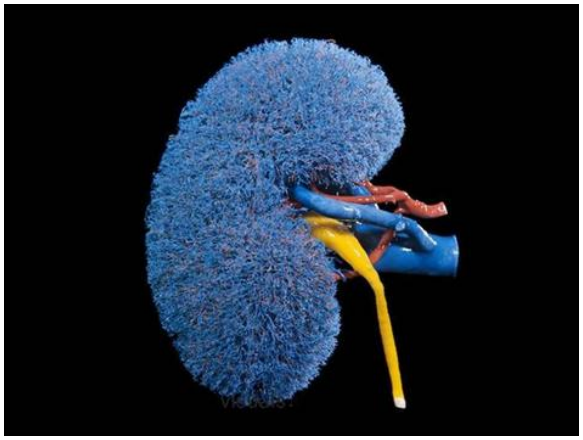
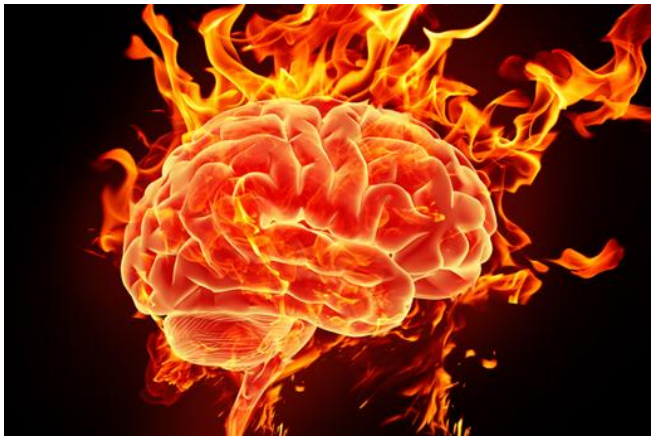
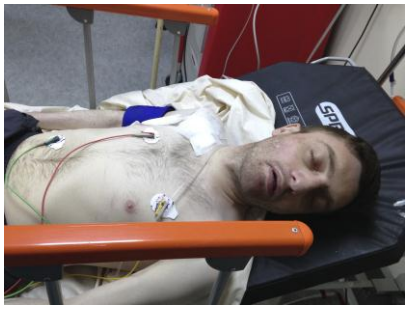




UREMIC ENCEPHALOPATHY (UE)

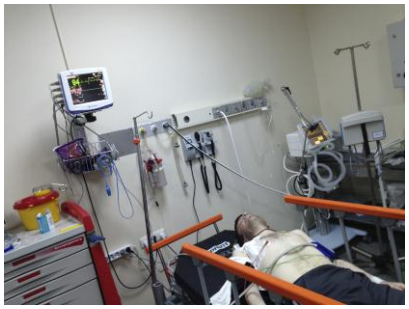

MUCAHIT EMET

ATATURK UNIVERSITY MEDICAL FACULTY, ERZURUM

DEPARTMENT OF EMERGENCY



Saturday, May, 2014



- 33 yo M, complaint: nause, vomiting and malaise
- History:

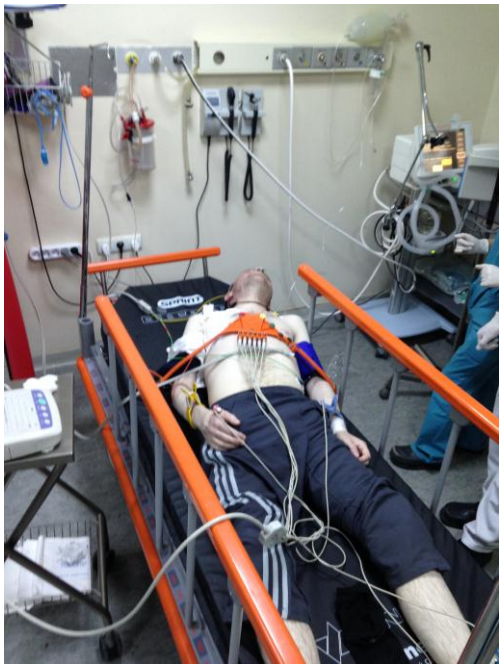
1. Type 1 DM for 14 yrs,
2. chronic pancreatitis,
3. HT (1 yr),
4. ESRD on dialysis treatment for 1 yr

