Basic Distribution of Uraemic Changes and their Possible Prevention by Dialysis

V BONOMINI, M P SCOLARI, A ALBERTAZZI, G C BORTOLOTTI
S Orsola Hospital, Bologna, Italy

Introduction

This paper deals with the results of clinical, biochemical, morphological and metabolic investigations (1 - erythropoiesis; 2 - bone biopsy lesions; 3 - peripheral neuropathy; 4 - protein turnover; 5 - aminoacids; 6 - triglycerides; 7 - glucose A-V) serially carried out in chronic uraemic patients on various dialysis programmes. A retrospective analysis of the same data in a larger population of uraemics not on regular dialysis therapy (RDT) has also been performed.

These studies have been undertaken in an attempt to ascertain the correlation between renal lesions and distribution of uraemic signs, and the effects of dialysis on their arrest or reversal.

A dialysis strategy which includes an earlier starting-time seems appropriate at the present time.

MATERIAL AND METHODS

A retrospective analysis of all clinical and subclinical data of 365 cases of chronic uraemia has been made. Of these 365 cases 152 were included in our kidney replacement programme from 1966 to 1974. This total included 67 with glomerulonephritis, 43 with pyleonephritis, 19 with polycystic kidney and 23 with vascular nephrosclerosis. For 113 cases treatment was by dialysis only; 30 have been transplanted after at least 1 year of RDT; 9 have been transplanted only.

According to clinical indications and hospital facilities, dialysis programmes consisted of: intermittent (2 dialyses/week, 10 hr each dialysis), short-repeated (3 dialyses/week, 4–5 hr each dialysis) and daily (5–6 dialyses/week, 2 hr each dialysis). Details have been reported elsewhere (Bonomini et al, 1972). The
present results concern only the cases in whom a complete follow-up of the multiple previously-listed parameters was performed (75% of the cases).

RESULTS

Regardless of the quality of life and of general clinical conditions a rather close inverse correlation between the subclinical changes previously listed (nerve conduction velocity, bone biopsy lesions, etc.) and residual creatinine clearance ($C_\text{cr}$) was found. In the miscellaneous group of 365 uraemia studied with residual renal function above 40 ml/min, an average of 5% of subclinical uraemia occurred; with function between 30—40, the percentage was 16; between 20—30: 22%; between 10—20: 31%; below 10: 100%. A value of 10% of residual renal function seems to be critical considering the overlapping of documented subclinical changes below or above it.

Some signs have been found to be irregularly distributed according to the various renal lesions.

Hypertension responded to dialysis in 10 cases of chronic terminal uraemia due to polycystic kidney; 2 out of 26 cases of pyelonephritis; 29 out of 51 cases of glomerulonephritis; 19 out of 23 cases of vascular nephrosclerosis.

Anaemia has been found more pronounced in patients with glomerulonephritis and vascular nephrosclerosis as compared with pyelonephritis and polycystic kidney (Table I). The need for blood transfusions and their attendant risks may consequently be different in the various groups of uraemias.

Table I. Erythropoiesis Studies in 59 Cases of Chronic Terminal Uraemia after 2—4 years of RDT

<table>
<thead>
<tr>
<th></th>
<th>% Survival RBC (days)</th>
<th>Reticulocytes (%)</th>
<th>Erythroblasts (%)</th>
<th>$^{59}$Fe Turnover (mg daily/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis (28 cases)</td>
<td>22.5 ± 4.84SD</td>
<td>1.18 ± 0.73SD</td>
<td>8.7 ± 3.76SD</td>
<td>0.32 ± 0.027SD</td>
</tr>
<tr>
<td>Vascular neph. (11 cases)</td>
<td>17.2 ± 3.34SD</td>
<td>1.07 ± 0.51SD</td>
<td>6.2 ± 3.13SD</td>
<td>0.24 ± 0.046SD</td>
</tr>
<tr>
<td>Pyelonephritis (15 cases)</td>
<td>30.6 ± 4.91SD</td>
<td>2.02 ± 0.92SD</td>
<td>13.4 ± 5.18SD</td>
<td>0.35 ± 0.032SD</td>
</tr>
<tr>
<td>Polycystic kidney (5 cases)</td>
<td>32.4 ± 3.47SD</td>
<td>2.35 ± 1.45SD</td>
<td>16.8 ± 4.82SD</td>
<td>0.37 ± 0.041SD</td>
</tr>
</tbody>
</table>

