

# Uremic Encephalopathy

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## Introduction

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### Background

Uremia describes the final stage of progressive renal insufficiency and the resultant multiorgan failure. It results from accumulating metabolites of proteins and amino acids and concomitant failure of renal catabolic, metabolic, and endocrinologic processes. No single metabolite has been identified as the sole cause of uremia. Uremic encephalopathy (UE) is one of many manifestations of renal failure (RF).

### Pathophysiology

The exact cause of UE is unknown. Accumulating metabolites of proteins and amino acids affect the entire neuraxis. Several organic substances accumulate, including urea, guanidine compounds, uric acid, hippuric acid, various amino acids, polypeptides, polyamines, phenols and conjugates of phenols, phenolic and indolic acids, acetoin, glucuronic acid, carnitine, myoinositol, sulfates, phosphates, and middle molecules. Levels of some of the guanidine compounds, including guanidinosuccinic acid, methylguanidine, guanidine, and creatinine, increase in patients with uremia who are or who are not receiving dialysis. Endogenous guanidino compounds have been identified to be neurotoxic.<sup>1</sup>

Patients with terminal RF have >100-fold increases in levels of guanidinosuccinic acid and guanidine, 20-fold increases in levels of methylguanidine, and 5-fold increase in levels of creatinine in various regions of the brain. Disturbance in the kynurenic pathway, by which tryptophan is converted to neuroactive kynurenines, has also been implicated. Levels of 2 kynurenines, 3-hydroxykynurenine and kynurenine, are elevated in rats with chronic renal insufficiency; these changes lead to alterations in cellular metabolism, cellular damage, and eventual cell death. Kynurenine can induce convulsions.

Abnormalities that may be associated with UE include acidosis, hyponatremia, hyperkalemia, hypocalcemia, hypermagnesemia, overhydration, and dehydration.

No single abnormality is precisely correlated with the clinical features of UE. Increased levels of glycine, organic acids (from phenylalanine), and free tryptophan and decreased levels of gamma-aminobutyric acid (GABA) in the CSF may be responsible for early phases of the disorder. In rats with RF, brain levels of creatine phosphate, adenosine triphosphate (ATP), and glucose are increased, whereas levels of adenosine monophosphate (AMP), adenosine diphosphate (ADP), and lactate are decreased. This finding suggests that the uremic brain uses less ATP and produces less ADP, AMP, and lactate than healthy brains, consistent with a generalized decrease in metabolic function.

Transketolase, found mainly in myelinated neurons, is a thiamine-dependent enzyme of the pentose phosphate pathway; it maintains axon-cylinder myelin sheaths. Plasma, CSF, and low-molecular-weight (<500 Da) dialysate fractions from patients with uremia substantially inhibit this enzyme. Erythrocyte transketolase activity is lower in nondialyzed patients than in dialyzed patients. Guanidinosuccinic acid can inhibit transketolase.

Synaptosome studies of uremic rats have shown altered function of the sodium ATP and other metabolic pumps. Methylguanidine can induce a condition similar to UE that includes seizures and uremic twitch-convulsive syndrome. Guanidinosuccinic acid can also inhibit excitatory synaptic

transmission in the CA1 region of the rat hippocampus, an effect that may contribute to cognitive symptoms in UE.

Guanidinosuccinic acid, methylguanidine, guanidine, and creatinine inhibited responses to GABA and glycine (inhibitory amino acids) in cultured mouse neurons. Guanidino compounds (GCs) inhibit nitric oxide synthase (NOS) modulators in vivo and in vitro. Accumulation of asymmetric dimethylarginine (ADMA), a NOS inhibitor, has been observed in patients with uremia; this accumulation induces hypertension and possibly increases ischemic vulnerability to the uremic brain.

UE involves many hormones, levels of several of which are elevated. Such hormones include parathyroid hormone (PTH), insulin, growth hormone, glucagon, thyrotropin, prolactin, luteinizing hormone, and gastrin. In healthy dogs, high levels of PTH produce CNS changes like those seen in uremia. PTH is thought to promote the entry of calcium into neurons, which leads to the changes observed.