   3d/w → 2d/w

- Vitals: BP: 210/110 mmHg; HR: 107/min; RR: 19/min; no fever
- Neu Ex → horizontal nistagmus + flapping tremor + babinski
- Generalized tonic clonic convulsion
- Postictal blindness

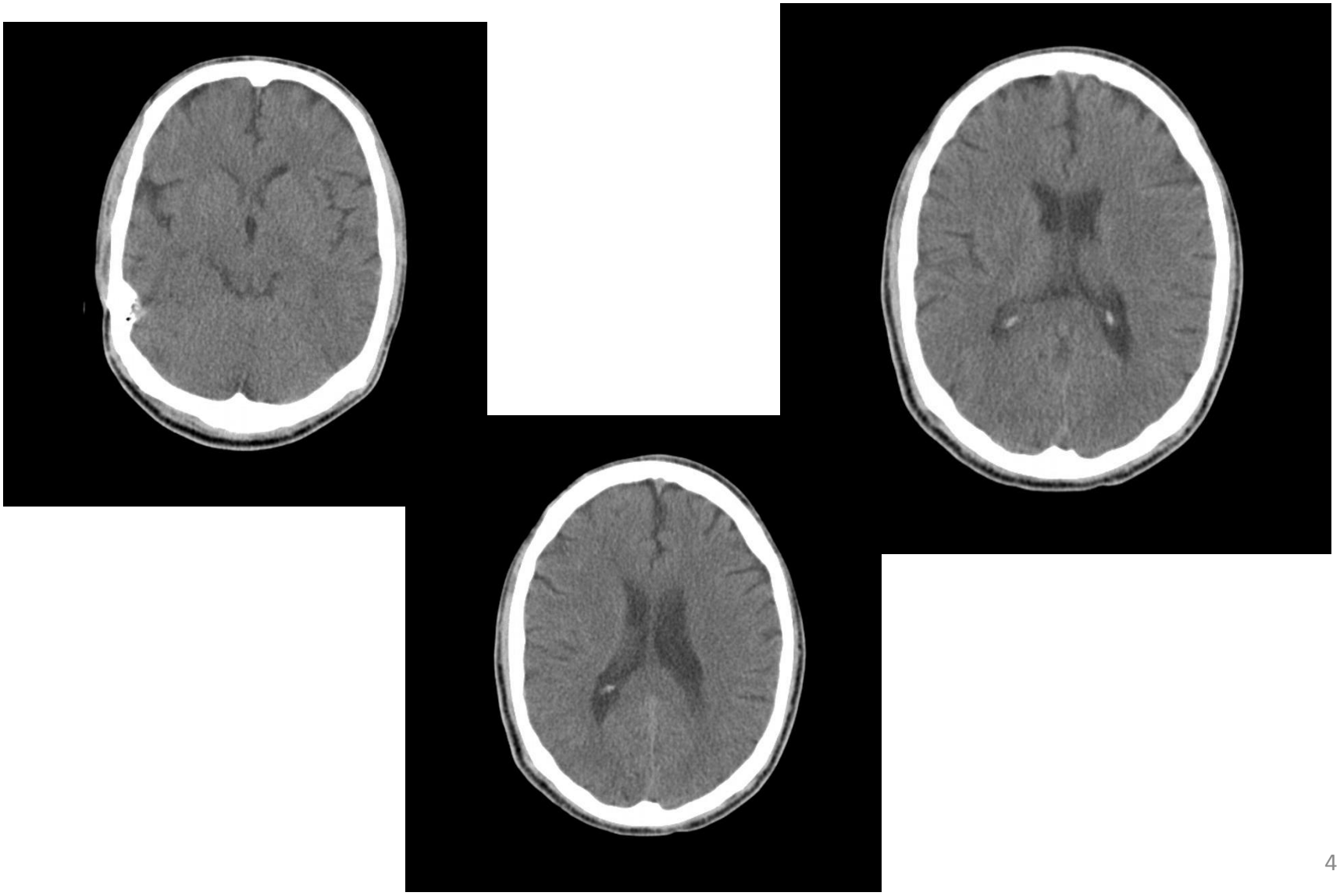
Lab

- Blood glucose: 277mg/dL
