Abstract: Neurovascular Complications of Dialysis and Transplantation

Dialysis and transplantation are now standard treatments for end-stage renal failure. Often, neurologists are consulted regarding the neurological complications of these therapeutic procedures. In addition to previously reported complications, neurovascular disease is being recognized as a cause of mortality and morbidity in these patients. We report two cases of apparent thromboembolic stroke in young patients with renal failure — one treated by dialysis and the other by renal transplantation. The risk factors of both dialysis and transplant are identified and data from the American College of Surgeons/National Institutes of Health Transplant Registry are reviewed.

Additional Key Words: cerebrovascular accident, accelerated atherosclerosis, subarachnoid hemorrhage, uremic lipemia, risk factors, subdural hematoma, diabetic lipemia

Introduction

Very little has been written regarding specific neurovascular disorders in uremic patients being treated by dialysis or transplantation. However, the American College of Surgeons/National Institutes of Health (ACS/NIH) Transplant Registry has shown that neurovascular disease is a cause of death in transplant recipients (table 1).

Neurologists are frequently consulted for the multiple neurological complications of both uremia and its therapies, dialysis and transplantation (which are standard treatments now). Neurovascular accidents are one of these neurological complications.

After suffering apparent neurovascular accidents, two uremic patients were seen at the Mayo Clinic. Both were less than 35 years of age. One was being dialyzed and the other had had a renal transplant. One patient recovered; the other died within a month. Both had sustained probable thromboembolic strokes and each had abnormal triglyceride and cholesterol metabolism. This altered lipid metabolism occurring in uremic and steroid-immunosuppressed patients may be related to known risk factors of neurovascular accidents.

Report of Cases

CASE 1

A 31-year-old, right-handed white woman was discovered to have glomerulonephritis in 1964. In 1968 she received a renal allograft from her mother and was given methylprednisolone and azathioprine during the period of allograft function. Since this time, she has had progressive difficulties. Complications have included chronic allograft rejection and side effects of immunosuppressive drugs, such as cataracts, hypertension, and cushingoid features.

In the fall of 1973 she was admitted to the hospital because of 24 hours of bizarre behavior and hallucinations. Examination revealed a possible left inferior quadrant-anopia and several other neurological abnormalities. Upon double simultaneous stimulation, she showed neglect of those stimuli on the left side. She could not detect traced figures on her palms. Even simple drawings were impossible for her to complete. Perception of spatial relationships within the environment was impaired. The clinical diagnosis was right parietal infarct.

Initial neurological work-up included an EEG that revealed a grade 2 delta focus in the right centroparietal-temporal region and grade 2 asymmetry, more pronounced on the right. Computerized tomography (EMI scan) demonstrated an area of decreased density in the right temporal fossa and an enlarged right lateral ventricle. Lipids were elevated; cholesterol concentration was 418 mg/dl and triglyceride concentration was 970 mg/dl (normal, <300 mg/dl).
and <150, respectively), with type III Fredrickson lipoprotein profile. The serum creatinine level was 5 mg/dl (normal, 0.6 to 0.9 mg/dl). Serum calcium was 9.7 mg/dl, serum phosphorus was 4.3 mg/dl, and fasting blood sugar was 75 mg/dl (all within normal limits).

She received anticoagulants and her condition improved neurologically. However, since early 1974, the renal failure has progressed and the allograft had to be removed. Chronic repetitive hemodialysis was reinstituted.

**CASE 2**

A 31-year-old white man afflicted with insulin-dependent diabetes mellitus for 20 years was first seen at the Mayo Clinic in the fall of 1972. Diagnoses then included: diabetes mellitus, diabetic nephropathy with nephrotic syndrome and renal failure, severe retinopathy, gynecostasia, and mild peripheral neuropathy. He required 130 units of NPH insulin every morning and 80 mg of furosemide four times daily. Laboratory results included: fasting blood sugar, 428 mg/dl (normal, 70 to 100 mg/dl); creatinine, 16 mg/dl; cholesterol, 321 mg/dl; and triglycerides, 446 mg/dl. A Fredrickson type IIb lipoprotein abnormality was found. Initial neurological examination demonstrated generalized hyporeflexia (more pronounced distally) and slight distal weakness and absence of sweating in the lower extremities. Babinski's sign was absent. Vibration sense was normal in the hands but impaired in the legs, especially below the knees. Sensation to pinprick was diminished below the knee.

His condition deteriorated gradually during the next year as his renal failure worsened. Early in 1973 chronic repetitive hemodialysis was begun. Because of recurrent clotting of the cannulae, multiple shunt revisions were needed. His arteries were severely atherosclerotic. By August he was classified as having end-stage renal disease and preparations were made to accept him into the transplant program as a high-risk candidate. His diabetes had stabilized and required less insulin than in 1972.

In August 1973, he was hospitalized for bilateral nephrectomy prior to receiving a living renal allograft from a relative. Pitting edema of the legs (more so on the left) and paresthesias of the toes occurred. Sensation to pinprick was diminished below the knee. The following day, the patient became stuporous and lethargic. After brief improvement, he lapsed into coma on October 13, 1973, and died four days later.

