Uremic Neuropathy

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AUTHOR AND EDITOR INFORMATION

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Author and Editor Disclosure

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Patient Education

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Background

Uremic neuropathy is a distal sensorimotor polyneuropathy caused by uremic toxins. The severity of neuropathy is correlated strongly with the severity of the renal insufficiency. Uremic neuropathy is considered a dying-back neuropathy or central-peripheral axonopathy associated with secondary demyelination. However, uremia and its treatment can also be associated with mononeuropathy at compression sites.

Charcot suspected the existence of uremic neuropathy in 1880, and Osler suspected it in 1892. Since the introduction of hemodialysis and renal transplantation in the early 1960s, uremic neuropathy has been investigated thoroughly. Asbury, Victor, and Adams described the clinical and pathologic features in detail in 1962.

In 1971, Dyck and colleagues established the current concept of uremic neuropathy based on their extensive nerve conduction studies in vivo and in vitro and on light and electron microscopy studies. Using quantitative histology, they demonstrated axonal shrinkage. Myelin sheaths appeared to be affected out of proportion to axons. The dysfunction of the neuron, rather than the Schwann cell, resulted in a decrease in the diameter of the axon, rearrangement of myelin, and finally, complete degeneration of the axon.

Nielsen published numerous papers on clinical and electrophysiologic studies from 1970-1974. He is a major contributor in uremic neuropathy. Bolton and Young summarized uremic neuropathy thoroughly in their 1990 book.

Pathophysiology

The mechanism of uremic neuropathy remains unclear. Fraser and Arieff postulated that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for maintenance of energy production. Although all neuronal perikarya would be affected similarly by the toxic assault, the long axons would be the first to degenerate since the longer the axon, the greater the metabolic load that the perikaryon would bear. In toxic neuropathy, dying back of axons is more severe in the distal aspect of the neuron and may result from a metabolic failure of the perikaryon. Energy deprivation within the axon may be especially critical at nodes of Ranvier, since these nodes demand more energy for impulse conduction and axonal transport.

Nielsen theorized that peripheral nerve dysfunction was related to an interference with the nerve axon membrane function and inhibition of Na^+/K^+-activated ATPase by toxic factors in uremic serum. Bolton postulated that membrane dysfunction was occurring at the perineurium, which functioned as a diffusion barrier between interstitial fluid and nerve, or within the endoneurium, which acted as a barrier between blood and nerve. As a result, uremic toxins may enter the endoneural space at either site and cause direct nerve damage and water and electrolyte shifts with expansion or retraction of the space.

Frequency

United States

According to Bolton and Young, the incidence of clinical uremic neuropathy varies from 10-83% in patients with renal failure.

International

According to Nielsen, of 109 patients in Denmark with chronic renal failure, 77% reported clinical symptoms, and 51% had clinical signs of a neuropathy.

Mortality/Morbidity

Hemodialysis has reduced the incidence of severe uremic neuropathy and the rate of mortality of renal failure. Although deaths associated with complications related to quadriplegia and respiratory failure have been reported, the death rate from uremic neuropathy is not known.

Race

No reported study has examined the role of race in uremic neuropathy.

Sex

Uremic neuropathy is more common in males than in females. Nielsen reported the female-to-male ratio as 49:60 in his 109 patients.

Age

Uremic polyneuropathy may occur at any age once the degree of renal failure is sufficient.

History

- Typical uremic neuropathy symptoms are insidious in onset and consist of a tingling and prickling sensation in the lower extremities.
  - Paresthesia is the most common and usually the earliest symptom.
  - Increased pain sensation is a prominent symptom.
  - Weakness of lower extremities and atrophy follow the sensory symptoms. As disease progresses, symptoms move proximally and involve the upper extremities.
  - Muscle cramps and restless legs syndrome were reported by 67% of uremic patients. These symptoms also can be seen in uremic patients without neuropathy.
  - Patients report that crawling, prickling, and itching sensations in their lower extremities are relieved partially by movement of the affected limb.
- Autonomic dysfunction was revealed in 45-59% of uremic patients by autonomic nerve tests. Patients may complain of dizziness. It usually is associated with postural hypotension.
- A Guillain-Barré type of presentation is rare, but a rapidly progressive course with respiratory failure has been reported. Generalized limb weakness develops over days or weeks with imbalance, numbness, and diminished reflexes.
- Mononeuropathies in the form of compressive neuropathy can occur in the median nerve at the wrist, in the ulnar nerve at the elbow, or in the peroneal nerve at the fibular head.