- BUN/Cr = 59/6.5
- Na/K : 134/4.7
- pH: 7.45
- HCO_3: 15
- pCO_2: 22
- pO_2: 81

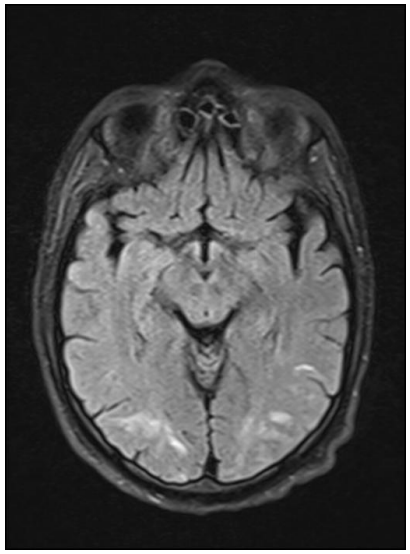
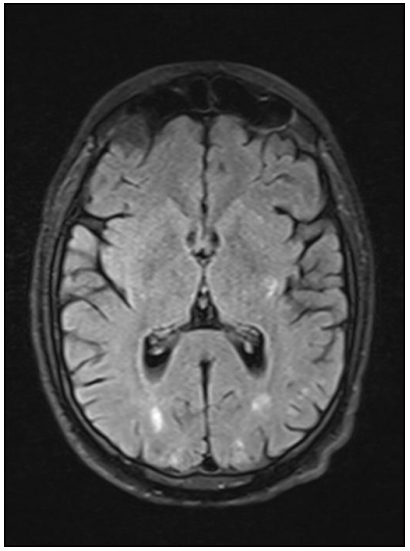
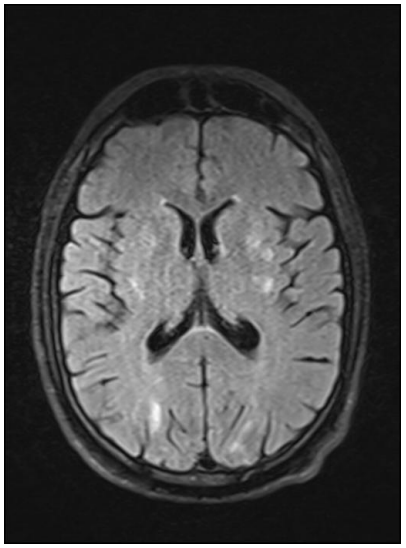
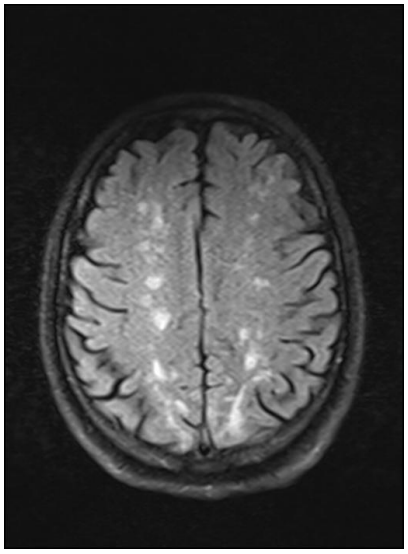
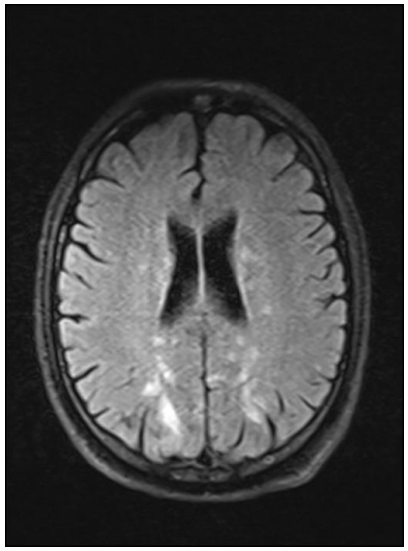