Autopsy findings included: pulmonary edema, interstitial fibrosis of the pancreas and depletion of the islets of Langerhans, severe arteriosclerosis of small cerebral vessels, multiple small thrombi and infarcts of the spinal cord and brain, and bilateral nephrectomy (microscopic examination of the kidneys at surgery disclosed Kimmelstiel-Wilson nephropathy).

**Discussion**

**NEUROVASCULAR COMPLICATIONS IN RENAL TRANSPLANTATION**

Clinically, the first patient had a cerebral infarction of the right parietal lobe, most likely of thromboembolic etiology. The complications of atherosclerosis are likely to develop in transplant patients because of the altered lipid metabolism encountered in steroid-immunosuppression and the renal failure of allograft rejection.

As of September, 1973, the ACS/NIH Registry had recorded 3,522 deaths from all causes in renal transplant recipients. In descending order of frequency the neurovascular causes were "cerebrovascular accident (CVA)," diffuse vasculitis, subarachnoid hemorrhage, and subdural hematoma (table 1). Most patients with diffuse vasculitis, subarachnoid hemorrhage, and subdural hematoma, and one-third of those with CVA, were under 36 years of age (table 1).

Because reporting institutions did not indicate whether the CVAs were thromboembolic or hemorrhagic, the Registry felt that no statement could accurately reflect which type of stroke had occurred. However, because another category (subarachnoid hemorrhage) is provided on reporting forms, the Registry concluded: (1) the CVA category probably represented predominantly thromboembolic phenomena, and (2) due to data collection difficulty, this may never be resolved.

Whether or not the deaths from subarachnoid hemorrhage were associated with berry aneurysms is not known. An increased incidence of berry aneurysms occurs in patients with polycystic kidney disease. However, none of these patients with subarachnoid hemorrhage had polycystic kidney disease.
NEUROVASCULAR COMPLICATIONS OF DIALYSIS AND TRANSPLANTATION

as the underlying cause for uremia and subsequent transplantation. Most of them had glomerulonephritis.

The fourth neurovascular cause of death, subdural hematoma, occurred exclusively in young patients. These patients ranged in age from eight to 18 years. Unfortunately, the cause or suspected cause of each subdural hematoma was not reported to the Registry.

As of May, 1974, 15,921 transplant recipients had been registered. Of these, 4,624 had died, 184 (or about 4%) from neurovascular complications (table 2). The neurovascular causes occur in approximately the same frequency as totals shown in table 1, although age breakdown is not included.

Schneck reviewed 300 renal transplants and 40 liver transplants at the University of Colorado and discovered four cases of intracerebral hemorrhage. These patients presented with focal signs and seizures. Impaired platelet function from decompensated renal disease was believed to be responsible. No other types of neurovascular disorders were reported.

Casaretto and colleagues documented hyperlipidemia after successful renal transplantation in 41 patients who had age-matched controls; both triglyceride and cholesterol levels were elevated. Fredrickson lipoprotein profiles were reported in 16: two patients had type IIA, eight had type IIB, and six had type IV.

POSTSURGICAL "HYPERCOAGULABLE STATE" AND NEUROVASCULAR COMPLICATIONS OF DIALYSIS

The second patient's status deteriorated from paraparesis to triaparesis with bilateral brainstem findings to coma and death in one month. Because each deterioration was acute, these episodes were believed to be vascular in origin and most likely due to the "hypercoagulable state" occasionally seen after surgical procedures. The autopsy findings of multiple thrombi in the central nervous system support this impression.

Von Kaulla has reviewed postsurgical hypercoagulability. It can occur after any major surgery and was initially investigated as a possible explanation for postoperative pulmonary embolism. The thrombin generation test, which measures coagulability, has demonstrated increasing hypercoagulability after kidney transplants in man. This is especially noticeable because uremic patients, before transplantation, have hypocoagulability. The posttransplant hypercoagulability is generally seen 10 to 17 days after transplant and similarly may account for the high incidence of postoperative pulmonary embolism seen in such cases.

Von Kaulla has also studied the uremic bleeding diathesis and believes that platelet dysfunction is responsible for this disorder. It may cause diffuse hemorrhage in any organ system, including the central nervous system (CNS).

Another neurovascular disorder, subdural hematoma, occurs with hemodialysis. This is a diagnostic problem because subdural symptomatology may mimic the acute encephalopathy that occasionally occurs during hemodialysis. A metabolic dysequilibrium syndrome is postulated to be responsible for the encephalopathy of hemodialysis. It has been explained as a "reverse urea effect," wherein removal of urea from the CNS lags behind urea removal from the blood (Tyler HR: The kidney and the brain. Read at the American Academy of

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. of deaths reported</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>1,568</td>
<td>33.91</td>
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<tr>
<td>Not known or given</td>
<td>505</td>
<td>10.92</td>
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<tr>
<td>Rejection and sepsis</td>
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<td>6.70</td>
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<tr>
<td>Rejection</td>
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<td>5.69</td>
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<tr>
<td>Unrelated to transplant</td>
<td>215</td>
<td>4.65</td>
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<tr>
<td>Surgical</td>
<td>213</td>
<td>4.61</td>
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<tr>
<td>GI hemorrhage and ulceration</td>
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<tr>
<td>Cerebral vascular accident</td>
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Total reported                          | 4,624                  | 100.00     |

Data from American College of Surgeons/National Institutes of Health Transplant Registry, Chicago, 1974.