Osteodystrophy also may show differences in the basic values of some bone biopsy parameters. In chronic uraemia due to pyelonephritis, for example, an osteoid surface larger than that in patients with glomerulonephritis, may sometimes be documented.

The daily catabolism and the serum toxicity (Figure 1) may sometimes be
Figure 1. Lymphocytes transformation test and uraemic serum of patients with chronic terminal uraemia of various etiology.

Figure 2. Serial studies on nerve conduction velocity in patients with 0–5 ml/min of $C_{cr}$ at the beginning of dialysis.

particularly high in chronic uraemic patients with vascular nephrosclerosis and chronic hypertensive glomerulonephritis. For unexplained reasons, the plasma of uraemic patients with chronic glomerulonephritis and normal blood pressure may not have the same effect on lymphocyte transformation as for patients with chronic hypertensive glomerulonephritis.

The effects of dialysis on the plasma from semiquantitatively evaluated
subclinical signs have been studied in relation to the rhythm of dialysis and the starting-time of treatment. Figure 2 shows the progressive changes in NCV on ‘daily’ and ‘intermittent’ programmes in patients with 0–5 ml/min $C_{cr}$ at the beginning of treatment. An invariable worsening occurred on intermittent dialysis. On daily dialysis a slowing in the progression rate was documented. However, a normalisation was never found.

In patients with an earlier dialysis starting-time different results have been observed. Figure 3 shows the progression in NCV in patients on short-dialysis schedule having 5–15 and 15–25 ml/min $C_{cr}$ at the beginning of treatment. Differences in respect to Figure 2 are remarkable for both basic values and progression rate.

Table II shows the results of bone biopsies in patients on dialysis grouped according to the $C_{cr}$. Once clearly established, as occurs in patients with 0–5 ml/min of $C_{cr}$, bone lesions invariably progress during dialysis. With minimal or moderate renal failure ($C_{cr}$ 15–20 ml/min) bone lesions may not progress even after four years of dialysis. Similar considerations may be extended to the other parameters studied (semiquantitatively).

Figure 4 shows the progression rate of NCV in 27 patients with 15–25 ml/min of $C_{cr}$ on low-protein diet and 47 cases with the same renal function on regular dialysis. Differences between the two groups are striking.

**DISCUSSION**

The merits of RDT in chronic uraemia are well established. The results are certainly less striking when the effective control of clinical and subclinical uraemia and the effective rehabilitation of the patients are critically evaluated. The control of uraemia by dialysis might be more appropriate if the basic distribution of uraemic changes could also be considered. For reasons largely unknown, hypertension, anaemia, osteoid surface, catabolism and serum toxicity have been found to have a non-uniform distribution among various populations of uraemics.

This seems to indicate a need for individual dialysis to achieve better clinical results since the same results do not necessarily follow the same strategy of dialysis. Further investigations in this field could possibly give results of considerable value.

In terms of rehabilitation, the results of dialysis are still questionable. Discrepancies between criteria used to indicate the rehabilitation of the patients, often regarded as synonymous with dialysis efficiency, may be partially responsible for this.

