THE EFFECT OF HAEMODIALYSIS AND TRANSPLANTATION ON AUTONOMIC NEUROPATHY

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Summary

Autonomic nerve function as measured by the Valsalva ratio and the blood pressure response to sustained hand grip, is impaired in chronic renal failure. Treatment with haemodialysis results in insignificant improvement in the Valsalva ratio and a trend towards improvement in the hand grip tests. Transplantation improves but does not return to normal the Valsalva ratio, whereas the hand grip test is rapidly restored to normal.

Introduction

Peripheral motor and sensory neuropathy is a recognised complication of chronic renal failure, and more recently involvement of autonomic nerves has been described [1,2]. Haemodialysis [3] and transplantation [4] have been demonstrated to have a beneficial effect on uraemic motor neuropathy and the present study was undertaken to determine the effect of these two methods of treatment on uraemic autonomic neuropathy.

Autonomic nerve function may be tested by the Valsalva manoeuvre [5] and by the rise in blood pressure during sustained hand grip [6]. In the present study both these methods have been employed in patients with severe chronic renal failure, patients on intermittent haemodialysis and patients following successful renal transplantation.

Patients and Methods

Ten patients (7 female, 3 male) aged between 33 and 55, with chronic renal failure were studied. In all patients the serum creatinine was greater than 700 μmol/L and no patient had evidence of systemic disease, other than uraemia, known to produce neuropathy.

Thirty-nine patients (18 female, 21 male) aged between 22 and 57 with chronic
renal failure, maintained on intermittent haemodialysis, were studied. No patient had systemic disease and they were all dialysed for 4 hours thrice weekly with a Meltec Multipoint 1.5 m² dialyser. All were receiving vitamin supplements (Aneurine Co Forte and Folic Acid). The pre-dialysis serum creatinine was in the range of 800–1200μmol/L.

Twenty patients (7 female, 13 male) aged between 20 and 58 and who had received a successful cadaver transplant were included. All had a creatinine clearance in excess of 40mLs/min and a plasma creatinine of less than 200μmol/L. All were receiving corticosteroids and azathioprine.

In addition 11 normal volunteers were studied.

Each patient performed a standard Valsalva manoeuvre with the heart rate response being measured from a simultaneously obtained electrocardiograph, and a sustained hand grip test during which the blood pressure response was measured by a sphygmomanometer. In haemodialysis patients the blood pressure was always measured in the arm without the arterio-venous fistula.

The statistical analysis of the results was performed using Wilcoxon's sum of ranks test for non parametric data.

Results

1 Valsalva Test: In the chronic renal failure patients the Valsalva ratio was significantly less than in the control group (R=62, p < 0.002). Following the institution of haemodialysis there appeared to be slight but insignificant improvement in this test. With successful transplantation there was an improvement compared with chronic renal failure patients, although the response was still significantly less than normal. (R=94.9, p < 0.01). (Table I).

<table>
<thead>
<tr>
<th>TABLE I. Valsalva Ratio and Sustained Hand Grip</th>
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<td>(Median Values)</td>
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<tr>
<td>Valsalva Ratio</td>
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<td>Hand Grip (mm Hg)</td>
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2 Sustained hand grip: In chronic renal failure patients there is an impairment in the diastolic blood pressure rise during sustained hand grip, but this only reaches statistical significance at the 5% level (R=69). The median rise in chronic renal failure patients was 10mmHg compared with 30 mmHg in normal volunteers. There is an improvement in the results obtained during treatment by haemodialysis, but this just fails to reach significance at the 5% level. After successful transplantation, the response returns to normal.

3 Effect of duration of treatment: To examine the effect of the length of haemodialysis and the time following transplantation on autonomic nerve func-
tion the results obtained in these groups of patients was re-examined. Each group was subdivided into three; those treated for less than one year, those treated for one to two years, and those who had been treated in excess of two years (Table II).