- Already partially dysfunctional peripheral nerves may be more susceptible to local compression.
- Connective tissues and tendons are found to have amyloid deposits surrounding the carpal tunnel.
- Multiple distal mononeuropathies present in an extremity following the construction of arteriovenous fistulas because of distal ischemia.

Physical

- Impaired vibratory perception and absent deep tendon reflexes are the most common clinical signs, noted in 93% of patients. Sixteen percent had sensory loss to pinprick in a glove and stocking distribution.
- Paradoxical heat sensation was found in the feet of 42% of patients with chronic renal failure, as compared to less than 10% of healthy controls.
- Muscular weakness and wasting were observed in 14%.
- Cranial nerve involvement is rare; transient nystagmus, miosis, impairment of extraocular movement, and facial asymmetry may be found rarely on physical examination.
- Focal weakness, sensory loss, and positive Tinel sign at compression sites can be observed in the median, ulnar, or peroneal nerve distribution if compressive mononeuropathy is present.
- Abnormal Valsalva maneuver and orthostatic hypotension may be noted in patients with autonomic neuropathy.

Causes

The nature of the toxic substances in uremia is unknown. Myoinositol, a precursor of phosphoinositide, is metabolized rapidly in neural membranes. It is elevated abnormally in chronic renal failure, poorly eliminated by hemodialysis, but excreted by the renal cortex of successfully transplanted kidneys. Substances of moderate molecular weight (ie, 300-2000 Daltons) can be toxic agents in uremia. Advanced glycosylated end products and parathyroid hormone generally are recognized as major uremic toxins. Possible uremic toxins are listed here but remain unproven.

- Small water-soluble compounds
  - Guanidines
  - Asymmetric dimethylarginine
  - Creatinine
  - Purines
  - Oxalate
  - Phosphorus
  - Urea
- Middle, large molecules
  - Advanced glycosylated end products
  - Parathyroid hormone
  - Oxidation products

- Peptides (beta-endorphin, methionine-enkephalin, beta-lipotropin, granulocyte inhibiting proteins I and II, degranulation-inhibiting protein, adrenomedullin)
- Beta 2-microglobulin
- Complement factor D

- Protein-bound compounds
  - Indoles
  - 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid
  - Hippuric acid
  - Homocysteine
  - Indoxyl sulfate
  - P-cresol
  - Polyamines

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DIFFERENTIALS

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WORKUP

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Lab Studies

- Uremia is only one of the possible causes of neuropathy in chronic renal failure. Other metabolic disorders, neurotoxins, or inflammatory disorders may occur in association with chronic renal failure. Other causes of neuropathies, including diabetes, vitamin deficiencies, thyroid dysfunction, inflammatory disorders, and toxins

should be excluded by blood tests for hemoglobin A1C, B-12, folate, thyroid-stimulating hormone, erythrocyte sedimentation rate, antinuclear antigen, serum protein electrophoresis/immunofixation electrophoresis, and urine heavy metal screen.

- Patients with uremic neuropathy have creatinine clearance less than 10 mL/min.
- Cerebrospinal fluid protein often is elevated; cell count and glucose are normal.

Imaging Studies

- Imaging is not useful in making the diagnosis of uremic neuropathy.

Other Tests

- Nerve conduction study is a sensitive test for diagnosis of neuropathy in patients with uremia. Both sensory and motor nerve conduction velocities are reduced.
    - Prolonged distal latencies are due to involvement of distal nerve segments; reduced compound action potential amplitudes are due mainly to reduced densities of large myelinated motor and sensory fibers.
    - In compressive mononeuropathy, slow conduction velocity is found across the compression site.
    - A Guillain-Barré type of neuropathy in chronic renal failure has moderate-to-severe conduction slowing; conduction block may occur.
    - Prolonged F wave latencies of tibial and peroneal nerves and prolonged H reflexes are the profound and reproducible abnormalities in patients with chronic renal failure.
- Bolton found that needle electromyography revealed minimal or absent fibrillation or positive sharp wave. Only more advanced cases of uremic neuropathy lead to predominantly distal muscle denervation.
- Autonomic nerve tests reveal dysautonomia by reduced R-R interval variation and delayed or absent sympathetic skin response. Esophageal manometry has been used to study subclinical manifestations of autonomic neuropathy in uremia. Abnormal motility in the lower two thirds of the esophageal body was reported in 11 of 16 patients.

Histologic Findings

In uremic neuropathy, the pathologic features are striking axonal degeneration in the most distal nerve trunks with secondary segmental demyelination (see Images 1-2). Dyck et al found that the number of myelinated fibers was approximately one half of normal at the mid calf level and only one third of normal at ankle level in their patients. In transverse electron microscope sections, most of the myelinated fibers of the uremic nerve had a normal appearance except for irregularities of the myelin sheath, such as splitting of the myelin lamellae and separation of axolemma from compact myelin.

