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PORPHYRIN PRECURSORS AND PORPHYRINS IN THREE PATIENTS WITH ACUTE INTERMITTENT PORPHYRIA AND END-STAGE RENAL DISEASE UNDER DIFFERENT THERAPY REGIMES.

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Abstract – Porphyrin precursors and porphyrins were measured in three patients with recurrent attacks of acute intermittent porphyria and end-stage renal disease (ESRD): Two patients on hemodialysis and one on peritoneal dialysis. Plasma porphobilinogen (PBG) and porphyrins were considerably increased in the three patients. In a previous study, the mean urinary and plasma PBG/ALA ratio in biochemically active AIP patients with conserved renal function was 2.0 (normal 0.3) and plasma porphyrin levels were normal (< 10 nmol/L). In this study we show that the progression to ESRD was paralleled by an increase in urinary and plasma PBG/ALA ratio reaching levels above 6 and higher. Plasma porphyrin increased to levels above 1000 nmol/L causing cutaneous lesions resembling porphyria cutanea tarda. The porphyrin precursors were readily filtered by dialysis membranes but not the porphyrins. The development of kidney failure was a devastating complication in these AIP patients with chronic active disease, leading to unavoidable deterioration of peripheral veins, progression of peripheral neuropathy, dialysis treatment and secondary cutaneous lesions. The clinical course could not be reversed by medical treatment in any of the cases. Today, combined liver and kidney transplantation should be considered as a therapeutic option.

Key words: Acute intermittent porphyria (AIP), porphobilinogen (PBG), 5-aminolevulinic acid (ALA), porphyrins, endstage renal disease (ESRD), hemodialysis, peritoneal dialysis

INTRODUCTION

Acute intermittent porphyria (AIP) is a metabolic disorder caused by the deficient activity of the third enzyme in the heme biosynthetic pathway, porphobilinogen deaminase (PBGD) (1). The disease is characterized by acute attacks with neuropsychiatric symptoms such as abdominal pain, peripheral and autonomic neuropathy and mental disturbances. Symptoms are triggered by factors that may deplete the hepatic intracellular regulatory heme pool leading to increased demand for heme. The consequentially increased flux of metabolites through the deficient PBGD step results in accumulation of the heme precursors, PBG and ALA, which are found in high concentration in plasma and urine (1, 23). Treatment of severe acute attacks is based on heme therapy, which represses hepatic 5-aminolevulinic acid synthase (ALAS1) (14) and consequently decreases the levels of ALA and PBG. A small number of patients develop a condition characterized by recurrent acute attacks requiring hospitalization and specific treatment. These patients are more prone to develop late complications associated with acute porphyria as hypertension, renal impairment, chronic peripheral neuropathy, and later in life, hepatocellular cancer (2-4, 6, 7, 27).

We report the clinical and biochemical outcome/pattern in three women affected with chronic disease and recurrent acute attacks who developed end-stage renal disease (ESRD). The patients were followed at our clinic and porphyrin precursors and porphyrins in plasma and urine were analysed at the Porphyria Centre Sweden (9-11).

CASE 1

Patient ED was a female born in 1953 (†2004), who carried the 593G>A (W198X) *PBGD-gene* mutation. She was severely afflicted by recurrent acute attacks during 1993-1999 requiring over 220 hospitalizations and repeated heme arginate infusions corresponding to a total amount of 110 g (9.4 g Fe). Her kidney function (estimated glomerular filtration rate [eGFR] according to Cockcroft&Gault) (25), progressively deteriorated in this period as shown in Figure 1. She was normotensive with specific treatment. During the porphyric crises she was afflicted by peripheral neuropathy comprising her limbs, which advanced to tetraparesis. Liver and renal transplantation was considered in 1999 but abstained from due to the poor condition of her vessels and the uncertainty whether immunosuppressive treatment could exacerbate acute porphyria crises.

In 1993-1996 the excretion of urinary PBG and ALA was relatively constant with a mean value of 19.7 mmol/mol creatinine (normal<1.2) and 9.8 mmol/mol creatinine (normal<3.1), respectively (Figure 1). The mean PBG/ALA ratio during this period was 2.4 (range 1.7-3.0). In a previous study, the mean plasma and urinary PBG/ALA ratio was 2.0 (normal <0.3) in asymptomatic but biochemically active AIP patients with conserved renal function, and plasma porphyrin levels were normal (9). In year 1999, when the renal function was severely reduced, eGFR 19.2 mL/min, there was a dramatic increase in urinary PBG/ALA ratio to 5.4. The ratio was further increased to 9.1 the year after and to 13.1 in 2001 (Figure 1 and 2). During 1999-2001 the mean urinary concentration of PBG and of ALA was 31.9 and 8.1, respectively (Figure 1).

