Delayed onset of overt porphyria cutanea tarda in a patient on long-term haemodialysis
A case report

J. KING, R. S. DAY, F. J. MILNE, W. R. BEZWODA, J. D. VILJOEN, S. KRAMER

Summary

After 7 years on haemodialysis, a 37-year-old anephric man developed cutaneous lesions of the hands, arms and face, shown by skin biopsy to be compatible with porphyria cutanea tarda (PCT) (symptomatic porphyria). Elevated levels of plasma uroporphyrin and 7-COOH porphyrin were detected alongside a predominant isocoproporphyrin fraction in the faeces by means of quantitative thin-layer chromatography, confirming the diagnosis of overt PCT. The plasma uroporphyrin did not pass into the dialysate, even after chloroquine therapy. There was no evidence of hereditary PCT, chronic liver disease or iron overload, although the patient had a history of excessive alcohol consumption. The overt PCT developed after 8 months of home dialysis using softened water with high aluminium concentrations and subsided clinically and biochemically when the softened water was replaced by de-ionized water.


The occurrence of cutaneous blistering eruptions in azotaemic patients undergoing haemodialysis has been reported recently by several workers. In the majority of these cases the porphyrin levels in plasma, stool, dialysate and urine (where available) have appeared to be within normal limits, although the cutaneous lesions are morphologically and histologically indistinguishable from those found in porphyria cutanea tarda (PCT) (symptomatic porphyria),1,2 to the extent that the condition has been called pseudoporphyria. Several factors have been implicated as possible precipitants of these pseudoporphyric dermatological symptoms in patients on dialysis, including aluminium hydroxide3 and haemodialysis,4 while one pair of authors found significantly elevated uroporphyrin levels in the plasma of all dialysis patients.5 In a few cases the cutaneous symptoms are accompanied by biochemical abnormalities very similar to those found in PCT, including markedly elevated levels of uroporphyrin and 7-COOH porphyrin in the plasma and the urine (if urine is being produced) and the predominance of isocoproporphyrin in the faeces. In one case decreased activity of the erythrocyte enzyme uroporphyrinogen decarboxylase was evident in the patient and some members of his family,6 indicating a dominant pattern of inheritance. The other cases of overt PCT in patients on dialysis have appeared to be sporadic, the possible precipitating factors implicated being alcohol5,7 and chronic renal failure itself.5,6

Since in the uraemic patient on haemodialysis the urine may not be representative of porphyrin status, it is possible that some pseudoporphyries may be found to have overt PCT if plasma or faecal porphyrins were to be measured, for example by thin-layer chromatography. In addition, several reports have relied solely on the estimation of porphyrin levels in the urine and faeces by such methods as solvent extraction.

We report a further case of overt PCT in a patient who had been on dialysis for 6 years. Despite the presence of possible precipitating factors (high consumption of alcohol and use of ferrous sulphate) throughout this time he only developed overt PCT after a period of haemodialysis on softened water containing high concentrations of aluminium.

Case report

A 37-year-old South African man presented at the Johannesburg Hospital in 1971 with chronic renal failure caused by analgesic nephropathy. He admitted to constant analgesic abuse over the preceding 15 years on account of troublesome headaches. In May 1971, soon after haemodialysis had been commenced using de-ionized water, bilateral nephrectomy and an unsuccessful cadaver kidney transplant were performed. He started training for home haemodialysis using softened water from November 1977 and remained well until May 1978, when increased skin fragility became evident on minor trauma and/or exposure to the sun. There was blistering of the face and the dorsum of both the hands, arms and face, shown by skin biopsy to be compatible with porphyria cutanea tarda (PCT) (symptomatic porphyria). Elevated levels of plasma uroporphyrin and 7-COOH porphyrin were detected alongside a predominant isocoproporphyrin fraction in the faeces by means of quantitative thin-layer chromatography, confirming the diagnosis of overt PCT. The plasma uroporphyrin did not pass into the dialysate, even after chloroquine therapy. There was no evidence of hereditary PCT, chronic liver disease or iron overload, although the patient had a history of excessive alcohol consumption. The overt PCT developed after 8 months of home dialysis using softened water with high aluminium concentrations and subsided clinically and biochemically when the softened water was replaced by de-ionized water.


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areas on the face and the dorsum of the hands and forearms. Tense vesicles were present on the dorsum of the hands and fingers. Hypertrichosis of the face and forearms and brownish hyperpigmentation of areas exposed to the sun were evident. There was no evidence of chronic liver disease. He had mild hypertensive heart disease, but the remainder of the examination was negative.

The methyldopa, ferrous sulphate and aluminium hydroxide were withdrawn soon after the appearance of the skin lesions. The blood pressure was controlled on propranolol alone and the hypertensive heart disease while being dialysed on softened water in September 1978 after developing severe dialysis-induced bone disease while being dialysed on softened water. The bone disease then settled.

**Laboratory investigations**

The porphyrins present in the red cells, plasma, urine and stools were esterified, extracted and measured using the quantitative thin-layer chromatographic method previously described.\(^8\) Plasma \(\delta\)-aminolaevulinic acid (ALA) and porphobilinogen (PBG) were measured by a modified method of Mauzerall and Granick,\(^6\) using a Beckman model 25 spectrophotometer. Porphyrin isomer composition was determined by high-performance liquid chromatography using a sensitive adaptation of the method described by Battersby \textit{et al.}\(^1\) Plasma porphyrin levels before and after chloroquine therapy were measured by a modified method of Schwartz \textit{et al.}\(^2\) (Table I).

