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Rapid Reversal of Uremic Neuropathy Following Renal Transplantation in an Adolescent

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Abstract

Clinical and pathologic studies on adults with uremic neuropathy are numerous, but less is known about this disorder in children and adolescents. We report the clinical, electrophysiologic, and pathologic findings in an adolescent female with uremic neuropathy. Electrophysiologic findings were consistent with a primarily axonal sensorimotor polyneuropathy. Sural nerve biopsy revealed areas of focal depletion in myelin sheaths and loss of axons. Axonal degeneration with secondary myelin changes appears to be the characteristic pathology in this case, one of the youngest to our knowledge for which nerve biopsy data are available. Our patient experienced dramatic recovery after renal transplantation, similar to reports of older patients.

Keywords

Renal transplantation; renal failure; uremia; neuropathy

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Introduction

Although uremic neuropathy is a common complication of end stage renal disease, the exact mechanism of uremic neuropathy remains unknown (1). Pathological studies of adult patients with uremic neuropathy have demonstrated axonal degeneration with secondary demyelination. Existing studies focus on adults with uremic neuropathy; however, studies in younger individuals are limited. We report the clinical, electrophysiologic, and pathologic findings in an adolescent with this disorder who demonstrated dramatic improvement after renal transplant.

Case Report

A 16-year-old girl with focal segmental glomerulosclerosis presented with progressive weakness of her lower extremities, at first in association with leg cramping. The weakness progressed over three months and she began to have frequent falls. She also developed weakness in her hands and a left facial droop. She denied paresthesias, numbness, dysphagia, dysarthria, or breathing difficulties. She otherwise had no antecedent illnesses or fevers.

Birth history was unremarkable. She presented with nephrotic syndrome associated with normal renal function at age 12 years and was initially treated with prednisone 60 mg daily. After four weeks of therapy, she had no improvement and therefore underwent percutaneous renal biopsy. The pathology was consistent with focal segmental glomerulosclerosis. She was subsequently treated with a 12 week course of oral cyclophosphamide and weaning doses of prednisone but remained resistant to therapy. Further immunosuppressive therapy was discussed but declined. She was provided supportive management and had progressive decline in renal function. Approximately four years after presentation, she reached end-stage renal disease and initiated hemodialysis. Her leg weakness developed at the same time. Medications at presentation were enalapril, losartan, calcitriol, iron polysaccharide, and darbepoetin alpha. She was a high school senior who lived at home with her parents. She had not traveled recently and had no significant family history.

On her initial physical examinations, she was alert and appeared well. She had paralysis of both upper and lower portions of her left face. A hemodialysis catheter in the right subclavian vein limited assessment of strength in the proximal right arm. In the upper extremities, she had mild distal weakness in bilateral finger intrinsic muscles but normal proximal left arm strength. In the lower extremities, she had no antigravity movement in bilateral distal leg muscles, mild weakness in knee flexion and extension and full strength in bilateral hip flexors. Muscle bulk, tone, and coordination were normal. She had mildly decreased vibration at the toes. Reflexes were absent in all extremities with flexor plantar responses. She could rise from a seated position with minimal support. She was unable to stand independently and she had difficulty lifting her feet off the ground when she walked.

Serum creatinine and blood urea nitrogen were 10.3 mg/dl and 157 mg/dl, respectively (glomerular filtration rate < 10 ml/min/1.73M²). Total carnitine, thyroid stimulating hormone, vitamin B12, human immunodeficiency virus, lyme antibodies, and urine heavy metal screen were unremarkable. Examination of cerebrospinal fluid revealed 0 erythrocytes/mm³, 2 leukocytes/mm³, glucose 71 mg/dl (normal 60–80 mg/dl), and protein 31 mg/dl (normal 15–45 mg/dl). Magnetic resonance imaging of the thoracic and lumbosacral spine with contrast was normal. Nerve conduction and needle electromyography demonstrated significant axonal loss in the lower extremities.

For her renal failure, she received hemodialysis followed by continuous ambulatory peritoneal dialysis. Because of the facial and upper extremity involvement, chronic inflammatory demyelinating polyradiculoneuropathy was considered as a diagnostic alternative to uremic neuropathy. Plasma exchange was initiated, but then discontinued after one exchange due to patient discomfort. Her bilateral leg weakness continued to worsen. She underwent a course of intravenous immunoglobulin without improvement in symptoms. She began to experience dysesthesias in her feet and pain in the soles of her feet. Walking was limited by the ankle and foot weakness and sensory changes but was considerably improved by the use of well padded foam and semi-pneumatic full length walking braces.