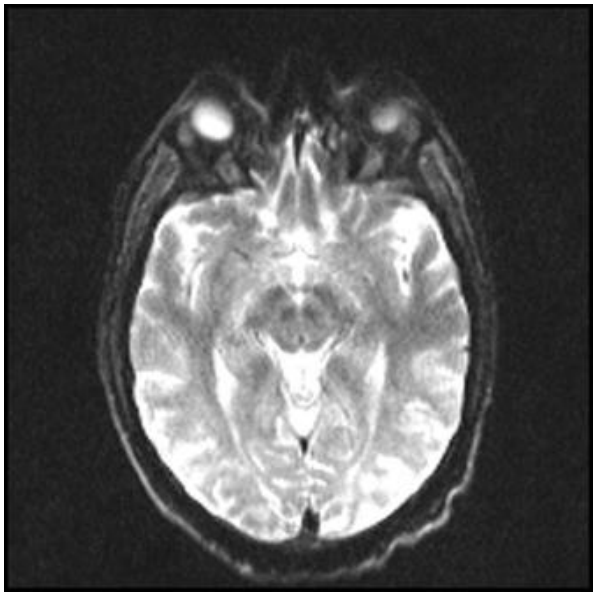
- Lac: 1.8
- CBC: N
- Ammonia: N
- ECG: sinus tach
- Chest x-ray: N