In year 2000, when her eGFR was reduced to 12.4 mL/min, she was started on hemodialysis 3 times weekly after an arteriovenous fistula was in operated, receiving intermittently erythropoietin (Eprex, 4000 units/weekly) and parenteral iron (20 mg/ml, 5ml/weekly) inoperated. Plasma PBG and ALA concentrations were measured before and after dialysis sessions on five occasions and the results are shown in Figure 3. The plasma analysis showed a considerable selective accumulation of PBG between the dialysis sessions. PBG and ALA were readily filtrated by the dialysis membrane and the PBG/ALA ratio decreased in plasma after each dialysis session to about 70% of the value before dialysis (Figure 3).

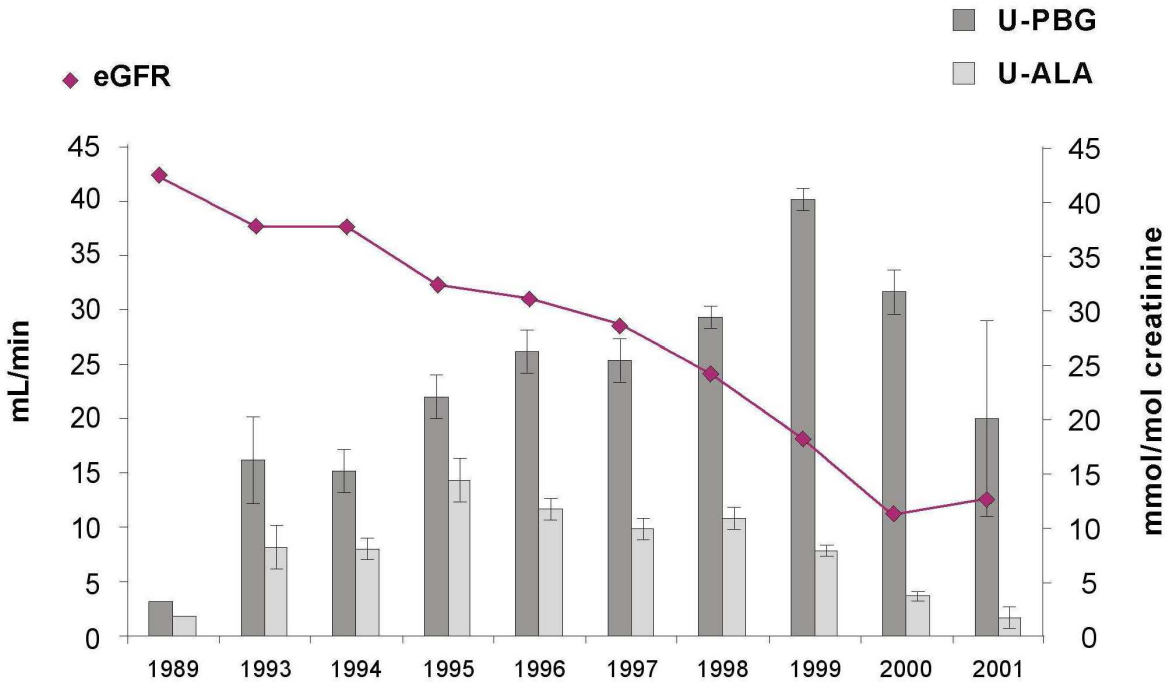

Figure 1. Patient ED. The mean urinary excretion of PBG and ALA and the corresponding eGFR during 1989-2001. During 1999 -2001, the kidney function was severely reduced and the mean urinary concentration of PBG increased and the respective ALA concentration decreased.
U-PBG, normal < 1.2 mmol/mol creatinine, U-ALA, normal < 3.1 mmol/mol creatinine, eGFR, normal > 90 mL/m

Before start of hemodialysis, she had developed skin lesions with blisters and skin fragility resembling porphyria cutanea tarda (PCT) (Figure 4, right panel). Plasma porphyrin concentration ranged between 970-2700 nmol/L (normal < 10) and remained almost unchanged after hemodialysis sessions (Figure 4, left panel).

