Recently, demyelinating polyneuropathies have been reported in end-stage renal disease patients. These acute and subacute neuropathies share a demyelinating feature and may develop after the initiation of continuous ambulatory peritoneal dialysis. The pathogenesis of these non-chronic forms of neuropathy remains unclear. We report a case of subacute polyneuropathy that posed a clinical dilemma.

Key words
End-stage renal disease, Guillain–Barré syndrome, subacute polyneuropathy, continuous ambulatory peritoneal dialysis

Introduction
Uremic neuropathy is the most common neurologic complication of uremia, affecting more than 60% of end-stage renal disease (ESRD) patients undergoing dialysis (1–3). The most frequent clinical features reflect large-fiber involvement, manifesting as paresthesias, reduction in deep tendon reflexes, impaired vibratory sense, weakness, muscle wasting, or autonomic dysfunction. On electrophysiologic assessment, this symmetric polyneuropathy presents in an axon-dominant pattern, with the large-fiber involvement being more appreciable in the lower than the upper limbs. Although the clinical course and intensity of uremic neuropathy are variable, the condition generally develops only at glomerular filtration rates of less than 12 mL/min (1–5). Coexisting chronic conditions such as diabetes mellitus may also affect the disease course (2,3). The reported cases of acute and subacute demyelinating neuropathy in end-stage renal disease patients on peritoneal dialysis (PD) often describe a history of prolonged diabetes mellitus.

The pathophysiologic basis of uremic polyneuropathy is poorly understood and may be multifactorial. Existing mechanistic postulates include retention of neurotoxic molecules in the middle molecular range, chronic hyperkalemic depolarization of nerve fibers, and prolonged nerve conduction velocities induced by high parathyroid hormone (2–6).

Case Report
Our patient, a 55-year-old right-handed man, had a past medical history of end-stage renal failure on PD, coronary artery disease status post–coronary artery bypass grafting, type 2 diabetes mellitus, diabetic retinopathy, and polyneuropathy of diabetic and multifactorial causation. He had been on PD while awaiting kidney transplantation, during which time he developed a 4-month history of painless symmetrical lower extremity weakness with more proximal than distal involvement.

Although the course of the weakness had been progressive, 2 episodes of rapid deterioration leading to an inability to walk had occurred. The first episode had begun 2 months before the admission reported here; the second episode occurred within the week before presentation. The patient reported no back pain, myalgias, or bladder or bowel incontinence. The only sensory complaint was new-onset tingling in the distal digits of both hands.

On examination, the weakness was bilateral, although more pronounced on the left. The lower extremities were affected to the greater degree, with a proximal-to-distal gradient. The upper extremities
were affected to a milder degree, with moderate triceps weakness and relatively mild hand weakness. Atrophy of the calf and thigh muscles was apparent. There was loss of hair from the legs, and the skin of the calf showed sudomotor changes. Notably, the patient had swollen lower extremities that appeared “woody.” Vibration perception was diminished below the level of the knee and in the fingers, and proprioception was severely reduced at the toes. Deep tendon reflexes were diminished in the upper extremities and absent in the lower extremities.

After a review of the patient’s PD prescription and trend in creatinine clearance, we attributed his worsening neuropathy to uremic neuropathy with accumulation of “middle molecules” as a contributory factor. The patient was therefore placed on continuous cycling PD to facilitate middle molecule clearance. Despite this new approach, with adequate clearances achieved, no significant improvement was observed.

Although the patient was uremic, with a history of diabetic polyneuropathy, the patient’s diabetic state would not be expected to produce this relatively acute and debilitating presentation. Aside from uremic neuropathy, major categories of disease in the differential diagnosis included toxins, vitamin deficiencies, endocrinopathy, inflammatory disorders, motor neuron disease, peripheral nerve disorders, neuromuscular junction disease, or myopathy. An extensive workup, including testing for folate, $B_{12}$, human immunodeficiency virus, thyrotropin, erythrocyte sedimentation rate, antinuclear antibody, serum or urine protein electrophoresis, and urine heavy metal, produced unremarkable results. With a metabolic process thus appearing to be remote, a process involving neurons, neuromuscular junctions, or muscle seemed more likely (Table I).

Because the patient presented with swollen lower extremities that appeared “woody,” skin biopsy was pursued in an attempt to rule out nephrogenic systemic fibrosis. The results were negative for that condition, but did reveal increased calcium deposits. A subsequent evaluation for paraneoplastic disorders was normal.

The relatively acute onset of weakness, exam findings of large-fiber neuropathy in the hands and legs, and worsened weakness after intense physical therapy raised concerns that an inflammatory immune-mediated demyelinating process such as Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP) was present. Electromyography had been performed 3 weeks before admission, and although it did not reveal findings consistent with demyelinating disease at that time, the study may have been performed too soon after the onset of weakness to show characteristic changes.

In consideration of the patient’s sensory changes, a defect of neuromuscular junction transmission was not under major consideration; however, such a defect cannot be excluded. Certain neuromuscular junction disorders such as Lambert–Eaton myasthenia syndrome may present with similar complaints, but the sensory symptoms were out of proportion to the norm. Additionally, inflammatory myopathy, which

<table>
<thead>
<tr>
<th>Condition</th>
<th>Weakness in extremities</th>
<th>Cranial nerve involvement</th>
<th>Reflexes</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Randomly</td>
<td>Yes</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Immune-mediated inflammatory polyneuropathy</td>
<td>Distal&gt;proximal</td>
<td>Rare</td>
<td>Decreased distally</td>
<td>Generally lost distally&gt;proximally</td>
</tr>
<tr>
<td>Lambert–Eaton syndrome</td>
<td>Lower&gt;upper, proximal&gt;distal</td>
<td>Rare</td>
<td>Decreased or absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Upper&gt;lower proximal&gt;distal</td>
<td>Yes</td>
<td>Normal or decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Proximal&gt;distal</td>
<td>Occasionally</td>
<td>Normal or decreased</td>
<td>Normal</td>
</tr>
</tbody>
</table>
often presents with proximal muscle weakness, was considered. In the absence of creatine kinase elevation and pain, that possibility became remote.