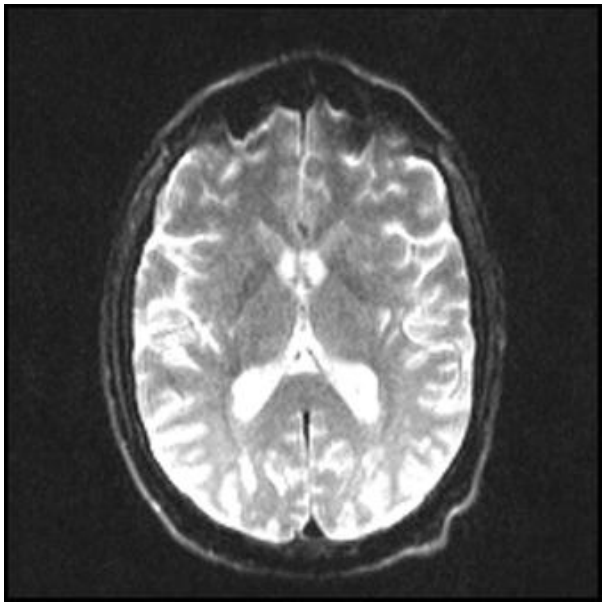
Brain CT

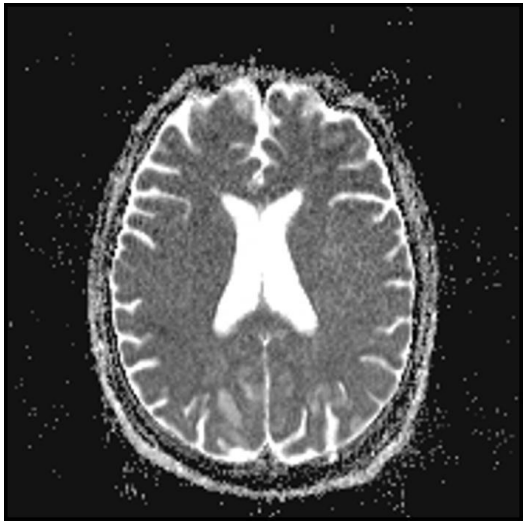


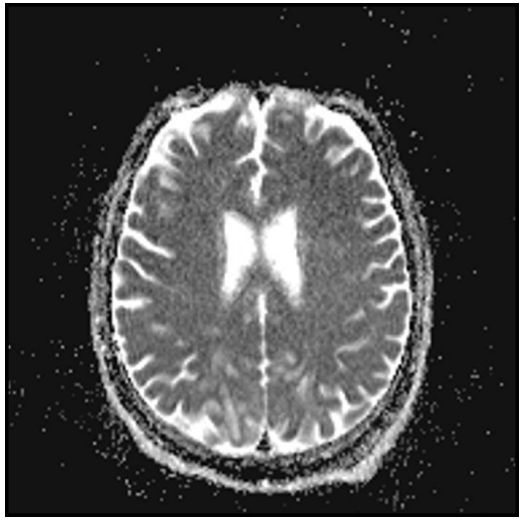
Brain MRI

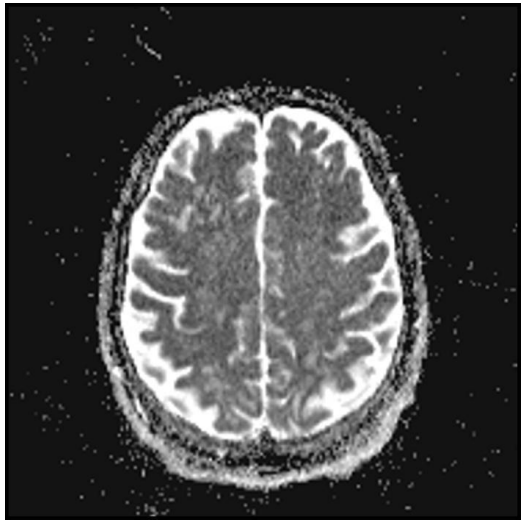








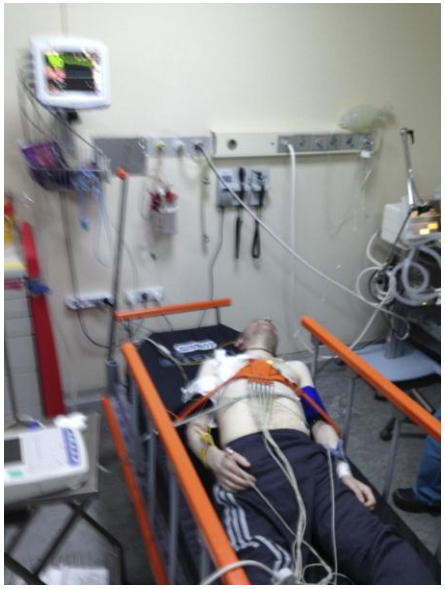






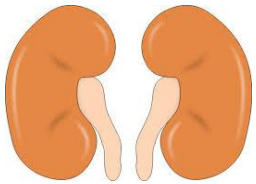


- Consultations: Neurology and Nephrology
- Neurologist → Uremic Encephalopathy
- Nephrologist → Hypertansive Encephalopathy
- Head physician of hospital →



Uremic Encephalopathy (UE)

- Diagnosis
- Pathophysiology
- Differential Diagnosis
- Imaging
- Treatment



UE = acute toxic-metabolic encephalopathy

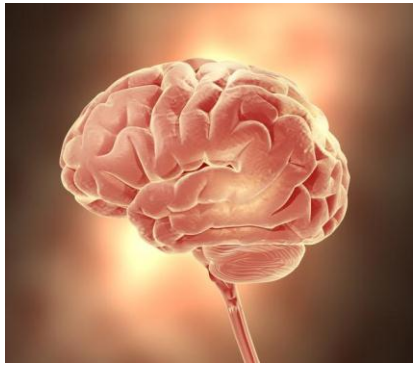
- an acute condition of global cerebral dysfunction **in the absence of primary structural brain disease**
- encompasses delirium and the acute confusional state
- Admixture of clinical signs of cerebral depression and signs of cerebral excitation is distinctive of UE

-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; last updated: Agust 9, 2013.
-Chen, R, Young, GB. Metabolic Encephalopathies. In: Bolton, CF, Young, GB, (Eds), Baillere's Clinical Neurology, Balliere Tindall, London 1996. p.577.