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Neurology, April, 1974, San Francisco). Of course, an encephalopathy may also be caused by subdural hematoma. Talalla and colleagues\(^1\) have studied subdural hematomas in this setting. They stress that a high index of suspicion is required to rule out coexisting subdural hematoma.

The cause of the hematoma is uncertain but may involve the bleeding diathesis of uremia or the use of anticoagulants to prevent clotting of the arteriovenous canulae. The differentiation among an encephalopathy due to the hemodialysis disequilibrium syndrome, to uremia, or to subdural hematoma is difficult but essential.

Subdural hematoma should be suspected if the patient (1) is receiving anticoagulants, (2) develops meningsmus indicating possible intracranial hemorrhage, or (3) acquires a focal neurological deficit. A history of trauma is rarely if ever obtained in these patients.

Lindner et al.\(^1\) demonstrated accelerated atherosclerosis in prolonged maintenance hemodialysis. Twenty-three of 39 patients receiving long-term regular hemodialysis had died by the end of the 13-year follow-up period. In 14 of these, death was caused by a complication of atherosclerosis (myocardial infarction, eight; cerebrovascular accident, three; and refractory congestive heart failure, three).

**STROKE RISK FACTORS IN UREMIC AND IMMUNOSUPPRESSED PATIENTS**

In 1971, Kannel,\(^8\) of the Framingham Study Group, reviewed the epidemiology of cerebral infarction. Environmental factors, genetic factors, individual ingredients of the stroke profile, and stroke profiles proper were analyzed. Atherogenic precursors such as elevated serum lipids, diabetes, hypertension, cardiac impairments, and elevated hemoglobin were found to be risk factors. Many of these occur in young patients with renal failure, diabetes, or steroid immunosuppression.

Cerebral infarction has been shown to be related to elevated serum lipid levels in young patients but not in patients over age 50.\(^9\) In our two cases, marked elevation of the serum lipid levels, especially of triglycerides, occurred. One case had a large amount of pre-beta lipoproteins; the other, a large amount of beta lipoproteins. Both of these lipoprotein abnormalities are associated with premature vascular disease. Uremia and steroid therapy were at fault in the first patient; uremia and diabetes caused these increases in the second patient.

Bagdade and colleagues\(^12\) have studied diabetic, uremic, and steroid-induced lipemia. They demonstrated that non-nephrotic uremia could cause hypertriglyceridemia, probably via insulin antagonism. (Other possibilities included abnormal circulating triglycerides and abnormal triglyceride removal.) Hence, they concluded more frequent hemodialysis would partially correct these abnormalities, by reducing the degree of insulin antagonism in uremia.

Bagdade and colleagues\(^12\) reported "steroid-induced" lipemia in two patients receiving large doses of corticosteroids as treatment for collagen disease. The four features of this phenomenon are: (1) abnormal accumulation of dietary fat (chylomicrons), (2) impaired triglyceride removal, (3) glucose intolerance and reduced insulin responses during oral glucose tolerance tests, and (4) reversal of these abnormalities when the steroid dose was gradually reduced. Bagdade et al.\(^12\) concluded that steroid-induced lipemia results from decreased pancreatic insulin reserve with resultant chronic insulin deficiency. This condition resembles fat-induced lipemia found in poorly controlled diabetics.\(^12\)

**Summary**

Two cases of stroke syndromes occurred in young patients who were uremic and under treatment by dialysis or transplantation. Factors that predisposed these patients to strokes were discussed and include the abnormal lipid metabolism caused by their underlying disease and its therapy. Data regarding the deaths of patients through age 35 years from neurovascular disease recorded in the ACS/NIH Registry were reviewed and interpreted. The postoperative hypercoagulable state was implicated as a stroke risk factor.

Another neurovascular complication of both dialysis and transplantation was subdural hematoma. Registry data indicate this is confined to the younger transplant recipients. When it occurs in the setting of hemodialysis, subdural hematoma is a diagnostic challenge — a high index of suspicion is required to differentiate it from the more common metabolic derangements encountered in hemodialysis.

With increasing frequency, the neurologist is consulted by his colleagues in nephrology to diagnose and treat the myriad neurological complications of uremia and its therapies. Regarding neurovascular complications specifically, stroke prevention remains the best method of avoiding catastrophic brain destruction from vascular disease. Prevention of the complications of uremia, hemodialysis, and transplantation and reduction of neurovascular risk factors require the cooperation and mutual concern of surgeon, nephrologist, and neurologist.

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