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Case report

Hereditary corpoporphyria presenting with deep jaundice and photosensitivity

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SUMMARY

Hereditary coproporphyria is a rare hepatic porphyria with symptoms similar to acute intermittent porphyria. Photosensitivity is not described in the latter. We report the case of a young female with deep jaundice, photosensitivity, anemia, renal failure and no abdominal pain. Hereditary coproporphyria was diagnosed and the patient was discharged after 111 days in full recovery. She was readmitted after 45 days with abdominal pain and no jaundice or photosensitivity. Severe neuropathy developed which caused tetraparesis and deterioration of the respiratory muscle function. Haem arginate was administered with gradual improvement of neuropathy.

Key words: Hereditary corpoporphyria, jaundice, photosensitivity, neuropathy, haem arginate

INTRODUCTION

Hereditary coproporphyria is a very rare hepatic porphyria with clinical presentation similar to acute intermittent porphyria, except that cutaneous photosensitivity is also present in 30% of cases of the former. We present a young female with acute cholestasis and cutaneous photosensitivity without neurological symptoms at presentation, who proved to have hereditary coproporphyria.

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CASE REPORT

A 20-year old woman was referred to our department from another hospital in May 2000, due to painless jaundice and pruritus. She reported having dark urine and pale stools for two weeks and jaundice for 10 days before admission.

The patient had no past medical history, with no neonatal jaundice, had received no medications during the previous months and had no alcohol consumption in the past. She was on a diet in order to lose weight (her initial weight was 80 kg) and had been using home insecticides several days before. Her parents reported a family history of thalassemia major.

On admission she was icteric. She had 2-3 blisters on her face with serous yellow colored fluid. The blood pressure was 100/70 mm Hg, the pulse was 60 per minute and the temperature was normal. The liver was not palpable but the spleen was palpable 2 cm below the costal margin. There was no lymphadenopathy and no signs of ascites or peripheral edema. Heart sounds and pulmonary auscultation were normal.

The results of the hematological and biochemical analysis on different days of her hospitalization are shown in Table 1. HBsAg, anti-HBs, HBeAg, anti-HBe, anti-Hbc, anti-HCV, HCV-RNA by PCR, IgM anti-HAV, anti-HIV1,2, IgM anti-CMV, IgM anti-EBV, IgM anti-HSV1,2 were negative. Antinuclear, antimitochondrial and anti-smooth muscle antibodies were also negative. Serum ceruloplasmine was 0,49gr/L (normal 0,22-0,58) and copper 1,68μg/ml (normal 0,7-1,4) and 24hour urine copper was 300μg/ml (normal<100). Serum immunoglobulins were: IgA 126mg/dl, IgG 395mg/dl, IgM 69mg/dl. a-1 antithrypsin was 211μg/dl (93-224). No Keiser-Fleischer rings were detected. Tuberculin test and multiple blood cultures were negative.

Table 1. Hematological and biochemical values

	Day 1	Day 24	Day 45	Day 66	Day 111	Day 139
Leucocytes k/μl	7	11,6	10,6	16,7	5	6
Hb g/dl	9,4	6,9	11,8	8,1	8,2	9,8
PLS k/μl	116	233	91	155	112	120
PT sec	12/12	12,5/10,5	13/10.5	12,8/10,5	10,6/10,5	11/11
LDH IU/L	247	312	401	349	130	143
AST IU/L	57	66	48	85	41	25
ALT IU/L	56	60	80	88	29	17
γ-GT IU/L	13	16	47	29	29	22
ALP IU/L	256	224	190	288	145	148
Protein g/dl	5,8	5,6	6,1	5	6,2	6,9
Albumin g/dl	3,1	3,3	4,3	3,2	4,4	4,6
Bilirubin mg/dl	14,6	47	63,9	45,4	5,8	1,9
Direct bil.	10,35	44	45,8	33,8	4,4	0,58
Glucose mg/dl	92	139	90	85	75	91
Urea mg/dl	17	143	89	76	48	36
K meq/L	4,9	3,4	4	4,1	4,5	4,7
Na meq/L	149	138	136	134	146	145
Creatinin mg/dl	0,9	4,3	1	2,7	0,9	1,1

