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Hepatoerythropoietic porphyria precipitated by viral hepatitis

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Abstract

Porphyria cutanea tarda (PCT), the condition resulting from a deficiency of hepatic uroporphyrinogen decarboxylase activity, is the commonest form of porphyria. Both acquired and familial form exist and are commonly associated in adults with liver disease and hepatic iron overload. The condition is extremely rare in children; most cases of childhood PCT are familial and some particularly severe cases have been shown to have a hepatoerythropoietic porphyria or homozygous uroporphyrinogen decarboxylase deficiency. A case is described of hepatoerythropoietic porphyria in which the disease was first precipitated at the age of two by a coincidental hepatitis A infection and improved as the hepatitis cleared. This paper reviews the evidence that viral hepatitis may precipitate overt PCT in children in a manner analagous to the precipitation of PCT in adults by alcohol associated liver disease.

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Porphyria cutanea tarda (PCT) is characterised biochemically by the increased urinary excretion of the water soluble porphyrin intermediates uroporphyrin, hepta, hexa, and pentacarboxylic porphyrin, and the accumulation of porphyrins in the plasma and liver. It occurs as a result of a defect of the haem synthetic enzyme uroporphyrinogen decarboxylase. Whereas all other forms of porphyria are inherited as classic Mendelian traits, PCT is usually an acquired illness, which typically develops in adult life. Characteristically the condition occurs in association with liver disease (usually secondary to alcohol) and is associated with hepatic iron overload. Other rarer associations include exposure to polyhalogenated hydrocarbons, oestrogen treatment, lymphoma, carcinoma, systemic lupus erythematosus, and chronic renal failure treated by haemodialysis. The principal symptom is photosensitivity, resulting in blistering, scarring, milia, pigmentation, and hirsutes in sun exposed areas. Occasionally the damage is severe enough to mimic scleroderma.

A familial form, inherited as a Mendelian dominant trait, is well described. Though the clinical features are the same, the familial form may be distinguished from the acquired form by the presence of a family history and by the finding of reduced uroporphyrinogen decarboxylase activity in erythrocytes as well as hepatocytes. The familial form, interestingly, also becomes clinically manifest in later adult life and the same association of liver disease and iron overload is often noted.

PCT is rarely manifest in infancy or childhood, and with the exception of an outbreak in Turkey, where large numbers of children developed PCT after ingesting wheat contaminated with hexachlorobenzene,[2] few cases of infantile PCT have been described.[3-17]

A subgroup of affected children have a form of PCT characterised by severe photosensitivity starting in early childhood, considerably raised porphyrins, and a characteristic raised erythrocyte protoporphyrin.[18-22] These changes are often severe enough to mimic congenital erythropoietic porphyria. This condition has been shown to represent the homozygous form of familial PCT, with uroporphyrinogen decarboxylase activities typically being less than 10% of the control range,[23] and has been labelled hepatoerythropoietic porphyria. The underlying genetic defect has now been determined in some patients.[24-25] Both homozygous and compound heterozygous mutations have been identified.

We describe here a two year old child in whom severe PCT was apparently precipitated by hepatitis A. Biochemical characterisation of the enzyme defect suggests the presence of hepatoerythropoietic porphyria, the severity of the PCT declined as the hepatitis improved.

Case report

A two year old black child presented to a paediatric hospital. The child had passed red urine and had developed a skin eruption over the preceding month. Both parents were healthy, and the child had had no previous medical or dermatological problems. There was no history of exposure to medicines, chemicals, or pesticides. The parents were not consanguineous.

The child was well nourished; height and weight fell on the 50th percentile. Hypo and hyperpigmented patches on the nose and cheeks were noted. Erosions, scabs, and pigmentary changes were noted on her hands, cheeks, and forehead. Her hands and fingers were foreshortened. The nails showed onycholysis. She was mildly jaundiced. Her liver was slightly enlarged but not tender. No splenomomegaly was noted and there were no signs of hepatic decompensation.

Serum chemistry suggested hepatitis (Table I). A full blood count was normal. IgM antibodies to hepatitis A virus were found, confirming an acute hepatitis A infection. Iron studies and serum ferritin showed no evidence of iron overload. Urine, stool, plasma, and erythrocyte porphyrins were esterified and extracted into chloroform, separated by thin layer chromatography and assessed by fluoroscanning, using a commercial standard kit (Porphyrin Products, Logan, Utah) as the standard.[26-27] Table II shows the urinary porphyrin concentrations, which were among

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TABLE I *Tests of liver function and iron storage in the patient*

		Reference range
Total protein	80 g/l	(60–80)
Albumin	29 g/l	(35–55)
Total bilirubin	39 umol/l	(1–17)
Conjugated bilirubin	26 umol/l	(1–17)
Aspartate aminotransferase	454 IU/l	(7–25)
Alanine aminotransferase	501 IU/l	(1–25)
γ glutamyl transpeptidase	85 IU/l	(0–50)
Serum iron	17 umol/l	(8–30)
Total iron binding capacity	45 umol/l	(48–67)
Transferrin saturation	38%	(18–52)
Ferritin	166 ng/ml	(20–300)

the highest ever encountered in our laboratory. These, together with stool and plasma porphyrins, were diagnostic of PCT.

Repeated porphyrin measurement in the urine, stool, red cells, and plasma of the mother showed no abnormality. The father, however, who was clinically normal, showed biochemical evidence of PCT. Normal iron studies and serum ferritin excluded iron overload in his case, though a liver biopsy showed moderate amounts of haemosiderin as the only abnormality.