Muscle biopsy revealed fiber type grouping from chronic denervation and reinnervation (see Image 3). Muscle was denervated severely in Guillain-Barré–type neuropathy. In advanced neuropathy, necrosis of myofibers, streaming of Z line, which anchors actin, and aggregation of glycogen also were found by electron microscope.

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TREATMENT

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Medical Care

Available therapies for uremic neuropathy, including dialysis and vitamin supplementation, are not satisfactory. Erythropoietin has showed improvement in motor nerve conduction velocity in predialysis patients. Renal transplantation in early stage uremic neuropathy has achieved a favorable outcome.

- Different dialyzer membranes have been investigated for treatment of uremic neuropathy.
  - Djukanovic's group found that hemodialysis using membranes with high permeability to molecules of middle molecular weight (ie, 300-2000 Daltons) prevented excessive accumulation of these molecules in plasma and significantly improved neuropathy in patients with high levels of mid-weight molecules. High-flux membranes can remove mid-weight molecules.
  - Bolton et al reported improvement of polyneuropathy with high-flux hemodialysis. They indicated that modern methods of managing renal failure have decreased the incidence of uremic neuropathy.
  - Chronic hemodialysis may stabilize neuropathy in most patients. However, the course of neuropathy cannot be improved with certainty simply by manipulating the hemodialysis schedule. Paresthesia may improve rapidly once hemodialysis is started, but other symptoms persist.
- In the past, peritoneal dialysis was associated with a lower incidence of uremic neuropathy than hemodialysis because peritoneal dialysis often was characterized by better removal of mid-weight molecules. No significant differences have been demonstrated in the effects of peritoneal dialysis and current high-flux membrane hemodialysis on peripheral nerve function.
- Biotin is a low molecular weight coenzyme loosely bound to serum proteins, which likely would be lost during dialysis. Yatzidis et al recommended a 10 mg dose of biotin 3 times a day. In a small group study, they found that all 9 patients experienced improved mental function, sensory symptoms, and walking after 3 months of treatment. In addition, they found that biotin counteracts the inhibitory effect of uremic plasma on microtubule formation in vitro.

Surgical Care

- Numerous case reports exist on the beneficial effect of renal transplantation. Nielsen reported that all patients who underwent successful transplantation showed definite improvement. Paresthesia disappeared within 1-3 months in mild uremic neuropathy. The remission after transplantation had 2 phases, with an early rapid phase and a late slow phase in moderate-to-severe neuropathy. Rapid improvement in nerve conduction velocity was noted shortly after successful transplantation. Renal transplantation reverses sympathetic and parasympathetic autonomic dysfunction in as little as 3-6 months after the procedure.
- Patients with diabetes do not show improvement with their neuropathy, which suggests that the underlying cause of the neuropathy is mainly the diabetes mellitus and not the renal insufficiency.

Consultations

- Nephrologist for hemodialysis
- Transplant team for renal transplantation

Diet

A low-protein diet is recommended; this requires periodic assessment of dietary compliance and nutritional status.

Activity

If the patient has significant weakness, devices such as ankle/foot orthosis, cane, walker, or wheelchair may help mobility.

Paresthesia symptoms can be treated like other neurogenic pain, with anticonvulsants or tricyclic antidepressants (TCAs). See medications listed in Traumatic Peripheral Nerve Lesions. Obviously, the dosing must be adjusted to the renal function or timing of dialysis.

Drug Category: *Tricyclic antidepressants*

This complex group of drugs has central and peripheral anticholinergic effects, sedative effects, and central effects on pain transmission. TCAs block active reuptake of norepinephrine and serotonin. Nortriptyline is a TCA but has less anticholinergic effects in neurogenic pain.

Drug Name	Nortriptyline (Pamelor, Aventyl HCl)
Description	Has demonstrated effectiveness in treatment of chronic pain; may increase synaptic concentration of serotonin and/or norepinephrine in CNS by inhibiting presynaptic reuptake. Pharmacodynamic effects, such as desensitization of adenyl cyclase and down-regulation of beta-adrenergic receptors and serotonin receptors, also appear to be involved in mechanisms of action.
Adult Dose	25 mg PO qhs, not to exceed 150 mg qhs
Pediatric Dose	<25 kg: Not established 25-35 kg: 10-20 mg/d PO 35-54 kg: 25-35 mg/d PO >54 kg: Administer as in adults
Contraindications	Documented hypersensitivity; narrow-angle glaucoma; MAOIs within 14 d
Interactions	Cimetidine may increase levels; may increase PT in patients whose coagulation parameters have been stabilized with warfarin
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution in cardiac conduction disturbances or history of hyperthyroidism or renal or hepatic impairment; because of pronounced effects in cardiovascular system, best to avoid in elderly, or check ECG before using and at doses above 75

	mg/d

Drug Category: *Anticonvulsants*

These agents are used to manage paresthesia and have central effects on pain modulation. Although carbamazepine and valproic acid are useful in controlling neurogenic pain, gabapentin currently is the most frequently used anticonvulsant.