"Return to work" may be a misleading criterion. Many patients do not admit it for insurance purposes and there is no relation between subjective capacity to work and the objective progression of uraemia. The rehabilitation of the patients
<table>
<thead>
<tr>
<th></th>
<th>C$_{cr}$ 0–5 ml/min</th>
<th>C$_{cr}$ 5–15 ml/min</th>
<th>C$_{cr}$ 15–25 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases: 21</td>
<td>Biopsies: 85</td>
<td>Cases: 38</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>1–2 years</td>
<td>3–4 years</td>
</tr>
<tr>
<td>Volume density mm$^3$/cm$^3$</td>
<td>325 ± 58SD</td>
<td>327 ± 60SD</td>
<td>331 ± 63SD</td>
</tr>
<tr>
<td>Volume density of osteoid mm$^3$/cm$^3$</td>
<td>62.0 ± 12.8SD</td>
<td>70.5 ± 14.1SD</td>
<td>82.1 ± 15.8SD</td>
</tr>
<tr>
<td>Osteoid surface %</td>
<td>40.6 ± 12.8SD</td>
<td>47.5 ± 14.1SD</td>
<td>55.0 ± 15.8SD</td>
</tr>
<tr>
<td>Surface density of osteoid mm$^3$/cm$^3$</td>
<td>1600 ± 550SD</td>
<td>1895 ± 736SD</td>
<td>2290 ± 1120SD</td>
</tr>
<tr>
<td>Active Howship L. surface %</td>
<td>6.8 ± 3.5SD</td>
<td>7.6 ± 3.8SD</td>
<td>11.1 ± 4.9SD</td>
</tr>
<tr>
<td>Surface density of Active Howship L. mm$^3$/cm$^3$</td>
<td>253 ± 3.5SD</td>
<td>310 ± 3.8SD</td>
<td>456 ± 4.9SD</td>
</tr>
<tr>
<td>Surface density of endosteal fibrosis mm$^3$/cm$^3$</td>
<td>392 ± 130SD</td>
<td>480 ± 148SD</td>
<td>590 ± 280SD</td>
</tr>
<tr>
<td>Osteoclast Index</td>
<td>14.8 ± 392SD</td>
<td>16.1 ± 480SD</td>
<td>20.5 ± 590</td>
</tr>
</tbody>
</table>
The progression rate may be only slowed-up by changing the dialysis rhythm from intermittent to daily. This occurs despite a so-called reasonable quality of life and a possible return to work for the patients.

The cyclical removal of toxins by dialysis may not be satisfactory, added to which, uraemia is made worse by loss of non-excretory renal function.

The disappearance of clinical and subclinical changes cannot be assured by dialysis, but most of the systemic changes of uraemia may be avoided by starting treatment earlier (C\text{cr} not less than 10 ml/min).

These preliminary results simply indicate that, regardless of the general clinical condition, the usual starting times of treatment (0–5 ml/min C\text{cr}) are not associated with an ‘effective’ rehabilitation of the patient. Unfortunately prophylactic use of regular dialysis may meet with several logistic difficulties and its widespread clinical use today is only a pious hope.

CONCLUSIONS

1. Clinical and subclinical chronic uraemic changes may have not a uniform distribution according to the nature of renal lesions.

2. Dialysis does not reverse ‘systemic’ uraemia. Most of the systemic changes may be prevented provided that dialysis starting time is gauged earlier.

3. Dialysis rehabilitation may be ‘effective’ or ‘apparent’, according to the criteria employed.

References


Bonomini, V, Vangelista, A, Albertazzi, A and Stefoni, S (1974) (This volume)

Open Discussion

V CAMBI (Italy) The patients that are starting dialysis with creatinine clearance of 15 ml/min will drop eventually to 3 ml/min. Did you compare these patients as far as erythropoiesis or peripheral nerve status with the patients that started when the creatinine clearance was already 3 ml/min? Did you find differences between both groups, and how many patients did you evaluate? What kind of statistical analysis did you do?

BONOMINI We were forced to study the effect of earlier dialysis because of the clear demonstration of the incapacity of dialysis to reverse systemic uraemia when once systemic uraemic changes are clearly established, as occurs in patients with 0–5 ml/min of residual creatinine clearance.
CAMBI I think that it is common experience that some of the changes of uraemia can be reversed. For instance, the peripheral nerve status, starting with a creatinine clearance of zero, can improve and sometimes reach normality. This is also partly true of erythropoiesis.

