Middlesex Hospital. The work was supported by grants from St. George's Hospital Research Fund and the Wellcome Foundation.

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PRELIMINARY COMMUNICATIONS

Free erythrocyte protoporphyrin level and nerve conduction velocity in end-stage renal disease

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British Medical Journal, 1975, **4**, 324-325

Summary

Increased free erythrocyte protoporphyrin concentrations and depressed motor nerve conduction velocities (MNCV) were observed in 45 patients on maintenance haemodialysis. Neither of these findings could be correlated with age, duration or frequency of dialysis, or the degree of uraemia present. A strong negative correlation ($r = -0.53$; $P < 0.001$), however, existed between the free erythrocyte protoporphyrin level and the MNCV, which suggested either (a) a direct effect of iron status on nerve function, or (b) a toxic factor in "uraemia" that depresses both nerve conduction and haemoglobin synthesis activity.

Introduction

There are few published descriptions of abnormalities of haemoglobin precursors in end-stage renal disease. Increased plasma levels of δ -aminolaevulic acid and porphobilinogen were, however, reported by Leber *et al.*¹ in 15 patients. Their findings were consistent with the frequency of anaemia, a common complication of advanced renal insufficiency. Since hepatic porphyrias and uraemia are often associated with clinical or latent neuropathies^{2,3} we were interested in dialysed patients

(a) to measure some haeme precursor abnormalities, and (b) to establish the relation between these abnormalities and motor nerve conduction velocities (MNCV).

Patients and methods

Forty-five patients (27 men and 18 women) with chronic end-stage renal disease on maintenance haemodialysis were investigated. Their ages ranged from 19 to 68 years with a mean of 40.5 years. Altogether 20 had chronic glomerulonephritis, 12 chronic interstitial nephritis, 4 polycystic kidney disease, 6 malignant nephrosclerosis, and 3 other renal diseases. The patients had been dialysed for five to seven hours three times a week for an average of 37 months (range 6-85 months) before the study, a 1.03-m² Cuprophane RP-5 machine being used. All had an internal arteriovenous fistula. Protein intake was not restricted, and the patients received a phosphate binder (aluminium hydroxide), calcium carbonate, and multivitamin preparations. None had hepatitis or clinical evidence of peripheral neuropathy.

Blood chemical values were measured every two weeks, and MNCV of peroneal nerves every two months. All chemical, haematological, and electrical studies reported here were performed the same day before dialysis was begun. Blood urea, creatinine, urate, calcium, phosphate, and electrolytes were measured by standard methods on an AutoAnalyzer, and haemoglobin was measured with a Coulter counter. The Hyland Ferro-Chek II colorimetric test^{4,5} was used for the serum iron and total iron-binding capacity. Free erythrocyte protoporphyrin was determined spectrophotometrically.⁶ The MNCV of peroneal nerves was measured in a warm laboratory (22-23°C), the nerves being stimulated supramaximally with a Racia apparatus and skin electrode. The responses were picked up with skin electrodes and amplified by an electromyograph. The mean of two or more velocities measured was recorded as the value for a given day. Normal values for the investigations are given in the table.

Results

The mean free erythrocyte protoporphyrin level was significantly higher ($P < 0.001$) in the uraemic patients than in a group of normal controls (table), no correlation being observed with age, duration or frequency of dialysis treatment, or the degree of uraemia as assessed biochemically. There was, however, a close correlation between these levels and serum iron ($r = -0.58$; $P < 0.001$), total iron-binding capacity ($r = +0.53$; $P < 0.001$), and transferrin saturation ($r = -0.62$; $P < 0.001$) (fig 1) but no correlation with haemoglobin.

MNCV was significantly decreased ($P < 0.001$) in the uraemic patients (table), no correlation being observed with age, duration or frequency of dialysis treatment, or severity of uraemia. It was, however, closely correlated with the protoporphyrin concentration ($r = -0.53$; $P < 0.001$) (fig 2) but not with serum iron ($r = 0.31$; $P < 0.05$) or transferrin saturation.