A combination of factors, including increased calcium and decreased GABA and glycine activity, leads to a distorted balance of excitatory and inhibitory effects that contributes to systemic changes associated with UE.

## **Frequency**

### **United States**

The prevalence of UE is difficult to determine. UE may manifest in any patient with end-stage renal disease (ESRD), and directly depends on the number of such patients. In the 1990s, more than 165,000 people were treated for ESRD, compared with 158,000 a decade earlier. In the 1970s, the number was 40,000. As the number of patients with ESRD increased, presumably so did the number of cases of UE. On a yearly basis, 1.3 per 10,000 patients develop ESRD.

### **International**

The worldwide prevalence is unknown. In Western Europe and in Japan, ie, countries with healthcare systems similar to that of the United States, statistics parallel to those of United States are expected. In general, the care of patients with UE depends on costly intensive care and dialysis that is not available in developing nations.

## **Mortality/Morbidity**

RF is fatal if untreated.

- UE reflects worsening renal function, with symptoms worsening as RF progresses. If untreated, UE progresses to coma and death.
- Patients need aggressive care to prevent complications and maintain homeostasis. They depend on intensive care and dialysis. In the United States, more than 200,000 patients are currently receiving hemodialysis.

## **Race**

RF is more common in African Americans than in other races. Of all patients in the Medicare ESRD treatment program in 1990, 32% were African American, though African Americans account for only 12% of the US population. The overall incidence of ESRD is 4 times greater in African Americans than in whites.

## Sex

Incidences are equal in men and woman.

## Age

People of all ages can be affected, but the fastest growing group with ESRD is the elderly, ie, persons older than 65 years. RF has a proportionally increased prevalence in this group compared with any other age group.

## Clinical

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### History

- Uremic encephalopathy (UE) is a consequence of renal failure (RF).
- Symptoms begin insidiously and are often noticed not by the patients but by their family members or caregivers.
- In many cases, impairment of the nervous system provides the first indication of metabolic derangements.
- Symptoms may progress slowly or rapidly.
- Changes in sensorium include loss of memory, impaired concentration, depression, delusions, lethargy, irritability, fatigue, insomnia, psychosis, stupor, catatonia, and coma.
- Patients may complain of slurred speech, pruritus, muscle twitches, or restless legs.

### Physical

Physical findings are variable and depend on the severity of the encephalopathy. Neurologic findings range from normal to a comatose state. Cases of Wernicke syndrome associated with UE have been described in the literature, and Wernicke syndrome has been observed in patients with UE, dialysis dementia, or dialysis disequilibrium syndrome.

- Findings include the following:
  - Myoclonic jerks, twitches, or fasciculations (ie, uremic twitch-convulsive syndrome postulated by Adams et al in 1997)
  - Asterixis
  - Dysarthria
  - Agitation
  - Tetany
  - Seizures, usually generalized tonic-clonic
  - Confusion, stupor, and other alterations in mental status
  - Coma
- Some patients undergoing long-term dialysis acquire dialysis encephalopathy (or dialysis dementia), which is a subacute, progressive, and often fatal disease.<sup>2</sup> Aluminum toxicity either from aluminum phosphate salts or from aluminum in the dialysate were linked to the pathogenesis of dialysis dementia. Starting in the early and mid 1980s, aluminum was actively removed from the dialysate with a large reduction in the incidence of dialysis dementia.
  - Dialysis encephalopathy is believed to be part of a multisystem disease that includes encephalopathy, osteomalacic bone disease, proximal myopathy, and anemia.
  - Symptoms include dysarthria, apraxia, personality changes, psychosis, myoclonus, seizures and, finally, dementia.
  - In most cases, the condition progresses to death in 6 months.

