THE EFFECT OF TRANSPLANTATION ON DIALYSIS DEMENTIA

A M Davison, G R Giles

St James’s University Hospital, Leeds, United Kingdom

Summary

Seven patients with dialysis dementia are described. Three patients, symptomatic from dementia at the time of transplantation, had a rapid exacerbation of their symptoms with deterioration to death. Four patients, asymptomatic at the time of transplantation, developed symptoms of dementia after surgery. Two of these had a rapidly fatal illness while the remaining two had a mild illness. One subsequently died from a myocardial infarction while the other gradually improved sufficiently for her to return to work. This experience indicates that transplantation is to be avoided in patients with dialysis dementia.

Introduction

Dialysis dementia is a progressive encephalopathy which occurs in dialysis patients and follows a fairly characteristic clinical course. It commonly presents as a speech disorder, initially slurring of speech and stuttering, progressing to dysarthria and eventually mutism. This is associated with dementia, myoclonus, grand mal seizures and variable focal neurological deficits. It was initially described by Alfrey and his co-workers [1] and since then there have been many confirmatory reports [2–5].

The aetiology of this distressing condition is unknown. It has been suggested that it is caused by an accumulation of aluminium in the brain [6, 7] due to the aluminium present in the dialysis fluid [5, 8]. No satisfactory treatment has been demonstrated and most patients progress to death over a variable period of time. It has been suggested that transplantation and the restoration of satisfactory renal function may produce an arrest and reversal of the symptoms [9]. We report here our experience of transplantation in patients with dialysis dementia.
Patients and Methods

Two hundred and fifty patients have received haemodialysis for more than six months under the care of the Regional Renal Unit in this hospital. One hundred and forty of these patients have received more than six months haemodialysis at home and of these 20 developed dialysis dementia. No patient dialysed exclusively in the renal unit has developed dementia.

Dialysis has been performed with a 1m² Kil dialyser for six hours three times weekly until 1976 when all home patients and many hospital patients were transferred to a 1.5m² dialyser for four hours thrice weekly. The dialysate contained 1.5mmol/L calcium, and aluminium hydroxide (Aludrox) was prescribed routinely only since 1975 in a dose adequate to maintain the pre-dialysis plasma phosphate at 2mmol/L.

Three patients with symptoms of dialysis dementia and four patients who developed symptoms of dementia after surgery received cadaver grafts. Immunosuppression was undertaken with prednisone and azathioprine. Prednisone was started at 100mg daily for ten days and then gradually reduced to 25mg daily by one month and further reduced to 15mg daily by four months. Azathioprine dosage was dependent on the WBC and platelet count but was between 100 and 150mg daily. All patients received Mucaine (Oxethazine, Magnesium trisilicate and Aluminium hydroxide mixture) as an antacid.

Results

Patients Symptomatic Before Transplantation

Case One SK. Female aged 28. On haemodialysis for seven years of which six years ten months was home dialysis. The mean aluminium concentration of the home water supply was 0.19mg/L during this time. After five and a half years dialysis she developed myoclonus of the right leg which was more severe after dialysis. Four months later she developed dysphasia and this progressed to periods of mutism. After transplantation her symptoms became more severe and more frequent producing considerable difficulty with walking. She became anxious, agitated and progressed with the typical features of dementia. Her transplant had good primary function and showed no evidence of rejection. She died from dementia two months after transplantation.