The plasma iron level was measured by the recommended ICSH method\(^13\) and the unsaturated iron-binding capacity by the method of Herbert \textit{et al.}\(^14\) Plasma ferritin concentrations were measured using the radio-immunoassay described by Deppe \textit{et al.}\(^15\) The aluminium concentrations in the softened and de-ionized water were measured using flameless atomic absorption spectrophotometry.

**Results**

Laboratory investigations performed when the skin lesions appeared revealed a haemoglobin concentration of 8.0 g/dl and a white cell count of 10 x 10\(^9\)/l. Blood biochemical values were as follows: urea 24 mmol/l, creatinine 1160 \(\mu\)mol/l, uric acid 0.7 mmol/l, calcium 2.67 mmol/l, and phosphate 1.41 mmol/l. Apart from an elevated alkaline phosphatase level (219 U/l) (normal 30–100 U/l) the results of liver function tests were normal. The plasma iron level was 79 \(\mu\)g/dl (normal 60–150 \(\mu\)g/dl), the oxygen saturation 35% (normal 25–40%) and the serum ferritin level 270 \(\mu\)g/l (normal 50–200 \(\mu\)g/l).

The results of the porphyrin analyses performed on the patient, his sister and his mother are given in Table I. Latent familial PCT would be expected to produce abnormal urinary porphyrin profiles, but there were no indications of abnormal porphyrin levels in either relative. The patient’s faecal and plasma porphyrin levels were at all times diagnostic of overt PCT. The plasma uroporphyrin level of 60.4 \(\mu\)g/dl detected in February 1979 while he was on home dialysis was very high. After the dialysate had been changed back to de-ionized water a dramatic decrease in plasma porphyrin levels to 10.3 \(\mu\)g/dl was found by February 1980, at which time it was also clear that the

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*Porphyrin units: urine = \(\mu\)g/dl; stool = \(\mu\)g/g dry weight.
plasma = \(\mu\)g/dl.

Results obtained by the modified method of Schwartz \textit{et al.}\(^2\) during chloroquine therapy; all other values obtained by the quantitative thin-layer chromatography method of Day \textit{et al.}\(^8\)

Uro. = uroporphyrin; Isocopro. = isocoproporphyrin; Copro. = coproporphyrin; Proto. = protoporphyrin.
The haemodialysis period coupled with the long maintenance of CRF describe a transitory dramatic increase in urinary uroporphyrin and 7-COOH porphyrin levels, lasting up to 14 days. Yet in neither of these reports was the expected increase in plasma porphyrin levels remain in the region found in non-dialysed CRF patients with PCT. In our patient, briefly mentioned in one of these reports, the patient's lesions improved after removal from home dialysis for less than a year and had no concomitant biochemical or clinical evidence of liver disease or iron overload. A major difference between the two types of dialysis was the treatment of the water, the home dialysis water being 'softened' and de-ionized water being used in the dialysis clinic. Softened water does not lose its aluminium content. Hudson et al. showed that symptomatic osteomalacia and osteopenia occur more frequently in patients dialysed on softened water, which has a higher aluminium content than de-ionized water. The fact that this patient developed severe bone disease on home dialysis in less than a year indicates that the plasma aluminium level was probably high. Both the bone disease and the cutaneous lesions improved when he reverted to hospital dialysis with de-ionized water. At the same time the aluminium hydroxide and ferrous sulphate were discontinued. Although an elevated blood aluminium level would have been diagnostic, blood aluminium assays were unobtainable at the time. It is unlikely that the concomitant reduction in iron intake caused the improvement in the patient's PCT, since at no stage during his illness were iron levels (including plasma ferritin) within the range normally encountered in patients with severe iron overload. Furthermore, the iron supplementation was recently recommenced without any recurrence of skin blistering. The implication is that in this case the high aluminium content of the water used for dialysis precipitated the overt PCT. (It is not clear whether the aluminium alone was responsible or whether there was an additive effect along with the other precipitating factors present, i.e. alcohol, iron and CRF, but the latter is more likely.) Preliminary experiments by one of the authors on normal and partially nephrectomized rats indicate that increased plasma aluminium levels cause a disturbance in porphyrin biosynthesis which in a way resembles PCT in humans.

The fact that chloroquine therapy had no effect on porphyrin status in this patient and in 1 other reported case of PCT on dialysis is surprising. Chloroquine is thought to form a complex with uroporphyrin which is more easily excreted in the urine, and all reports of its administration to PCT patients without CRF describe a transitory dramatic increase in urinary uroporphyrin and 7-COOH porphyrin levels, lasting up to 14 days. Yet in neither of these reports was the expected increase in plasma and dialysate porphyrin levels observed. It is hard to explain how the absence of kidneys in these patients could inhibit the effect of chloroquine unless the kidneys themselves are normally involved in the drug's precipitation of excessive porphyrinuria.

The role of porphyrins as photosensitizers is clear, yet their mode of action, if any, in the production of porphyric and 'pseudoporphyric' cutaneous lesions has not been established. There is no direct relationship between plasma porphyrin levels and cutaneous involvement, yet in PCT especially high plasma porphyrin levels are usually accompanied by skin lesions. In this case, the patient's lesions improved after removal from home dialysis. His plasma porphyrin levels decreased to one-sixth their earlier value, despite continued alcohol abuse. Nevertheless, his plasma porphyrin levels remained in the region found in non-dialysed CRF patients with PCT.

High aluminium levels in the dialysis fluid were therefore presumably a major factor precipitating the PCT in this patient.
We are grateful to Professor J. Rippey for reviewing the skin histopathology specimens and to the Porphyria Research Unit at Groote Schuur Hospital, Cape Town, for performing the porphyrin analysis.

REFERENCES