- Dialysis disequilibrium syndrome occurs in patients receiving hemodialysis.
  - Symptoms include headache, nausea, emesis, blurred vision, muscular twitching, disorientation, delirium, hypertension, tremors, and seizures.
  - The condition tends to be self-limited and subsides over several hours.
  - Dialysis disequilibrium syndrome is attributed to a reverse urea effect. Urea is cleared more slowly from the brain than from the blood, an effect that causes an osmotic gradient leading to the net flow of water into the brain and to transient cerebral edema.
- Complications of renal transplantation can lead to UE. This occurrence has become more common as more patients are receiving renal transplants.
  - This condition is characterized by edema of the white matter.
  - Patients are at risk for primary brain lymphoma and opportunistic infections because of long-term immunosuppression.
- Rejection encephalopathy has been observed in patients undergoing transplantation. They have systemic features of acute graft rejection, more than 80% of whom have symptoms in the first 3 months after transplantation. Overall prognosis is good, with rapid recovery after treatment of the rejection episode. The presumed pathology is cytokine production secondary to the rejection process.
- Uremic polyneuropathy is the most common neurologic complication of RF.

## **Causes**

- The exact cause of UE is unknown.
- Accumulation of metabolites and, perhaps, imbalance in excitatory and inhibitory neurotransmitters are possible etiologies.
- PTH and abnormal calcium control have also been identified as possible important contributing factors.

## **Differential Diagnoses**

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Alzheimer Disease

Alzheimer Disease in Individuals With Down Syndrome

Aphasia

Apraxia and Related Syndromes

Complex Partial Seizures

Dementia in Motor Neuron Disease

Dementia With Lewy Bodies

EEG in Dementia and Encephalopathy

EEG in Status Epilepticus

Frontal and Temporal Lobe Dementia

Generalized EEG Waveform Abnormalities

Huntington Disease

Intracranial Hemorrhage

Normal Pressure Hydrocephalus

Pick Disease

Status Epilepticus

Subdural Hematoma

Tonic-Clonic Seizures

Transient Global Amnesia

## **Other Problems to Be Considered**

Dementia

Complex partial status epilepticus

Dementia in Huntington disease

Dementia in Parkinson disease

Dementia in progressive supranuclear palsy

Epileptic encephalopathies

EEG in coma

Tonic seizures

Vascular dementia

## Workup

### Laboratory Studies

- Blood tests reveal electrolyte abnormalities and abnormal renal function. PTH and calcium levels are high.
- Results of routine CSF studies tend to be normal.

### Imaging Studies

- Brain imaging is of limited value.
- CT and MRI studies typically show cerebral atrophy and secondary ventricular dilatation.
  - These studies are valuable for excluding intracranial hemorrhage and subdural hematoma when patients have an acute change in mental status.
  - Case reports have documented increased signal intensity in the cortical and subcortical areas of the parietal and occipital lobes. These findings are thought to reflect local edema that resolved after dialysis treatments. Improvement on MRI has been correlated with improved serum creatinine and BUN levels.

### Other Tests

- EEG (especially serial EEG) is useful in assessing patients and in monitoring their progress.
  - The EEG is generally abnormal, showing generalized slowing that becomes more severe as the condition worsens.
  - In acute uremia, EEG is characterized by irregular low voltage with slowing of the posterior dominant alpha rhythm and occasional theta bursts. Characteristic findings are prolonged bursts of bilateral, synchronous slow and sharp waves or spike and waves.
  - Bilateral spike discharges may be associated with myoclonic jerks. Generalized or partial seizures may be observed.
  - After dialysis begins, EEG may worsen for up to 6 months before slowly normalizing as renal function improves. Dialysis itself tends not to affect the EEG.
  - In chronic uremia, the EEG stabilizes during long-term dialysis treatment. When changes occur during periods of deterioration corresponding to fluctuations in blood urea levels, the findings include diffuse delta and theta activity, generalized spike-wave activity, and heightened sensitivity to photic stimulation.
  - Quantitative EEG using real-time brain mapping computer-aided topographical electroencephalometry (CATEEM) technology has been shown to be useful in monitoring mental impairment and may serve as a control for monitoring therapeutic intervention.<sup>3</sup>
  - Sleep EEG may show long bursts of high voltage (12-13 waves per second with enhanced vertex sharp activity in drowsiness), lack of spindles (14/s) in stage 2 sleep, and prolonged high-voltage, slow bursts with awakening.
- Evoked-potential studies are of limited value, revealing only nonspecific changes or normal patterns.
  - Visual evoked potentials (VEPs): Studies may reveal no change before or after dialysis, or P100 may be absent or delayed. This abnormality is attributed to a circulating renal factor, which has a toxic effect on the papillomacular bundle or on demyelination. No relationship with BUN is known.

