absorb light in the 400 nm range and by transferring the absorbed energy to cellular structures, they cause photosensitizing damage.

The suggested chemical mechanisms can be divided into two main classes.[7] One possibility is that photosensitization involves free radicals. The other possible mechanism, of which there are several variations, invokes excited reactions with photosensitizer in triplet and oxygen in excited singlet states. But very propably both free radicals and excited states occur together.[7]

The syndromes, as recognized at present, are usually divided into two forms,[7] namely erythropoietic and hepatic (Table-II).

Table II. Classification of porphyrias

A. Erythropoietic
Congenital erythropoietic porphyria (Gunther's disease) (CEP)
Erythropoietic protoporphyria or erythro-hepatic protoporphyria (EPP)
Erythropoictic coproporphyria (ECP)
B. Hepatic
Porphyria cutanea tarda (symptomatic porphyria) (PCT)
Acquired
Familial (controversial)
Variegate porphyria (South African genetic porphyria, Mixed porphyria) (VP)
Acute intermittent porphyria (AIP) (Swedish genetic porphyria)
Hereditary coproporphyria
C. Classification uncertain
Hepato-erythrocytic porphyria

CLINICAL FEATURES

Congenital erythropoietic porphyria Gunther's disease (CEP)

Congenital erythropoietic porphyria is one of the rarest human diseases. About one hundred cases of the disease have been described by various authors.[37-40] Hereditary transmission is of autosomal recessive type according to most authorities.[41] Role of consanguinity is not well-established.

Occurrence of congenital erythropoietic porphyria in several siblings is still uncommon.[39] The condition may be present at or soon after birth. The child's diapers are coloured red by the urine. Latent, mild or overt cases apparently with late onset are known. The main clinical features are : Excretion of burgundy red urine, photosensitivity of skin, hypertrichosis and erythrodontia. All these symptoms may not be present at one time or in one patient. Photosensitive skin lesions in erythropoietic porphyria are due to uroporphyrin which is the most photodynamic of all porphyrins. The skin lesions begin with itching and erythema and are followed by a vesiculo-bullous eruption that forms crusts and leaves behind pigmented scars. The scarring when deep may involve cartilage, ligaments and bone with severe mutilation of finger tips, ears and nose. Hypertrichosis may be very extensive. Erythrodontia and pigmentation of bones are due to continuous deposition of uroporphyrin-I in the tissues. Both deciduous and permanent teeth are involved and fluoresce under Wood's lamp. Bhutani[40] described the post-mortem findings in a case of CEP.

Hepatosplenomegaly and anaemia are common in many cases of CEP. Broad diagnostic features of CEP and its differentiation are given in Table-III.

Erythropoietic protoporphyria (EPP) or (EHP)

EPP (or EHP) has an early onset and is relatively more common. The disease was first described in UK by Magnus et al[42] in 1961.

The disease starts in the first two or three years of life. Photosensitivity is the only symptom. Cholecystitis and cholelithiasis may also occur.[43]

Acute episodes of photosensitivity affect the face predominantly, back of the hands commonly,

Table III. Diagnostic features of various types of porphyrias

Name	Incidence	Diagnosis
1. Congenital erythropoietic porphyria (CEP) Gunther's disease	Very rare, autosomal recessive	All porphyrins (mostly isomer I) greatly increased in urine, stools and red cells. Red cells show stable fluorescence
2. Erythropoietic protoporphyria (EPP)	Common, dominant transmission	Protoporphyrin increased in RBCs, and often in faeces. Urinary porphyrins normal. Red blood cells show transient fluorescence
3. Porphyria cutanea tarda (PCT), also known as Hepatic porphyria or symptomatic porphyria	Common, depending on social conditions occurs in any race. Rarely familial	Urinary uroporphyrin fraction raised during active phase. Faecal porphyrins may be increased in remission.
4. Variegate porphyria (VP), also known as mixed porphyria or South African genetic porphyria	Very common in White Afrikaners, less common in other races. Dominant transmission	Faecal porphyrin increased especially proto- and "X" porphyrins. Urinary PBG increased during attacks
5. Acute intermittent porphyria (AIP)	Relatively common, dominant transmission	Urinary PBG greatly increased during and usually between attacks

and other regions less commonly. The lesions may be erythematous (immediate), or oedematous (delayed in onset), less often petechial and rarely urticarial. Vesicular lesions are not characteristic. Subjective symptoms e.g. burning sensation may be the main feature. Very superficial, linear or small, shallow circular scars may be noticed. Slight thickening of the skin on the dorsal aspects of hands is possibly pathognomonic.[7] Skin biopsy of the exposed areas shows excess PAS staining in and around the subpapillary capillaries.[44, 45] Monochromatic study has shown negative result in half of the cases, the remaining cases showed spectral sensitivity at or near 400 nm, less often at 500-600 nm.