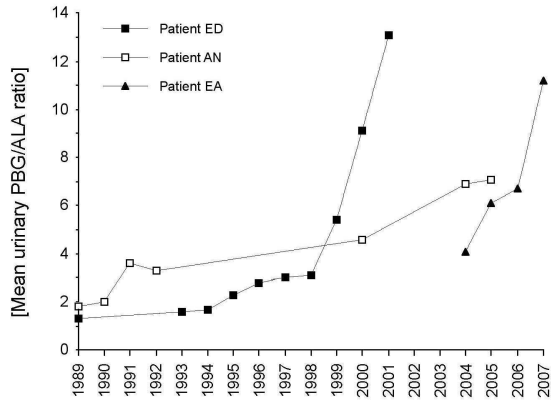

Figure 2. The mean urinary PBG/ALA ratio during 1989-2007 in patients ED, AN and EA. The PBG/ALA ratio in healthy subjects is about 0.3 and about 2.0 in AIP patients with chronic high urinary excretion of PBG and ALA and conserved renal function (Floderus).

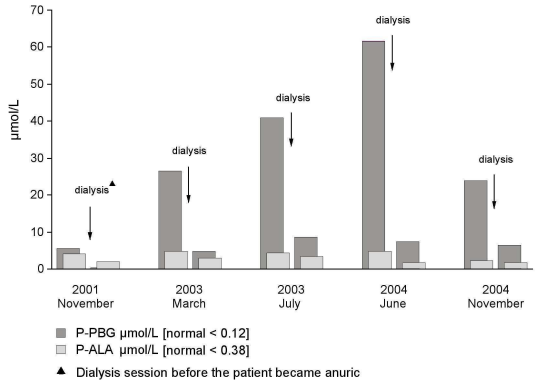

Figure 3. Patient ED. The plasma PBG/ALA ratios before dialysis were 1.3▲, 6.0, 9.3, 13.1 and 11.4 respectively compared to the corresponding values after dialysis 0.15▲, 0.85, 2.6, 4.7 and 3.9.

CASE 2

Patient AN is a female born in 1963 and carrier of the 593G>A (W198X) *PBGD-gene* mutation. She has been afflicted by recurrent acute attacks since 1980, and has received a total of 40 g of heme arginate (3.4 g Fe). She has moderate hypertension (150/80 mm Hg). Her kidney function was mildly reduced in 1990, and the mean level of urinary PBG and of ALA was 35.1 and 18.9, respectively. In 2001, the eGFR was reduced to 43.9 mL/min, she was oliguric and peritoneal dialysis was started. The mean urinary concentration of PBG and ALA were then 45.3 and 9.6, respectively. Shortly after, she developed PCT-like skin lesions on her hands and severe disabling peripheral neuropathy comprising her distal limbs. Liver and renal transplantation was discussed in 2004 but the patient declined.

The urinary PBG/ALA ratio was 2.0 (range 1.0-2.8) in 1990 when the kidney function was mildly reduced and 4.5 soon after start of peritoneal dialysis, and 6.8 in 2004 (Figure 2). In a single determination performed after start of dialysis, the concentration of plasma PBG and ALA were 26.7 µmol/L and 10 µmol/L, respectively, and the plasma ratio was 2.7 (Figure 5). Plasma porphyrin concentration was constantly high, mean 1020 nmol/L (range 778-1270, normal<10) and remained unaffected by peritoneal dialysis treatment.

CASE 3

Patient EA is a woman born in 1980 who carries the mutation 104-105insGTCT in the *PBGD-gene*. The AIP diagnosis was confirmed in 2004 after one year with several hospitalizations due to acute abdominal pain, hypertensive crises and peripheral neuropathies. Since diagnosis she has so far received 20 g of heme arginate (1.7 g Fe). At diagnosis her kidney function was already severely reduced, eGFR 14.7 mL/min, a sequelae from an infectious disease in her childhood, and possibly from the year with recurrent acute attacks before the AIP diagnosis. The mean urinary concentration of PBG was 13.5 and of ALA 2.5 during this year and the urinary ratio was 4.1 but has rapidly increased to 11, as eGFR has deteriorated (Figure 2). A single determination of plasma PBG and ALA in the predialysis stage gave the results 17.6 and 5.1, respectively, the ratio was 3.7 (Figure 5).