Blood hemoglobin was 9,4g/dl on admission, but it gradually fell to 6,9g/dl. MCV was 63,7, MCH 20,2, MCHC 31,6. Reticulocyte count was 2,1%. Serum iron was 73μg/dl and ferritin 18,1ng/ml. Gene analysis by PCR for C282Y and H63D mutations of the hemochromatosis HFE gene was negative. Direct and indirect Coomb's test were negative. The examination of the G6PD enzyme was normal. Red cell osmotic resistance was increased and the sickle test was negative. Hemoglobin electrophoresis was normal. She had no obvious blood loss. Twelve units of red cells were transfused during her hospitalization. A bone marrow aspiration showed increased cellularity, indicating that anemia and thrombocytopenia was caused by peripheral destruction. This was attributed to hypersplenism.

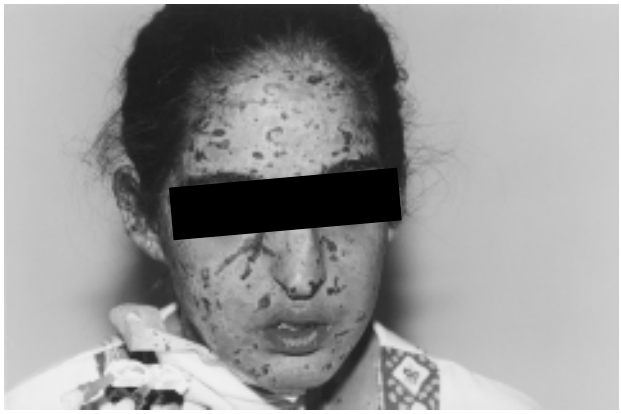
Abdominal ultrasound revealed homogenous echogenicity of the liver with normal intrahepatic and extrahepatic ducts. The gallbladder was normal. There was portal and splenic vein dilatation (18mm and 12mm respectively). The spleen diameter was 126mm.

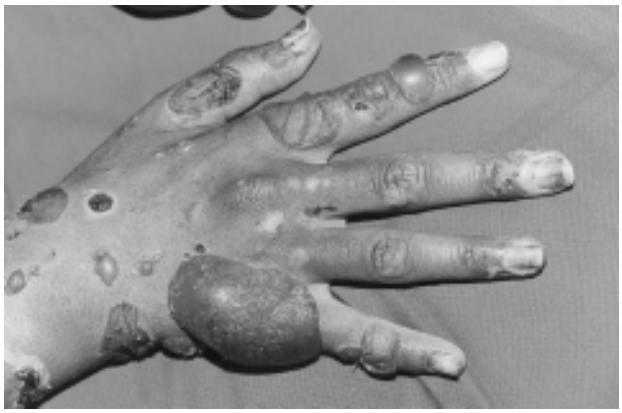
Computerized tomography of the abdomen and thorax was performed (without contrast medium, due to intercurrent renal failure). It revealed ground glass appearance in the right lung with no other abnormal findings. MRI of the upper abdomen and MRCP were performed and showed normal bile ducts, with surrounding fibrosis and compartmentalization of the liver parenchyma. Because of these findings she underwent an ERCP, which is a much more sensitive diagnostic method than MRCP, for detecting bile duct abnormalities, that revealed normal bile duct appearance. Mild duodenitis was found on esophago-gastro-duodenoscopy.