A sural nerve biopsy was performed approximately six months after onset of leg weakness. It demonstrated a paucity of large myelinated fibers, an increase in collagen, and loss of axons (Figures 1 and 2). Twelve months after initiation of dialysis, the patient underwent renal transplantation. She reported a dramatic improvement in strength in the first one to two weeks after surgery, followed by slower improvement over months. Post-operatively, her medications included tacrolimus, mycophenolate mofetil, prednisone, nifedipine, potassium and sodium phosphate, valganciclovir, and sulfamethoxazole with trimethoprim. Five weeks after renal transplantation, her follow-up exam demonstrated significant improvement. She had full strength in all muscles in her upper extremities except for continued mild weakness in finger intrinsic muscles. Strength in lower extremities was full except for mild weakness in ankle and toe dorsiflexion. Her dysesthesias and gait improved. She declined repeat electrophysiologic testing after transplantation.

At the age of 21 years, about 4 years after transplantation, she reports that she is able to run, jump, climb stairs, and rise from the floor. She exercises regularly and participates in recreational swing dancing activities.

Discussion

Uremic neuropathy is a well-known complication of renal failure in adults, but in children, uremic neuropathy has only recently been reported (2). In adults, peripheral neuropathy occurs in 50–60% of patients who require hemodialysis (3). The prevalence of uremic neuropathy in the pediatric population is unknown.

Studies of adults with renal failure have shown that uremic neuropathy develops when glomerular filtration rates are less than 10–12 ml/min. Both slowly and more rapidly progressive sensorimotor axonal neuropathies have been described in adults (1). The exact mechanism of uremic neuropathy remains unknown. It is widely believed that nerve damage occurs secondary to accumulation of uremic toxins, such as guanidine compounds, parathyroid hormone, and myoinositol, examples of so-called “middle molecules,” (e.g., molecules in the range of 300–2000 daltons), which cross dialysis membranes much more slowly than substances such as creatinine and urea (1, 3, 4). It has been argued that in adults, certain factors including diabetes, advanced age, and low creatinine clearance may predispose one to the development of uremic neuropathy (5). To date, we do not know what predisposes certain children with renal failure to develop uremic neuropathy.

As occurred in our patient, uremic neuropathy in adults typically progresses despite dialysis (6, 7). In adults, renal transplantation is thought to be the only way to arrest progression of uremic neuropathy, although the extent of recovery may depend upon duration of neuropathic symptoms prior to transplantation (8). Clinical and electrophysiologic parameters have both been shown to improve in adults after renal transplantation (9). In children, there are no studies comparing electrophysiologic parameters before and after renal transplant. El-Husseini and colleagues evaluated the electrophysiologic abnormalities in

pediatric patients after renal transplant and found neuropathic changes in 19% of their 31 cases (10). The electrophysiologic findings were that of a distal sensorimotor polyneuropathy in the lower extremities, with the extensor digitorum brevis the most commonly affected muscle. The duration of pretransplant dialysis was almost twice longer for the patients with abnormal electrophysiologic studies than for the patients with normal studies. This finding underscores the importance of prompt recognition and diagnosis of uremic neuropathy in children, rare as it may be.

Our patient's clinical presentation was similar to patterns seen in adults with uremic neuropathy in two other ways. First, her initial symptom of leg cramping was a classic presentation described in adults; in early reports of uremic neuropathy, Nielsen and colleagues noted that muscle cramping frequently occurs in uremic patients and can mark the onset of peripheral neuropathy (5). Second, her two phases of recovery, (i.e., her dramatic improvement in the first two weeks after transplant, followed by a slower protracted improvement) has been demonstrated in adults in original reports of uremic neuropathy (5, 11).

The present case is unique, however, in that it provides an opportunity to correlate pathological findings with clinical and electrophysiologic features in an adolescent with uremic neuropathy. Even in adults, studies of pathologic findings associated with uremic neuropathy are rare (2). Although early literature suggested that demyelination was the primary process in uremic neuropathy (12), studies by Dyck have shown that axonal degeneration and atrophy are the primary features in uremic neuropathy (13). Said and colleagues examined the sural biopsies of 10 patients with uremia and found a variety of pathological findings; acute axonal neuropathies, progressive axonal neuropathies with secondary demyelinating features, and predominantly demyelinating neuropathies were reported. In all 10 patients, degeneration of axons was found (14).

Our patient's sural nerve biopsy demonstrated depletion of large myelinated axons and supernumerary Schwann cells surrounding unmyelinated axons. There was no active degeneration of myelin or axons observed, most likely due to the timing of the biopsy in the course of her neuropathy. In adults, it has been shown that both axonal degeneration and demyelination/remyelination are important features of uremic neuropathies with demyelination and remyelination thought to be secondary to axonal degeneration (13, 14).

Our patient demonstrated a dramatic recovery in strength following renal transplantation. Possible factors influencing the tempo and extent of recovery may include immunosuppressive drugs, graft dysfunction, and anemia (10). This is an area of interest for future research, given the morbidity associated with uremic neuropathy in both adults and children.

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Figure 1.

Figure 2.