<table>
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<th>TABLE II. Valsalva Ratio and Sustained Hand Grip in Relation to Length of Treatment</th>
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<td>(Median Values)</td>
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<td>Hand Grip (mmHg)</td>
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In dialysis patients the Valsalva ratio was not significantly improved whatever the duration of dialysis compared with untreated chronic renal failure patients. However, the rise in diastolic blood pressure on sustained hand grip showed an improvement in the median values for each of the three groups although this failed to reach significance at the 5% level. On the contrary, in transplant patients, although the Valsalva ratio did not change significantly in the first year, there was a significant improvement at 1–2 years (R=20.5, p < 0.05) with a further improvement in patients transplanted for greater than 2 years (R=19, p < 0.01). The response in the hand grip test was quicker, with a significant improvement in the first year (R=60, p < 0.05) and this was maintained at 1–2 years (R=16, p < 0.02) and at greater than 2 years (R=15.5, p < 0.02).

Discussion

The results of this study confirm the involvement of autonomic nerve fibres in the neuropathy of chronic renal failure. In addition it demonstrates that with treatment either by dialysis or transplantation, there can be an improvement in autonomic nerve function.

Dialysis appears to have an insignificant effect on the Valvalsa ratio, even with dialysis for periods in excess of two years. The reason for this is not apparent and is contrary to that found in peripheral motor nerves where improvement may occur in a slow but steady manner over many years [3]. However, the blood pressure response to sustained hand grip shows a trend towards improvement with continuing dialysis although this just fails to reach statistical significance. The reason for this disparity is not apparent, but may reflect the fact that these tests are measuring two different autonomic pathways and it is possible that the healing response of dialysis is different in these different paths. Patients were not on hypotensive drugs, and this is not a factor.

The suggestion of improvement with time on dialysis is contrary to the findings reported by Ewing and Winney [2] and the reasons for this are not apparent. The dialysis details with respect to length of time on dialysis and dialysis tech-
nique do not appear to be significantly different, although it does appear that their patients had more severely impaired autonomic function, which might be an important factor.

Transplantation appears to be superior in restoring autonomic nerve function. However, even this form of treatment does not return the Valsalva ratio to normal, while the sustained hand grip test is restored fairly rapidly. This may indicate that the fibres involved in the baroreceptor reflex are irreversibly damaged by uraemia, while those involved in peripheral vasoconstriction are relatively spared. The difference between the improvement in dialysis and transplant patients most likely reflects the better biochemical status of the transplant patient not only with respect to urea and creatinine but also to the so called 'middle molecules' which have been implicated as a cause of uraemic neuropathy.

Acknowledgments

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References

2 Ewing, DJ and Winney, R (1975) Nephron, 15, 424
5 Ewing, DJ, Campbell, IW, Burt, AA and Clarke, BF (1973) Lancet, ii, 1354

Open Discussion

BRUNNER (Basel) Your normal controls were healthy people. What would the result of these tests be in anaemic patients or patients with heart disease but normal renal function?

DAVISON We have not looked at patients with other chronic debilitating disease, particularly anaemia and heart disease but I think these would be well worth examining. The only other group that have been looked at are the patients with diabetes mellitus, but of course in this condition there is a neuropathy for quite different reasons.

WALLS (Leicester) You obviously have a range of Valsalva ratios. If you take somebody who is at the top end of the range and you take somebody who is at the bottom end of the range and if you ultrafiltrate them do you find any differences in changes in pulse rate which may indicate that the autonomic nervous system is clinically involved in the maintenance of pulse rate and blood pressure during ultrafiltration?
DAVISON I think it would be worthwhile to look at those patients who are symptomatic during haemodialysis, particularly those who drop their blood pressure during ultrafiltration, to see if there is any relationship between these two measures of autonomic nerve function and their symptoms.

WALLS We have been doing a very similar study using the exercise test and getting very similar data.

DRUEKE (Paris) In addition to Dr Brunner's comments I would make another suggestion, you should also examine patients with primary hyperparathyroidism as there could possibly be autonomic nervous insufficiency, just as has been proposed for dogs with secondary hyperparathyroidism for the motor system. You told us that the Valsalva ratio remained decreased after transplantation, but in the patients after two years of transplantation the mean of the ratio appeared to be in the normal range. Would you conclude that after two or more years of transplantation the Valsalva ratio becomes normalised?

DAVISON No, when we look at it statistically there is a slight improvement at 1–2 years and an even more marked improvement in those transplanted for greater than two years but the values do not return to normal. I take your point entirely about the parathyroid function. We have no evidence of hyperparathyroidism in our patients because it is well known that patients with hyperparathyroidism have a myopathy and we just do not know whether they have an autonomic neuropathy as well.