Before start of hemodialysis, the plasma porphyrin concentration was 422 nmol/L and she had no cutaneous symptoms. In 2007 the eGFR was 6.6 mL/min and hemodialysis was started. The plasma porphyrin concentration increased considerably after start of hemodialysis with plasma concentrations above 1000 nmol/L (Figure 6) and the porphyrins were neither filtered by the hemodialysis membrane nor by high flux hemodialysis (Figure 6). Combined liver and renal transplantation is at present discussed.

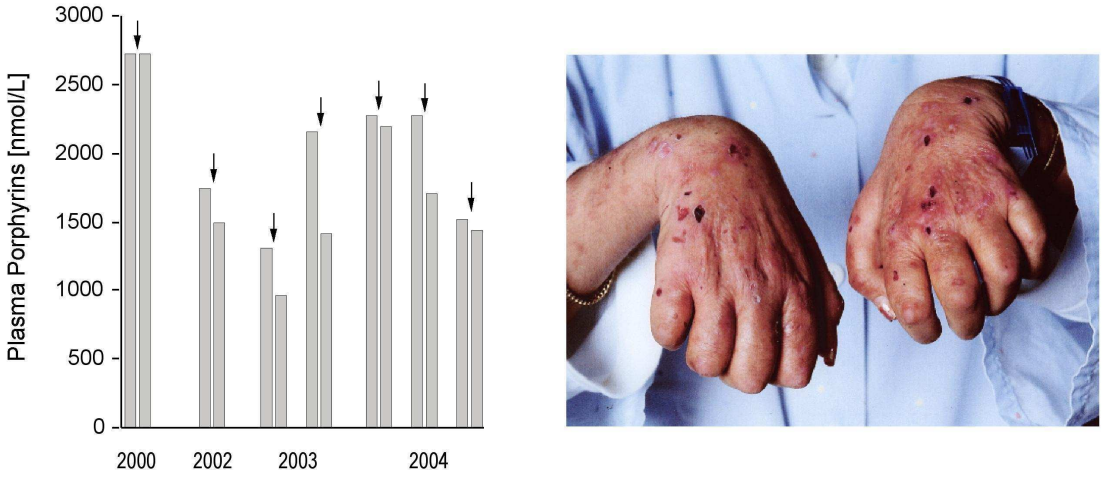

Figure 4. Patient ED. Plasma porphyrin concentrations (nmol/L) before and after dialysis sessions. The plasma porphyrins were mainly uroporphyrin I (80%) and remained unchanged after dialysis (left panel). The porphyrins accumulate and cause skin lesions in sun-exposed areas, resembling those seen in porphyria cutanea tarda (right panel). The picture shows the peripheral neuropathy and characteristic wrist drop in patient ED's hands, sequelae of chronic recurrent AIP attacks. Arrow indicates dialysis session. Plasma porphyrins; normal < 10 nmol/L.

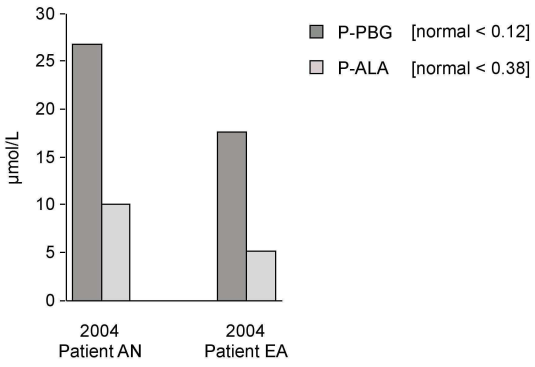

Figure 5. Plasma concentrations of PBG and ALA in patients AN and EA. The plasma PBG/ALA ratio in patient AN was 2.7 and in patient EA3.4.