The expectancy for life is excellent, though the possibility of developing cholelithiasis must be remembered.

Erythropoietic coproporphyria (ECP)

Heilmayer and Clotten[46] in 1964 described this very rare type of porphyria with skin photosensitivity, in which the red cells contain excessive quantities of coproporphyrin-III (as much as 385-457 ug/100 ml erythrocytes). The urine and stools had a normal porphyrin content. The author suggested that the disease is transmitted as a dominant character because the mother of the patient had similar biochemical disturbances.

Porphyria cutanea tarda or symptomatic porphyria (PCT)

Porphyria cutanea tarda is a relatively common, acquired disease which seems to occur in all ethnic groups. Rarely, the disease may be familial. It may be acquired due to chronic alcoholism with liver damage or hepato-toxic drugs. It may be precipitated by oestrogen-containing contraceptive pills.

Dermatological lesions consist of skin fragility, pigmentation, hypertrichosis and bullous lesions due to photosensitivity.

Bullous lesions may appear in summer each time the patient indulges in a spree with hard liquor together with solar exposure. In the quiescent stage, the lesions heal with scarring and hyperpigmentation. A characteristic finding is the presence of milia as small round cyst-like bodies, 2-5 mm in diameter. They lie fixed in the skin, most often on the finger and less often on the face and other exposed parts. Histology of the skin shows deposition of PAS positive material in the papillary capillaries. Electron microscopy shows reduplication of the dermo-epidermal basement membrane and reduction in the number of collagen fibres which may account for easy susceptibility to mild mechanical trauma.

Hypertrichosis is an important sign. The hair are present on the face particularly the cheeks, temples and eyebrows. Limbs may also be involved. Hyperpigmentation may be a presenting symptom. In coloured races, hypopigmented patches may occur at the sites of ulcers. Monochromatic photobiological tests reveal spectral sensitivity at about 400 nm and sometimes also at 500-600 nm.[47] Impaired liver function tests are frequent.

The prognosis in PCT is better than that in congenital erythropoietic porphyria or acute intermittent porphyria. It is usually not fatal unless liver function is profoundly affected or acute manifestations of a grave nature supervene. The tendency to skin photosensitivity may burn itself out after middle age, although the porphyrin dyscrasia remains.[48]

Bantu porphyria

The porphyria which occurs in the Bantus of South Africa and Rhodesia is almost entirely characterised by light sensitivity. The aetiology is related to the hepatotoxic effect of adulterated drinks brewed.[34]

The cutaneous features are similar to those of other forms of hepatic porphyria but extensive erosions with secondary infection; subungual, finger-tip or palmar bullae and gross secondary scleroderma, are more common.

Turkish porphyria

Since 1956, there has been an outbreak of thousands of cases of porphyria in South-East Turkey. It manifested after the accidental consumption of wheat dressed with hexachlorobenzene. Ockner and Schmid[49] confirmed the toxic origin of the disease due to hexachlorobenzene by showing its experimental reproduction in rats.

Variegate porphyria (VP)

Dean and Barnes[50] suggested the term variegate porphyria to describe a hereditary form of hepatic porphyria occurring in White South Africans. This form usually presents photocutaneous, abdominal and neural manifestations. The latter may or may not be concurrent with photosensitivity. Family relations may have latent porphyria.

Handa[51] reported a female patient with VP, and one of her family members with latent porphyria, as the first case in India. The acute systemic porphyria attacks may be precipitated by certain drugs like barbiturates, analgesics, sedatives, tranquillizers, sulphonamides, griseofulvin and oestrogens. The photobiologic features of VP are no different from those of photosensitive porphyria in general. The prognosis for life in variegate porphyria depends on the incidence and successful prevention and treatment of acute attacks.

Hereditary porphyria cutanea tarda

Barnes et al[52] considered this disease to be identical with variegate porphyria from the clinical point of view.

Acute intermittent porphyria

This has an autosomal dominant inheritance. Patients seldom exhibit cutaneous lesions. In four instances, hyperpigmentation has been noted. The disease commonly starts in the third decade and the symptoms primarily include abdominal pain with or without disturbance in gastro-intestinal mobility due to autonomic neuropathy. Approximately 15 percent patients do not manifest abdominal pain but exhibit pain elsewhere, epilepsy or mental depression. The disease may be precipitated by drugs like barbiturate, sulpha, griseofulvin, chloroquine, or oral contraceptives. Alcohol has a deleterious effect. Febrile illness, starvation, menstrual cycle or pregnancy may precipitate the disease. The patient often goes to the internist rather than the dermatologist. AIP, once called "the little imitator" remains difficult to diagnose.