Case Two GC. Male aged 44. On haemodialysis for 35 months of which 22 months was home dialysis. The mean aluminium concentration of his home water supply was 0.19mg/L. Prior to transplantation he had mild stuttering for several months but no other evidence of dementia. One month after transplantation his speech was noticed to be monotonous and shortly after this he had two right sided epileptiform convulsions. This was followed by aphasia, a complete absence of facial mobility and excessive salivation. Over the next six weeks he progressed to dementia and died of a chest infection. The transplant had good primary function and had no rejection episodes.
Case Three MB. Male aged 38. On haemodialysis for 67 months of which 36 were on home dialysis. Eight months after starting home treatment he developed myoclonus, dysarthria and a deterioration in his memory. He progressed to develop grand mal epilepsy. He returned to hospital dialysis and his symptoms improved. During home dialysis treatment the water supply mean aluminium concentration was 0.39mg/L while that of the hospital unit was <0.01mg/L. After transplantation his symptoms became more severe and he progressed to dementia. He died four weeks later from bronchopneumonia. His transplant had good primary function and had only one mild rejection episode which responded satisfactorily to Solumedrone.

Patients Becoming Symptomatic After Transplantation

Case Four LD. Male aged 46. On haemodialysis for six and a half years of which six years were on home dialysis. His home dialysis water supply had a mean aluminium concentration of 0.08mg/L during this period. Six weeks after transplantation he noticed transient expressive dysphasia and stuttering particularly in the evenings. He developed marked anxiety and agitation. At ten weeks he noticed paraesthesiae in his face. His symptoms remained unchanged over the next five months. His transplant had delayed function but this resolved satisfactorily and at no time showed any evidence of rejection. Seven months after transplantation he had a severe myocardial infarction from which he died.

Case Five RH. Male aged 52. On haemodialysis for 36 months of which 27 months were home dialysis. The mean aluminium concentration of his home water supply during this period was 0.36mg/L. One month after transplantation he became confused, disorientated, anxious and agitated. One week later he had a grand mal fit and subsequently developed aphasia. Six weeks after transplantation myoclonus appeared. He progressed to dementia and died from bronchopneumonia. His transplant had delayed function and one mild rejection episode. Renal function was good at the time of death.

Case Six SJ. Female aged 26. On haemodialysis for 53 months of which 48 months were home dialysis. The mean aluminium concentration of her home water supply during this period was 0.10mg/L. After transplantation she developed dysarthria, myoclonus and an acute anxiety state. Her symptoms became more severe and grand mal epilepsy developed. She gradually deteriorated and eventually became mute and totally immobilised. She died twelve months after transplantation from broncho-pneumonia. Her renal function was good throughout her illness.

Case Seven JH. Female aged 21. On haemodialysis for 56 months of which 48 months were home dialysis. The home dialysis water supply mean aluminium concentration during this time was 0.21mg/L. Two months after transplantation she developed stuttering speech and some dysphasia. She had episodes of anosmia and her symptoms tended to be more severe in the evenings. She later noticed
paraesthesiae of the face. Her symptoms became more severe and she developed grand mal epilepsy nine months after transplantation. She had frequent tonic attacks with rigidity and was treated with Clonazepam. The symptoms gradually improved and thirteen months after transplantation she was able to return to work. She is now asymptomatic. Her transplant had delayed function but subsequently had been very satisfactory with no evidence of rejection.

**Patients Asymptomatic Before and After Transplantation**

During the time that the patients with dementia or those who subsequently developed dementia were transplanted (36 months), some 75 other patients received renal transplants. None of these patients at any time showed any signs or symptoms of dementia.

**Discussion**

The seven patients described in this report all had illnesses compatible with the syndrome of dialysis dementia. There is no characteristic symptom or sign diagnostic of this condition, but they all developed a speech disorder and six of the seven had severe behavioural disturbances after transplantation. Although there are other causes for these symptoms we attribute them in these patients to dialysis dementia in view of the associated myoclonus and epilepsy and the negative results of studies looking for possible infective agents or vascular causes.

Dialysis dementia is a distressing condition and has been reported from a considerable number of centres in many countries. In our unit there is a marked geographical distribution of patients who develop dementia similar to that described by Platts and her colleagues from Sheffield [5]. The syndrome occurs in patients who are dialysed using a water supply with a high aluminium content and there appears to be a close relationship between the aluminium concentration and the speed at which the symptoms develop [10]. Aluminium accumulates in the brain and is found in much higher concentration in patients with dialysis dementia compared with other asymptomatic dialysis patients [6]. It would appear therefore that the syndrome is due to intracerebral accumulation as a result of trans-membrane transfer of aluminium during dialysis.