An extensive serologic and radiologic work-up, including magnetic resonance imaging of the brain and cervical spine, was unremarkable. No indication was found of any central neurologic process causing the chief symptoms. A lumbar puncture showed increased protein in the cerebrospinal fluid.

With albuminocytologic dissociation in the cerebrospinal fluid and progressive weakness and abnormal sensations spreading to the upper extremities, a diagnosis of demyelinating inflammatory polyneuropathy was again entertained. A new electromyelography study showed evolving acquired demyelination consistent with polyneuropathy from Guillain–Barré syndrome. The patient received intravenous immune globulin for 8 weeks and plasmapheresis for 5 days without improvement. He was then started on an 8-week prednisolone course and was switched to hemodialysis.

After 6 weeks, the patient still showed no spontaneous activity on electromyography, although in the weeks following, he began to regain function, beginning in the upper extremities. Conduction velocities on electrophysiologic testing likewise improved. In-center hemodialysis was switched to sustained low-efficiency dialysis, and the patient continued to improve. Within 2 months, all muscle weakness disappeared, except for mild residual foot drop. He now awaits renal transplantation.

Discussion
Acute and subacute demyelinating peripheral neuropathies have been reported in end-stage renal disease patients within a few weeks of CAPD start. They cause severe disabilities in the patients within 13 months (5–8).

Ropper (5) described 4 cases of subacute and acute neuropathy after the start of CAPD in ESRD patients. Electrophysiologic testing showed demyelinating features in these patients who had developed disabling generalized limb weakness, diminished deep tendon reflexes, and numbness within a few weeks. Spinal fluid analysis demonstrated elevated protein levels. The neuropathy improved after more frequent PD and kidney transplantation in 1 patient. In 2 patients with diabetes mellitus, the neuropathy progressed despite frequent PD. It seems that the combination of ESRD and diabetes predisposes patients to this type of neuropathy.

Toepfer et al. (6) reported 3 ESRD patients with acute inflammatory demyelinating neuropathy that developed a few weeks after the initiation of CAPD and that failed to improve with intensified PD, but that responded to immunomodulatory treatments. One patient responded to hemodialysis and improved completely after receiving a kidney allograft.

Lui et al. (8) described 2 patients with acute neuropathy that occurred 6 – 10 weeks after the initiation of PD. Demyelinating neuropathy improved in 1 patient after immunomodulatory treatment. The disease resolved in the 2nd patient after kidney transplantation.

Acute and subacute forms of nerve involvement—for example, plexopathy and radiculopathy—are common (9,10), but they affect the extremities asymmetrically. Uremic neuropathy has a symmetric pattern and affects upper and lower limbs at the same time.

Another plausible pathogenic cause of neuropathy in these patients includes inflammatory immune-mediated polyneuropathies such as Guillain–Barré syndrome or CIDP. Lymphocytic infiltration of peripheral nerves and spinal roots, with macrophage-mediated demyelination and variable degrees of axonal degeneration seem to play a common central role in both pathologic processes. Guillain–Barré syndrome develops acutely over a period of less than 1 month; CIDP presents as a more insidious process. Both can result in severe disability.

Although histopathology studies of CIDP have been complicated by a relapsing course of the inflammatory reaction and its predominance in proximal nerve segments, cellular and humoral immunity are likely both involved in its pathogenesis. Uncertainties remain regarding the provoking antigen or antigens, and the location of the initial T-cell activation. Breakdown of blood–nerve barrier by activated T cells and their cytokines is followed by a local intraneural immune response with recruitment of macrophages and secretion of toxic factors that cause damage to the myelin and axons. Activated T cells may also induce B cells to produce antibodies against nerve myelin antigens (11,12). High-dose intravenous immunoglobulin therapy and plasma exchange can aid in a more rapid remission (13,14).

When immunomodulatory treatments produce
a relative improvement, as in the present case, an inflammatory process and the coincidental occurrence of subacute inflammatory neuropathy of ESRD patients may play a role. Nonetheless, evidence argues against this explanation for subacute neuropathy in ESRD patients. First, immunomodulatory treatments are not always effective in these cases, and second, resolution of disease after kidney transplantation can provide a reason to reject the hypothesis. As with the patients in other studies (5–8), our patient developed polyneuropathy when he started PD. Peritoneal dialysis may induce an inflammatory response (15,16). Conversely, PD may remove an immune inhibitor or restore immune competency to a suppressed immune response related to renal insufficiency. Tumor necrosis factor α (TNFα) is central to several cellular immune responses that can induce demyelination in vitro, and transgenic models that overexpress TNFα reveal focal demyelination. Increased glucose concentrations and osmolality of peritoneal dialysate trigger increased TNFα production in peripheral blood mononuclear cells (6). However, a causal relationship between CAPD and inflammatory demyelinating neuropathy remains to be proven (6,7). Further studies are warranted to elucidate the pathogenesis of this disease (15–18).

Disclosures
The authors have no financial conflicts of interest to declare.

References

Corresponding author:
Rupesh Raina, MD, Rainbow Babies and Children’s Hospital, 11100 Euclid Avenue, Cleveland, Ohio 44106 U.S.A.
E-mail:
Rupesh.Raina@uhhospitals.org