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Mean blood values and motor nerve conduction velocities ($\pm$ SE of mean) in controls and uraemic patients

	Control subjects (n = 20)	Uraemic patients (n = 45)
Free erythrocyte protoporphyrin level (nmol/l)	635 $\pm$ 52	1078 $\pm$ 75*
Haemoglobin concentration (g/dl)	16.4 $\pm$ 0.8	7.0 $\pm$ 0.2*
Serum iron concentration (μ mol/l)	20.9 $\pm$ 0.4	16.8 $\pm$ 1.2*
Total iron-binding capacity (μ mol/l)	56.9 $\pm$ 0.8	58.9 $\pm$ 1.2
Transferrin saturation (%)	35.7 $\pm$ 1.1	29.7 $\pm$ 1.8
Motor nerve conduction velocity (m/s)	49.9 $\pm$ 1.1	39.1 $\pm$ 0.8*

*P < 0.001.

Conversion: SI to traditional units—Free erythrocyte protoporphyrin: 1 nmol/l $\approx$ 0.056 μ g/100 ml. Serum iron: 1 μ mol/l $\approx$ 5.61 μ g/100 ml. Total iron-binding capacity: 1 μ mol/l $\approx$ 5.59 μ g/100 ml.

FIG 1—Relationship between free erythrocyte protoporphyrin levels and serum iron concentration and transferrin saturation (semilogarithmic scale).

Conversion: SI to traditional units—Erythrocyte protoporphyrin: 1 nmol/l $\approx$ 0.056 μ g/100 ml. Serum iron: 1 μ mol/l $\approx$ 5.61 μ g/100 ml.

Comment

Neither the raised free erythrocyte protoporphyrin levels nor the depressed MNCVs in our patients were correlated with the degree of uraemia present, as shown by the routine measurement of blood concentrations of low molecular weight substances. In contrast the protoporphyrin levels and MNCVs were strongly correlated with each other. Neuropathies and changes in MNCV have been extensively described in hepatic porphyrias.^{2,3} Thus our results raise the question of the role of protoporphyrin in the still unknown mechanisms of depressed nerve conduction in dialysed patients.

Nerve conduction studies usually show a depressed conduc-

FIG 2—Relationship between free erythrocyte protoporphyrin level and motor nerve conduction velocity (semilogarithmic scale).

tion early in uraemia, even in the absence of any clinical or symptomatic evidence of neuritis.^{7,8} Although MNCV determinations may vary,⁹ periodic measurement serves commonly as a guide to the adequacy of dialysis. The rapid fluctuation in conduction rate suggests that this is a physiological rather than structural defect⁸ and is more probably due to a physiological tissue dysfunction than to a neuritis in a pathological sense. Possibly porphyrin precursors themselves are toxic.¹⁰ This mechanism, however, was difficult to invoke in our patients since the protoporphyrin levels were much lower than those observed in the porphyrias.

As shown previously¹¹⁻¹³ and in this report the free erythrocytic protoporphyrin level mainly reflects iron status. Thus there are two possible explanations for our findings. The first is that iron deficiency, which is common in dialysed patients,¹⁴ may per se be the cause of the nerve defect. However, the lack of correlation between iron status and MNCV and the absence of any real evidence of iron deficiency do not support this suggestion. The second possibility is that uraemia may have a toxic effect on haemsynthetase. The toxicity of uraemia could depress both nerve conduction and haemsynthetase activity. The correlation between MNCV and protoporphyrin levels could, therefore, be the result of this common factor.

This study was performed with the help of the Federation Nationale des Déportés Internés Résistants et Patriotes, 10 rue Leroux, Paris 75016; and the Association pour l'utilisation du Rein Artificiel (AURA) dans la région parisienne, 84 boulevard Masséna, Paris 75013.

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