Drug Name	Gabapentin (Neurontin)
Description	Has properties common to other anticonvulsants and has antineuralgic effects; exact mechanism of action not known; structurally related to GABA but does not interact with GABA receptors.
Adult Dose	Hemodialysis: 300 mg PO following each hemodialysis CrCl <15 mL/min: 300 mg PO qod CrCl 15-30 mL/min: 300 mg PO qd CrCl 30-60 mL/min: 300 mg PO bid CrCl >60 mL/min: 400 mg PO tid
Pediatric Dose	<12 years: Not established >12 years: Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Antacids may reduce bioavailability significantly (administer at least 2 h following antacids); may increase norethindrone levels significantly
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Overdose in severe renal disease

Drug Category: *Local anesthetics*

Lidocaine stabilizes neuronal membranes, possibly by inhibiting ionic fluxes required for initiation and conduction of impulses.

Drug Name	Lidocaine patch 5% (DermaFlex)
Description	Has relieved intensity of pain in postherpetic neuralgia.
Adult Dose	Apply to intact skin to cover most painful area for 12 h within each 24-h period, not more than 3 patches at any time
Pediatric Dose	Administer as in adults; patches may be cut into smaller sizes
Contraindications	Documented hypersensitivity; avoid in Adams-Stokes syndrome and Wolff-Parkinson-White syndrome
Interactions	None reported
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	For external use only; do not use in eyes

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FOLLOW-UP

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Prognosis

- Despite regular dialysis treatment, uremic neuropathy has been shown to progress, especially after 10 years and in the elderly. Renal transplantation can result in complete recovery from uremic neuropathy if the duration

between the onset of neuropathy and transplantation is short.

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MISCELLANEOUS

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Medical/Legal Pitfalls

- Failure to document neuropathy correctly
- Failure to exclude other cause of polyneuropathy in chronic renal failure
- Failure to adjust the dose of medication with renal function
- Failure to prevent falls in patients with gait difficulty

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MULTIMEDIA

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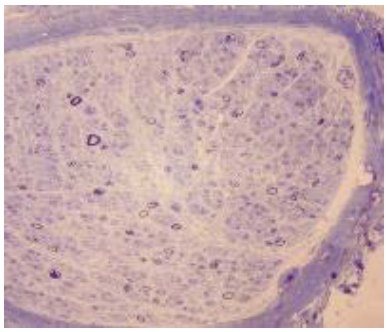
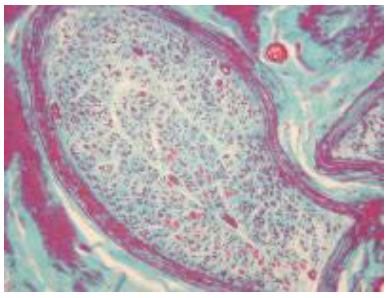
Media file 1: **Semithin transverse section of biopsied sural nerve in uremic neuropathy. The nerve shows severe axonal loss of large and small fibers. Toluidine blue stain, 200X. Image courtesy of Ling Xu, Consultants In Neurology, Kansas City, MO 64108. Used with permission 2001.**



View Full Size Image

Media type: Photo

Media file 2: **Modified trichrome-stained sural nerve in uremic neuropathy. The same nerve exhibited marked loss of myelinated fibers. 200X. Image courtesy of Ling Xu, Consultants In Neurology, Kansas City, MO 64108. Used with permission 2001.**



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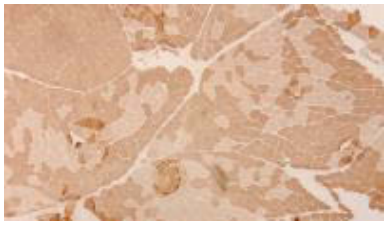
Media type: Photo

Media file 3: **Muscle biopsy in uremic neuropathy with ATPase stain (pH 9.4). The normal muscle mosaic pattern was replaced by fiber type grouping, which suggested chronic denervation and reinnervation. 100X. Image courtesy of Ling Xu, Consultants In Neurology, Kansas City, MO 64108. Used with permission 2001.**



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Uremic Neuropathy excerpt

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