An erythrocyte uroporphyrinogen decarboxylase activity assay, determined by measuring the production of coproporphyrinogen from pentacarboxyl-porphyrinogen III in haemolysates of anticoagulated whole blood samples, showed a reduction to 20% of expected activity in the patient, to 60% in the father, and to 50% in the mother (Table II). The concentration of immunoreactive uroporphyrinogen decarboxylase was determined by electroimmunoassay in agarose gels using a rabbit antiserum to human erythrocyte uroporphyrinogen decarboxylase and purified human erythrocyte uroporphyrinogen decarboxylase as the standard.[28] This showed a reduction to less than 20% in the patients, to 60% in the father, and 54% in the mother. Both assays were kindly performed by Professor G Elder, University of Wales College of Medicine.

No specific treatment other than topical sun blockers and advice about sun protection were given. The biochemical evidence of hepatitis resolved completely over two months, and disappearance of the anti-HAV IgM antibody was seen. Porphyrin excretion concentrations fell dramatically over the ensuing months in parallel with the improvement in liver function and the skin disease became less active. At six months, the total urinary porphyrins had declined from 119914 nmol/l to 1210 nmol/l and plasma porphyrins from 35 to 18 nmol/l. We lost contact with the family thereafter.

TABLE II *Porphyrin and enzyme values*

	Patient	*Father*	*Mother*	*Reference range*
Urine porphyrins (nmol/10 mmol creatinine)				
Uroporphyrin	77954·2	404·8	3·2	<20
7-COOH	29734·7	102·9	1·2	<1·5
6-COOH	6136·1	125·0	0·0	UD
5-COOH	5380·6	35·6	0·0	UD
Copro	709·7	97·1	36·1	<240
Stool porphyrins (nmol/g dry weight)				
Uroporphyrin	5·5	1·2	0·8	<1·7
7-COOH	4·4	7·3	0·0	UD
6-COOH	1·7	1·3	0·0	UD
5-COOH	5·6	12·0	0·0	UD
Isocopro	8·8	24·6	0·0	UD
Copro	4·9	14·9	16·9	<50
Proto	29·6	130·3	90·3	<200
Erythrocyte porphyrins (nmol/l)				
Copro	0·0	0·0	0·0	<80
Proto	1792	683·9	776·9	<800
Plasma porphyrins (nmol/l)				
Uro	12·1	5·9	UD	<2·5
7-COOH	6·6	2·9	UD	UD
6-COOH	6·0	1·6	UD	UD
5-COOH	7·1	0·0	UD	UD
Copro	0·0	3·0	UD	UD
Proto	3·0	0·0	UD	<1·0
Uroporphyrinogen decarboxylase activity (pmol/min/mg haemoglobin)	1·03	2·80	2·52	3·85–6·20
Immunoreactive uroporphyrinogen decarboxylase (arbitrary units)	<20	60	54	64–103

UD=undetectable.

Discussion

That uroporphyrinogen decarboxylase activity and immunogenic uroporphyrinogen decarboxylase material are decreased proportionately to about half of control values is compatible with a cross reacting immunomaterial negative uroporphyrinogen decarboxylase mutation in both parents, resulting in biochemically expressed though asymptomatic familial PCT in the father and a silent carrier state in the mother. The more severe deficiency in the child is highly suggestive of the presence of homozygous or compound heterozygous familial PCT, in other words, hepatoerythropoietic porphyria. This may account for the early onset, severity, and unusual biochemical findings such as the raised erythrocyte protoporphyrin.

Symptomatic PCT was apparently precipitated at an unusually young age in our patient by an intercurrent acute hepatitis A infection, a conclusion which is supported by its improvement as the hepatitis resolved. Though an association between PCT and viral hepatitis is recognised by some authorities (G Elder, personal communication), this is rarely reported, particularly in English publications. In children, precipitation of PCT by exogenous factors is occasionally described. PCT followed the administration of drugs (sulphonamides and griseofulvin, and hydantoin and benzodiazepines respectively) in two children who were shown to have the familial form of the disease.[9] Dopfer described a 6 year old girl who developed PCT after bone marrow transplantation for chronic myeloid leukaemia.[6] Though her transaminase activities were abnormal, she did not have clinical hepatitis or evidence of viral infection and the liver disturbance was felt to be secondary to methotrexate use. Prolonged administration of parenteral or enteral iron may have resulted in PCT in a susceptible child aged 8.[17]

With the exception of a recent surge of reports of adult onset PCT in association with HIV infection,[29-30] the association of PCT and viral infection is rare. Taylor[16] described the apparent precipitation of PCT in an 11 year old boy who developed infectious mononucleosis. French publications include a few reports on an associa-

tion between PCT and viral hepatitis. PCT was felt to have been precipitated by viral hepatitis in a 4 year old girl[4] and in a 5 year old child with trisomy 22 who had an intercurrent hepatitis A.[12] The possible role of hepatitis B surface antigenaemia in a case of PCT was discussed by Arlet[31] and an association between PCT and viral hepatitis in a child was postulated by Gajdos.[8]

Even with adult onset familial PCT, there is often a history of exposure to alcohol or other precipitating factors, suggesting that a liver specific process may also determine the onset of overt PCT.[32] Thus even the familial form may only become manifest where the uroporphyrinogen decarboxylase mutation underlying the condition is accompanied by a hepatic insult, such as alcohol, which leads by unknown mechanisms to the inactivation of uroporphyrinogen decarboxylase in sufficient degree to interfere with porphyrin metabolism. Our experience would suggest that viral hepatitis represents one such insult that might precipitate PCT in the genetically predisposed subject. Because the association has been rarely reported, the association would seem to be uncommon; it is however possible that overt PCT or hepatoerythropoietic prophyria is preceded by viral hepatitis more frequently than is recognised, as many infections, particularly in children, are subclinical or trivial.

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