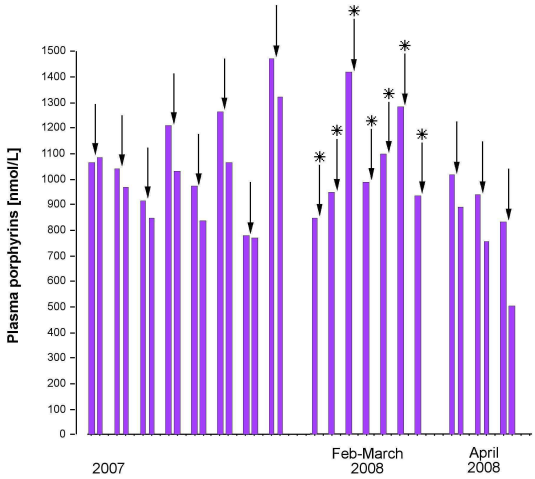

Figure 6. Patient EA. Plasma porphyrin concentration (nmol/L) before and after dialysis sessions. During February and March 2008 high-flux hemodialysis was performed. Arrow indicates hemodialysis session. Arrow * indicates high flux hemodialysis. Plasma porhyrins; normal < 10 nmol/L.

DISCUSSION

In spite of early recognition of symptoms and submission to specialized medical care and treatment, the three patients developed hypertension, renal failure, and advanced peripheral neuropathy. The severely deranged porphyria condition was avoided until severe renal failure arose. The progression of peripheral neuropathy was paralleled to the progression of renal failure and may partly be secondary to the accumulation of the porphyrin precursors that may exacerbate nerve damage (12, 28). The possible contribution of PBG and ALA is however unclear. There is no experimental evidence of PBG neurotoxicity and ALA, the metabolite suspected to cause nerve damage in the acute porphyrias, was present in blood and urine only in low concentration after development of ESRD (figure 2).

The PBG/ALA ratio in plasma and urine is 2.0 in AIP patients with conserved renal function (9). In these three patients the increase in urinary PBG/ALA ratio paralleled the impairment in glomerular filtration (Figure 2). The pathophysiological mechanism underlying the selective accumulation of PBG is unclear (Figure 1-3). One hypothesis could be a further inhibition of hepatic PBGD by its substrate PBG described in severely affected AIP patients (13), and in experimental trials (18, 19). The reason for the relatively low ALA concentrations observed in the three patients is unclear. The concentration was decreased in both plasma and urine, thus the observation cannot be explained by changes in the renal filtration of the metabolites. The theory that accumulated PBG could give rise to product inhibition of ALA-dehydratase (21) is not validated by these observations.

The precursors are readily filtrated by dialysis but not the porphyrins (Figure 3, 4, 5 (patient AN) and Figure 6). Hemodialysis is an intermittent procedure and a huge accumulation of predominantly PBG occurred between dialysis sessions (Figure 3).

In AIP patients with recurrent acute attacks and ESRD the very high concentration of porphyrins found in plasma reflects the non-enzymatic polymerization of four molecules of PBG to the linear tetrapyrrole hydroxymethylbilane, which spontaneously forms the cyclic tetrapyrrole uroporphyrin I (1).

The plasma porphyrin concentration remained almost unchanged after dialysis (Figure 4 and 6). A possible explanation to the poor filtration is that these molecules are strongly bound to plasma albumin. The accumulation of porphyrins causes skin lesions in sun-exposed areas, resembling those seen in porphyria cutanea tarda (Figure 4, right panel). The regimen of high flux hemodialysis applied in patients with PCT and ESRD (5) showed no effect in patient EA (Figure 6).

In patient AN, on peritoneal dialysis, plasma PBG/ALA ratios (Figure 2 and 5) were almost equal to those found in high excreters with normal kidney function (9). Thus, it may be concluded that peritoneal dialysis seems to have a more physiological clearence of the porphyrin precursors. However, it had no effect on the high levels of plasma porphyrins.

The cause of ESRD was not investigated by renal biopsy in any of the patients. The progression to ESRD can be secondary to factors such as hypertension (2, 3, 6, 16), interstitial tubular damage (17), and the noxious effect of porphyrin precursors on renal parenchyma (22). The repeated heme administration may also contribute (24), as may secondary kidney hemosiderosis. Our patients had however no significant laboratory signs of iron overload.

It has been reported that liver transplantation cured a young AIP patient affected by recurrent acute attacks (20). Kidney transplantation has been performed in AIP patients without complications (15, 26). A combined liver and kidney transplantation has been performed in several other disorders with acceptable outcome (8). This procedure should be considered in seriously affected AIP patients with recurrent acute attacks and decreasing renal function at a stage when this therapeutic alternative is still an option.

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