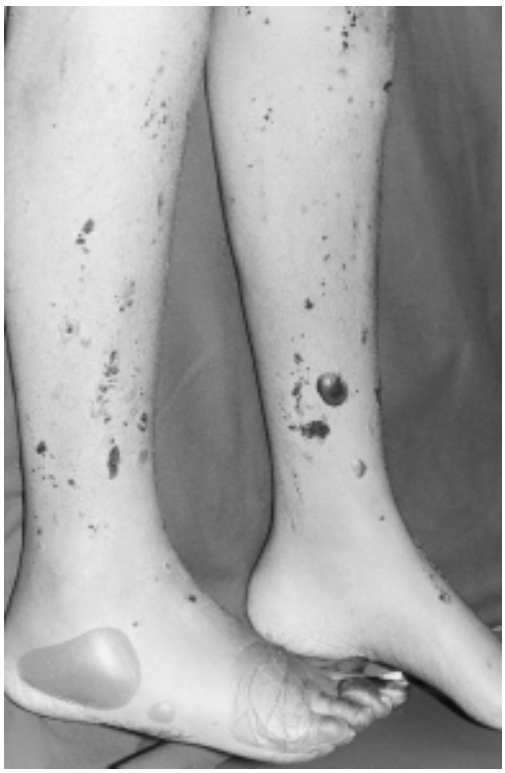
The percutaneous liver biopsy showed normal hepatic architecture. There was diffuse cholestasis, mainly extracellular and marked portal inflammation with polymorphonuclear cells. The inflammatory cells were destroying the wall of the bile ducts and epithelium and entered the lumen. There was mild intralobular inflammation and no fibrosis.

Following her admission the jaundice worsened and the blisters extended to the extremities but not the body. The fluid in the blisters was yellow at the beginning and it subsequently turned to hemorrhagic. The blisters were broken to eschars and healed, leaving discoloration of the epidermis, while new lesions appeared elsewhere (Figure 1, 2, 3). A skin biopsy showed subdermal blisters with red cells but no inflammatory cells. The findings were compatible to porphyria.

A urine porphyrin test was 13943μg/24h (normal<150). Blood, urine and feces samples were sent to King's College Hospital (SAS Porphyria Service), London. The results are shown in Table 2. It was concluded







Figures 1, 2, 3. Skin changes a few days after admission.

that the patient had hereditary coproporphyria.

Ten days after her admission she started to develop renal failure with normal urine output. There were no casts or red cells on urine examination. Excretion of sodium was 39mmol/24h. She underwent plasma exchange and hemodialysis that improved renal function tests but had no effect on jaundice.

Fifty days after her admission she developed an unexplained nonproductive cough disturbing her, especially in the supine position, that was not relieved by the usual symptomatic measures. Spirometry was normal. She also developed dystrophic nail changes and alopecia, although she had good nutrition.

A liver biopsy performed two months after the first biopsy, showed bile duct proliferation, biliary and fibrosing piecemeal necrosis and multiple areas with hepatocellular necrosis. Fibrosis in this biopsy was probably the result of a healing process.

The patient showed gradual improvement and was discharged 111 days after her admission, with no jaundice or photosensitivity (Figure 4, 5).

Forty-five days later she was readmitted to our department with abdominal pain, which, after thorough examination, was attributed to an acute attack of porphyria. She had no fever, jaundice or photosensitivity. She was given 400gr glucose i.v. daily for a few days without improvement. On the contrary, she developed neuropathy, which caused tetraparesis and deterioration of the respiratory muscle function although blood gases remained normal. Haem arginate (Normosang) was administered (3mg/Kg daily for ten days) with gradual improvement and she was discharged two months after her admission.

On February 2001 the patient was last seen in the outpatient clinic and she was able to move her hands and walk with assistance. She had no jaundice or photosensitivity.