There is no satisfactory treatment for dialysis dementia. It could be hoped, however, that by discontinuing dialysis and restoring satisfactory renal function the signs and symptoms would resolve. It is disappointing to note that in our patients this has not occurred and, indeed, four of our patients became symptomatic at a time of good transplant function. There was a surprising lack of rejection in these seven patients, there being only two mild rejection episodes. All our patients had good transplant function with a serum creatinine of less than 150μmol/L apart from during the terminal phase of their illness. The possibility is raised that the immunosuppressive therapy has, in some way, precipitated or aggravated the dementia in susceptible patients.

Steroid therapy has an osteolytic effect on bones and it is interesting to note that there appears to be a close association between dementia and renal osteo-
dystrophy [11], particularly osteomalacia, although this is not a universal finding. It is known that aluminium can accumulate in bone and it is possible that the steroids cause a release of aluminium thereby aggravating the dementia. Thus, although patients are removed from the source of aluminium by successful transplantation they may continue to be at risk due to ‘autotransfusion’ by the release of aluminium which has accumulated in bone.

Azathioprine has the ability to facilitate neuromuscular transmission [12] and thus may aggravate the myoclonus and dysarthria. In addition our transplant patients received aluminium containing antacids from which some aluminium is absorbed. However, it is unlikely that these medications were responsible for the dementia, as similar dosage schedules were used for all our patients undergoing transplantation.

We are not able to confirm the suggestion of Sullivan and his colleagues [9] that transplantation may be of benefit in the management of dialysis dementia. Indeed, in view of our experience, we would not recommend transplantation in such patients. Rather we would suggest removal of the patient from home dialysis or the installation of reverse osmosis water treatment plants to remove aluminium and other potentially toxic materials. It is therefore unjustifiable to consider transplantation as a method of treating dialysis dementia.

Acknowledgments

We wish to thank the many members of our medical, nursing and technical staff who were involved in the care of these patients.

Financial support from the Yorkshire Kidney Research Fund is most gratefully acknowledged.

References

Open Discussion

RAMIREZ-RUBIO (Monterrey, Mexico) Have you been able to determine brain aluminium levels on the patients who were transplanted and died?

DAVISON No, we have no data, as yet, on brain aluminium concentrations.

WALDEK (Sheffield, UK) We would concur with these results. In fact dialysis dementia is probably an absolute contraindication to transplantation. Two of our patients, who had had symptoms of dialysis dementia arrested by adequate treatment of their water supply, then had transplants and developed severe symptoms. However, we have one patient who deteriorated rapidly after transplantation and who now one and a half years later started to improve again. We would suggest that the possible mechanism for this rapid deterioration is that these patients, who had been exposed to aluminium, had storage somewhere. One of the most likely places for storage is the bones, and with the improved vitamin D status and the enforced immobilisation of these patients after a transplant, there is a rapid release of aluminium or other toxic substances into the blood, enhancing the rapid deterioration in these patients. I wonder if you have done any studies to support this?

DAVISON I think there are certain interesting points in our case number three, who developed dialysis dementia on dialysis. We removed him from home dialysis back to hospital dialysis and he symptomatically improved and he remained in a very stable state, only to deteriorate rapidly after transplantation. Like you, we were highly suspicious of what is happening after transplantation. It is possible that the immunosuppressive therapy is involved. Steroids have an osteolytic effect and this may cause the release of accumulated aluminium from bone. We know that aluminium accumulates in the bones of dialysis patients and the steroids may therefore produce an ‘autotransfusion’ of aluminium. Thus although patients may be removed from dialysis, aluminium ‘transfusion’ by successful transplantation may still be a risk.