- Brainstem auditory evoked potentials (BAEPs): Some studies of patients with UE show no abnormalities in BAEPs, whereas other studies of small numbers of patients revealed abnormalities, especially in the III-IV latencies. The abnormalities reversed with dialysis in some patients and did not reverse in others. Changes in BAEP were attributed to either toxic substances or demyelination. Other studies measuring the P300 latency and amplitude have shown improvement in patients with UE who were specifically treated for anemia. The improvement in the electrophysiological parameters accompanied improvement in cognitive function, suggesting that measurements of P300 may serve as an measurable marker for cognitive function.<sup>4</sup>
- Somatosensory evoked potentials (SEPs): Studies may show delayed sensory conduction in the peripheral nerve in patients with no symptoms of neuropathy. This was observed in the upper limb with electrically and mechanically evoked SEPs.
  - In 1 study, electrical stimulation of the ulnar nerve at the wrist showed abnormal conduction between the brachial plexus and the spinal cord and lower medulla. Other studies revealed abnormal conduction between the lower medulla and the thalamus and cortex.
  - Mechanical stimulation of the fingers showed abnormalities in the spinal cord to thalamus-cortex segment, whereas electrical stimulation did not.
  - Some studies revealed central delays and increased amplitudes in patients with chronic uremia, whereas others showed normal central conduction times in patients undergoing hemodialysis.
  - Abnormalities were observed in both upper- and lower-limb SEPs in patients with chronic renal failure.

## Procedures

- Hemodialysis
- Peritoneal dialysis
- Renal transplantation
- Neurosurgical intervention for intracranial hemorrhage or subdural hematoma

## Histologic Findings

Brain histologic findings in UE include meningeal fibrosis, glial changes, edema, vascular degeneration, focal and diffuse neuronal degeneration, and focal demyelination. Small infarcts are also seen and are probably due to hypertension or focal necrosis. Cerebellar acute granule cell necrosis is observed.

Patients with dialysis dementia have spongiform changes in the outer 3 cortical layers, with elevated aluminum levels in the cerebral cortex. Other changes include neuronal loss, accumulation of lipofuscin pigment, and neurofibrillary degeneration in the motor cortex and in the red, dentate, and olivary nuclei.

## Treatment

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### Medical Care

The medical care of uremic encephalopathy (UE) includes correcting the metabolic disturbance, which usually requires dialysis (hemodialysis or peritoneal dialysis) or renal transplantation. Symptoms improve as renal function improves.