DISCUSSION

Hereditary coproporphyria (HCP) is a very rare disorder. It is inherited in an autosomal dominant mode but fewer than 30% of patients have an acute attack. Its incidence has been estimated in Denmark to be 2 per million,[1] in Czech Republic 1:170000[2] and in Japan 1:184000.[3] The disease usually presents with symptoms identical to those of acute intermittent porphyria (AIP). Photosensitivity resembling that of porphyria cutanea

Table 2. Porphyrin analysis of urine, blood and faeces samples

Random urine		
5-aminolaevulinic acid (ALA)	4,8	μmol/mmol creat (normal <3,8)
Porphobilinogen (PBG)	1	μmol/mmol creat (normal <1,5)
Total porphyrin	2770	μmol/mmol creat (normal <35)
Uroporphyrin I	97	nmol/L
Uroporphyrin III	52	nmol/L
Total uroporphyrin (I+III)	149	nmol/L (normal <24)
Heptacarboxylate porphyrin	57	nmol/L (normal <4)
Coproporphyrin I	2010	nmol/L
Coproporphyrin III	11800	nmol/L
Total coproporphyrin (I+III)	13810	nmol/L (normal<115)
Urine creatinine	5,6	mmol/L
Blood		
Excitation maximum	401	nm
Emission maximum	618	nm
Faeces		
Coproporphyrin I	180	nmol/g dry wt
Coproporphyrin III	2750	nmol/g dry wt
Total coproporphyrin (I+III)	2930	nmol/g dry wt (normal <46)
Dicarboxylate porphyrin (protoporphyrin)	230	nmol/g dry wt (normal <134)

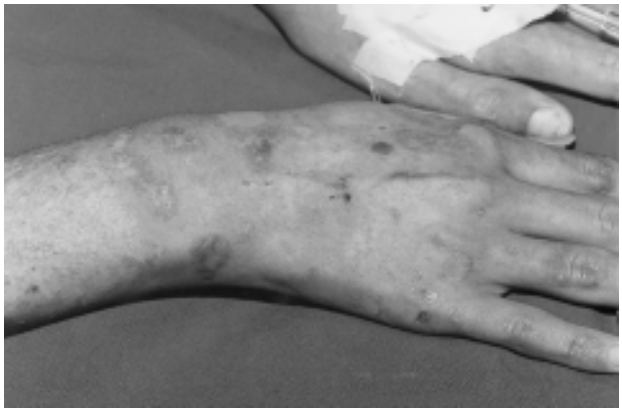
tarda (PCT) is seen in about 30 per cent, a finding that differentiates the clinical picture of HCP from that of AIP where no photosensitivity is noticed. The first days of her admission we thought that PCT was the diagnosis, a disease found in iron overload states. Although her serum ferritin was low, she could have had an HFE mutation without iron overload because of her young age. This is the reason we performed gene analysis for the HFE gene. It is remarkable that our patient had no abdominal pain in the first attack, a symptom expected in 80 percent of cases,[4] and that she was deeply jaundiced, a finding reported in 20 per cent of cases, with no obvious aetiology. It has been noticed that jaundice and photosensitivity appear simultaneously, as was the case in our patient.[5] Other interesting points for discussion are the anemia and the cough that our patient had, the role of plasma exchange in the course of her disease and the usefulness of hemin preparation several days after the second attack.

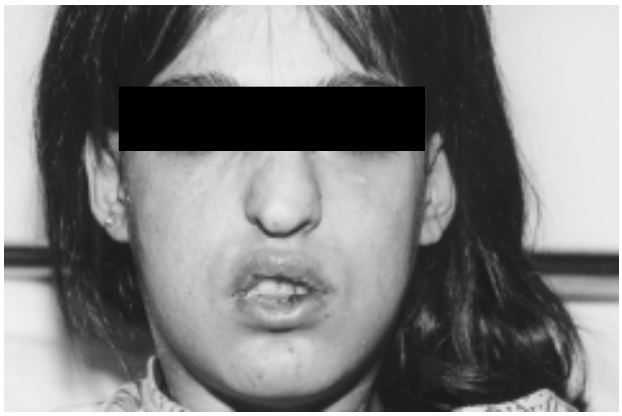
The cholestasis that was seen in our patient had the following characteristics: Bilirubin rose to 63 mg/dl, γGT, ALP, AST and ALT were normal or minimally elevated and "pure" cholestasis was noticed in the liver biopsy. A rise in serum bilirubin without a parallel rise in ALP was seen with hemolysis, bilirubinopathies, early stages of viral hepatitis or renal failure. Sometimes normal or minimally elevated γGT and ALP occur in cholestasis of pregnancy or cholestasis due to steroid use (especially 17-ketosteroids), or benign recurrent cholestasis.