Rarer type of porphyria

Sometimes a few patients apparently with porphyria are seen in whom the type of disease is unclassifiable.[7]

Hepato-erythrocytic porphyria

A few cases of what appears to be another type of congenital porphyria have been given this title. It is distinct from both Gunther's disease and EPP.[53,54] Probably only six cases are known. There is severe photosensitivity from birth or early childhood, resembling classical Gunther's disease. Biochemically the red cells show a moderately raised protoporphyrin concentration whereas the urinary excretion of the copro and uroporphyrin fraction III is high. Further studies on such atypical cases are needed.

TREATMENT

Prophylaxis

Relatives of all the patients having hereditary forms of porphyria should be surveyed for

porphyrins in the urine, faeces and/or blood to warn latent porphyric subjects of the dangers of barbiturates and alcohol.[16] No member of such a family should ever be given drugs like barbiturates, sulfa, anticonvulsants, griseofulvin, chlorodiazepoxide, meprobamate, ergot, methyl dopa, sedormid.

In porphyria cutanea tarda, drugs like oestrogen, iron compounds and chloroquine should also not be used. In the acquired forms of the disease, the incidence of toxic features and the treatment of hepatic diseases are clearly evident. Alcoholism is the commonest exciting factor and it is well established that a strict teetotal regime will produce good results.[55, 56]

The case of Turkish porphyria illustrates the dangers which may follow the application of pesticides to agricultural products. In our country, where agricultural pesticides are being increasingly used, this factor is to be reckoned with.

Pregnancy carries an added risk in cutaneous hepatic porphyria.[48] Eales[34], however, opines that the patient with variegate porphyria in South Africa withstands pregnancy well provided she does not receive barbiturates.

Management of the active disease

In the photosensitivity phase of the disease it is important to protect the patient from sunlight and as far as possible from minor trauma on light exposed areas. A protective wide-brimmed hat, gloves and shoes are helpful. It has been suggested that the night work provides the best protection from the sun, but the danger of UVR emitted by artificial lights cannot be ruled out. Creams containing zinc or titanium-dioxide are more suitable as sun-screens rather than those containing benzophenone derivatives or para-aminobenzoic acid.

Photosensitivity in patients with protoporphyria has been effectively treated with beta-carotene.[57, 58] Facial hair may require epilation or other depilatory measures. Antibiotics may be required to heal the infected skin lesions.

The neurological syndrome in cutaneous porphyria may require morphine, pethidine, physeptone or aspirin for pain. Promazine and chlorpromazine are also effective for the relief of pain, and the neural and psychological symptoms. Convulsions can be controlled with intramuscular use of paraldehyde. Fluid and electrolyte balance are most important in this phase of the disease because hyponatraemia and azotaemia occur commonly.[59, 60] A variety of factors can lead to volume depletion in these attacks.[61, 63] However, volume binding is contra-indicated. Blood volume determination and measurement of urinary sodium concentration should be used to direct management. If the blood volume is reduced and urine sodium concentration is low, volume should be replaced. In the event that the basis for the hyponatraemia cannot be determined, administration of hypertonic saline is the safest course. Artificial respiration with positive pressure has often saved lives. Physiotherapy must be instituted quickly and continued until maximal recovery has occurred.

Glucose loading of patients with acute intermittent porphyria was used to diminish the excessive production of ALA and PBG that occurs during acute attacks.[64] More recently, infusions of hematin have been successful in reversing the biochemical abnormalities and causing clinical improvement in patients experiencing acute porphyric attacks.[65, 68] The rationale for this was based on the observation that heme represses and inhibits ALA synthetase.[69, 70] Repeated phlebotomy (venesection) of patients with porphyria cutanea tarda has

lowered urinary uroporphyrin excretion with remission of skin lesions.[69-73] Venesection was continued until the haemoglobin fell to about 12 g/100 ml, the plasma iron to 50-60 ug/100 ml, or the urinary uroporphyrin excretion to 50-100 ug/24 hours. Some authors stop venesection as soon as the clinical remission occurs.

In EPP with hepatic involvement, cholestyramine has been found useful.[74] Theoretically, this occurs because cholestyramine limits protoporphyrin in the intestine and interrupts its entero-hepatic circulation.[75] Early recognition of hepatic disease is essential for success.

Surgical procedures

Splenectomy for CEP was first suggested by Sato and Takahashi[76] in 1926 and successfully used by de Marvel and Pons.[77] Splenectomy diminishes the haemolytic process and marrow hyperactivity, and thus causes a considerable reduction in porphyrin formation, and consequently, in photosensitivity. However, it did not alter the ratio of fluorescing to non-fluorescing normoblasts in bone marrow.

Cholecystectomy may be necessary in cases of EPP with chronic cholelithiasis.

The abdomen should be examined in a patient with the sudden onset of porphyrin photosensitivity for the rare possibility of a benign hepatic adenoma. Surgical removal of the adenoma often results in disappearance of the symptoms.

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