- Seizures may be treated with anticonvulsants.
  - These drugs should be administered at lower-than-usual doses to accommodate the low albumin levels observed in chronic renal failure (RF). These low albumin levels can lead to higher levels of unbound anticonvulsant.
  - The unbound drug is the therapeutically active fraction.
- Emergency treatment of subdural hematoma or intracranial hemorrhage is addressed in other articles.
- Cerebrovascular disease is a significant cause of morbidity and mortality in patients with chronic renal failure. The main causes of ischemic stroke are atherosclerosis and thromboembolic or intradialytic hypotension. Patients with chronic renal failure have a high prevalence of hyperhomocysteinemia, an independent risk factor for atherosclerosis. Most hemodialysis and renal transplant patients are partially refractory to treatment intended to reduce homocysteine levels. Dialysis itself appears to promote the development of arterial disease, perhaps due to oxidative stress. The progression of atherosclerosis is further speculated to be influenced by the use of immunosuppressive agents. Thromboembolic ischemic cerebrovascular accidents may result from cardiac disease (dilated cardiomyopathy, arrhythmia) or artery-to-artery embolism due to severe atherosclerosis.
- Ultrafiltration-related arterial hypotension is a common complication in hemodialysis, especially in older patients with anemia. Severe arterial hypotension can cause cerebral hypoperfusion leading to ischemic stroke in the boundary zones between vascular territories. Treatment consists of fluid repletion.
- Caution must be exercised in administering drugs whose metabolism is affected by impaired renal function because their levels can rise to toxic levels.
- Hypertension and diabetes mellitus can both exacerbate the encephalopathic symptoms. Hypertensive encephalopathy is thought to be caused by vasogenic edema due to impaired cerebrovascular autoregulation, endothelial injury, and elevated plasma concentrations of natriuretic peptides. Hypertensive encephalopathy is thought to occur in 5% of uremic patients. Recombinant human erythropoietin for correction of renal anemia can cause hypertension in up to 35% of patients. Patients with diabetes tend to do worse.
- Infections need to be treated appropriately.

## **Surgical Care**

The role of surgery in managing UE is limited to cases involving renal transplantation, neurosurgical care for subdural hematoma or intracranial hemorrhage, and vascular access.

## **Consultations**

- Specialist in critical care medicine
- Nephrologist
- Vascular surgeon
- Neurosurgeon
- Infectious disease specialist: Bacterial meningitis remains a high cause of mortality in hemodialyzed patients, often because of delay in treatment.<sup>5</sup>

## **Diet**

Patients must maintain a low-salt, low-protein (ie, renal) diet.

## **Activity**

In general, patients with UE are ill, and in the acute phase, their activity is limited to bed rest.

## **Follow-up**

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### **Further Inpatient Care**

- Patients need close follow-up in the acute stage of uremic encephalopathy.
- After the underlying problem is treated properly, the symptoms should resolve.
- levels of anticonvulsant drugs must be closely monitored to prevent toxicity.
- In cases of intracranial hemorrhage, serial head neuroimaging may be necessary.

### **Further Outpatient Care**

- Hemodialysis is needed on a regular basis.

### **Transfer**

- Transfer to a facility with staff and equipment for further evaluation and care may be necessary.
- As always, trained personnel with appropriate monitoring should perform the transfer.

### **Complications**

If untreated, uremic encephalopathy leads to coma and death.

### **Prognosis**

The prognosis is generally favorable if treatment is successful.

### **Patient Education**

To ensure that treatment is initiated early, instruct patients and their family members and caregivers about the need for prompt medical evaluation when mental status changes occur.

## **Miscellaneous**

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### **Medicolegal Pitfalls**

- Accidental falls may occur and can lead to litigation.
  - The slow onset of symptoms may lead to complications that might be grounds for litigation.
  - Failure to adequately monitor drug levels may lead to toxicity and further complications.
  - Failure to diagnose RF is another potential pitfall.
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## Multimedia

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Media file 1: EEG in a 56-year-old man with uremic encephalopathy. He became increasingly lethargic, requiring intubation. EEG shows absence of a posterior dominant alpha rhythm and diffuse bilateral slowing with mixed theta- and delta-frequency signal. A single sharp wave is present in the left occipital region, phase reversing at O1. From top to bottom: Fp1-F7, F7-T3, T3-T5, T5-O1, O1-O2, O2-T6, T6-T4, T4-F8, F8-Fp2, Fp2-Fp1, F3-C3, C3-P3, P3-O1, F4-C4, C4-P4, P4-O2, Fz-Cz, and ECG.



Media file 2: EEG in a 56-year-old man with uremic encephalopathy (same patient as in Image 1). From top to bottom: Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2, Fp1-F3, F3-C3, C3-P3, P3=O1, Fp2-F4, F4-C4, C4-P4, P4-O2, Fz-Cz, ECG.

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