Harderoporphyria, an erythropoietic variant of HC presenting in early life, is characterized by deep jaundice in the neonate and chronic hemolytic anemia. Our patient did not have such history and harderoporphyrin was not detected in urine and feces.

Profound hemolysis was not detected in our patient and her anemia could be attributed to hypersplenism and the toxic effects of bile acids on the red cell membrane. The liver biopsy excluded Dubin-Johnson syndrome (normal color of the specimen) and the urine coproporphyrin I to III ratio excludes both Dubin-Johnson and Rotor syndrome (which are characterized by coproporphyrin I in excess of coproporphyrin III). No known viral hepatitis was diagnosed and renal failure followed the appearance of jaundice, which persisted after normalization of renal function.

Despite our efforts we could not elicit any history of drug use, especially oral contraceptives. Home insecticides (which our patient used) contain chlorinated hydrocarbons, which usually cause central hepatic necro-





Figures 4, 5. Resolution of skin changes.

sis,[6] a feature not seen in her liver biopsy.

Benign recurrent intrahepatic cholestasis (BIRC) is a diagnosis of exclusion. The first attack usually occurs in young adults like our patient, γGT is normal in about 20 percent of cases[7] and pure cholestasis is seen in liver biopsy. ALP is usually elevated in contrast to our patient's ALP value, which was normal or almost normal. Bilirubin rises up to 20mg/dl, but renal failure and possible hypersplenism could explain the higher values in our patient. Hereditary coproporphyria is not reported to cause hepatocellular changes, so the jaundice could not be explained by porphyria per se. We postulate that, in our patient, jaundice of unknown aetiology was the precipitating factor for the attack of acute porphyria due to the inhibitory effect of bilirubin on coproporphyrinogen oxidase.[8] It is interesting that the cough was reported as a prominent symptom in one patient with BIRC.[9] Possible explanations of the nonproductive cough in our patient are a) an unusual presentation of porphyria related neuropathy with irritation of sensory nerves b) irritation of the airways by circulating substances of cholestasis, either directly or by releasing other factors mediating cough or c) stimulation of the vagus nerve in the liver and production of reflex cough.

Another issue is the role of plasmapheresis in the course of our patient's disease. Bilirubin may be toxic to cell respiration, membrane integrity and transport functions.[10] Bilirubin and bile salts may cause toxic tubular damage contributing to acute renal failure. A reduction in pulmonary surfactant factor and a toxic effect of bile in hepatocytes has been described.[10] Transformation of mononuclear cells is impaired by excess bilirubin, increasing susceptibility to infections.[11] In view of these observations, the removal of excess bilirubin and bile salts seems justified. Nevertheless there is controversy about the effectiveness of this manipulation, so it is not included in the standard plasmapheresis indications.[12] When hepatic failure is reversible, plasma exchange may be justified, but prognosis depends on the underlying disease.[13] In our case this procedure probably did not help in bilirubin reduction, perhaps due to short duration of plasmapheresis. (She had dyspnea and pulmonary edema was suspected, so the procedure was interrupted after two cycles.)

On her second admission, we noticed the therapeutic effect of the haem preparation on her disease, even after the development of severe neuropathy as it is reported in the literature.[14-16]

In summary, this patient presented with jaundice of no identified cause and photosensitivity without pain, which is an unusual presentation of hereditary coproporphyria. Later she had a typical acute porphyria attack with severe neuropathy, which responded to haem therapy.

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