BONOMINI What really improves in patients with 0–5 ml/min of residual creatinine clearance on dialysis is their sense of well being, but not objective criteria. At least, not in our experience. This applies to bone biopsies, erythropoiesis, except in polycystic patients, anaemia and so on. But the patient can still return to work.

H BUCHT (Sweden) In your penultimate slide you showed the nerve conduction time in dietary patients, and it certainly deteriorated. This is not in accordance with our experience. All of our 25 diet-controlled patients with clearances of less than 5 ml/min have unchanged or improved nerve conduction times. What diet do you use?

BONOMINI The patients receive 0.4 to 0.5 g of protein per kilogram body weight, and approximately 2,500 cal per day.

V PARSONS (UK) You suggested in one of your slides that patients with pyelonephritis entered their renal failure with worse bone disease than those with glomerulonephritis. I am sure it is partly true that you collect complications earlier in some renal diseases. Would you put hypertension high in your list of those that you would like to dialyse earlier despite reasonable clearances of around 10 ml/min?

BONOMINI The vascular necrosis of hypertension in chronic glomerulonephritis may not respond to dialysis despite a rational approach to sodium and water. Dialysis was successful in controlling the blood pressure in about 50 or 60% of the cases only. But hypertension associated with pyelonephritis or polycystic kidney disease was successful in about 90% of the cases. We have found low-renin and high-renin hypertension to correlate strictly with the behaviour of the blood pressure on dialysis.

S G MASSRY (USA) I still fail to understand what was your justification for dialysing patients with a clearance of 20. Since you feel you were justified, did you take the time to tell this poor patient that he did not really require dialysis, and he would be dialysed for four years for no obvious reason? We could not do this in the United States.

BONOMINI I can only repeat that we have had occasion to select only seven patients with high glomerular filtration rates. They accepted dialysis voluntarily, once it was clearly established that they could eat anything they wanted. Are you happy?

M FREIDBERG (Denmark) I think it is a selective approach, and in fact might yield very positive returns if we get some new data on what we all call “well-being”, which doesn’t mean anything at present. Is that your feeling?

ANDREUCCI (Italy) I agree with Dr Massry and Dr Cambi. I don’t think you can derive any conclusion from your very small number of patients who started
haemodialysis treatment with C_{cr} of 15 ml/min. We all know that it is always desirable to select patients for maintenance haemodialysis prior to their actual need for this therapy, because it is much better and much easier to prevent complications of uraemia, such as neuropathy, pericarditis, pruritus, metastatic complications, than to treat them. But I don’t think that we can accept your suggestion to start RDT with a C_{cr} of 15–20 ml/min just because you find quite early what you call the uraemic changes in a few patients. Everybody knows that some changes take place very early, when renal function is still high (e.g. 40–50 ml/min), but this is not a good reason for starting dialysis in Italy as well as the United States. We have shown in anaemia and peripheral nerve status that complete recovery of uraemic changes can be obtained.

BONOMINI Thank you. Of course we cannot draw any definitive conclusions from only seven cases. If you study the clearly established clinical changes by semi-quantitative programmed follow-up, the conclusion is that dialysis does not reverse systemic uraemia. We do not put patients on the chronic dialysis programme when the residual function is 15 or 20. The aim of our investigation was only to ascertain whether dialysis was effective in impeding the progression of uraemia.

FREIDBERG What is your dialysis schedule for patients with GFRs of 15 ml/min? Your conductivities in these patients were lower than in our patients on diet alone, or in patients on dialysis with very low renal clearance.

BONOMINI We put patients on dialysis only when they have a creatinine clearance ranging from 0–5 ml/min.

CHAIRMAN Thank you. We have to conclude. I think we are moving slowly but surely to the use of new techniques to analyse what is happening in uraemic patients.