Clinical Manifestations of Uremic Encephalopathy

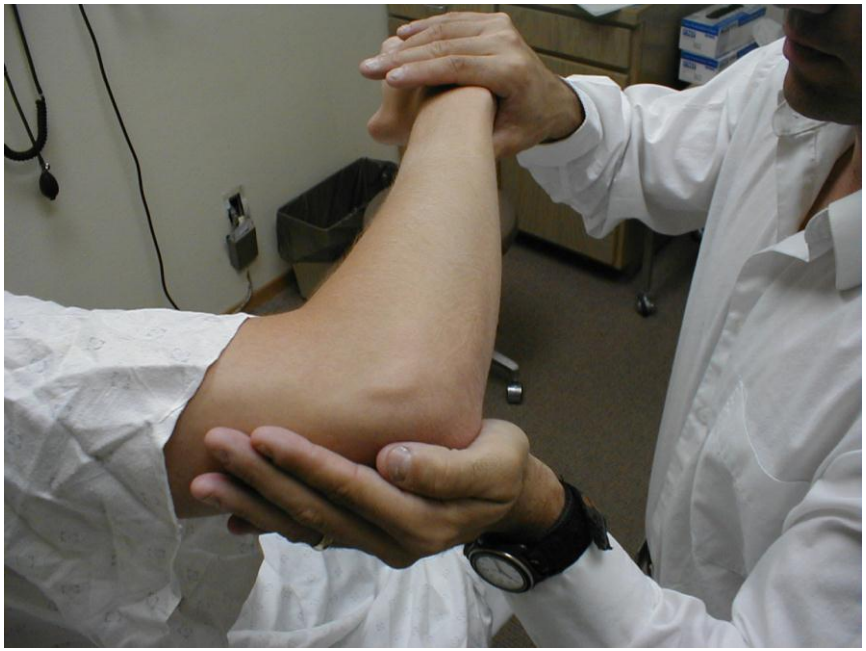
Early Encephalopathy	Late Encephalopathy
Mental Changes	
Mood swings, lethargy, irritability, disorientation	Altered cognition and perception
Impaired concentration, loss of recent memory	Illusions, visual hallucinations, agitation, delirium
Insomnia, fatigue, apathy	Stupor, coma
Motor Changes	
Hyper-reflexia	Myoclonus, **tetany**
Tremor, asterixis	**Hemiparesis**
Dysarthria, altered gait, clumsiness, unsteadiness	Convulsions

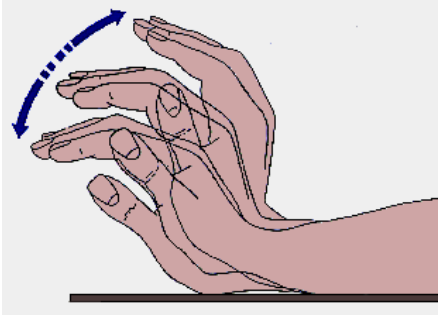
Julian Lawrence Seifter, Martin A. Samuels . Neurologic Complications of Chronic Kidney Disease . Chapter 82· Comprehensive Clinical Nephrology; 2010 P. 915



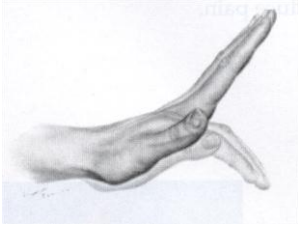
MOTOR EXAMINATION

- -TREMOR
- -ASTERIXIS
- -MYOCLONUS
- -SEIZURES

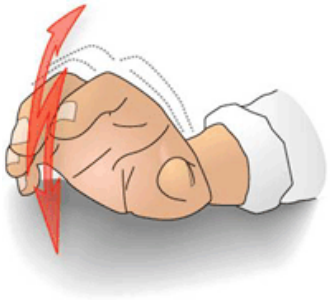




Asterixis



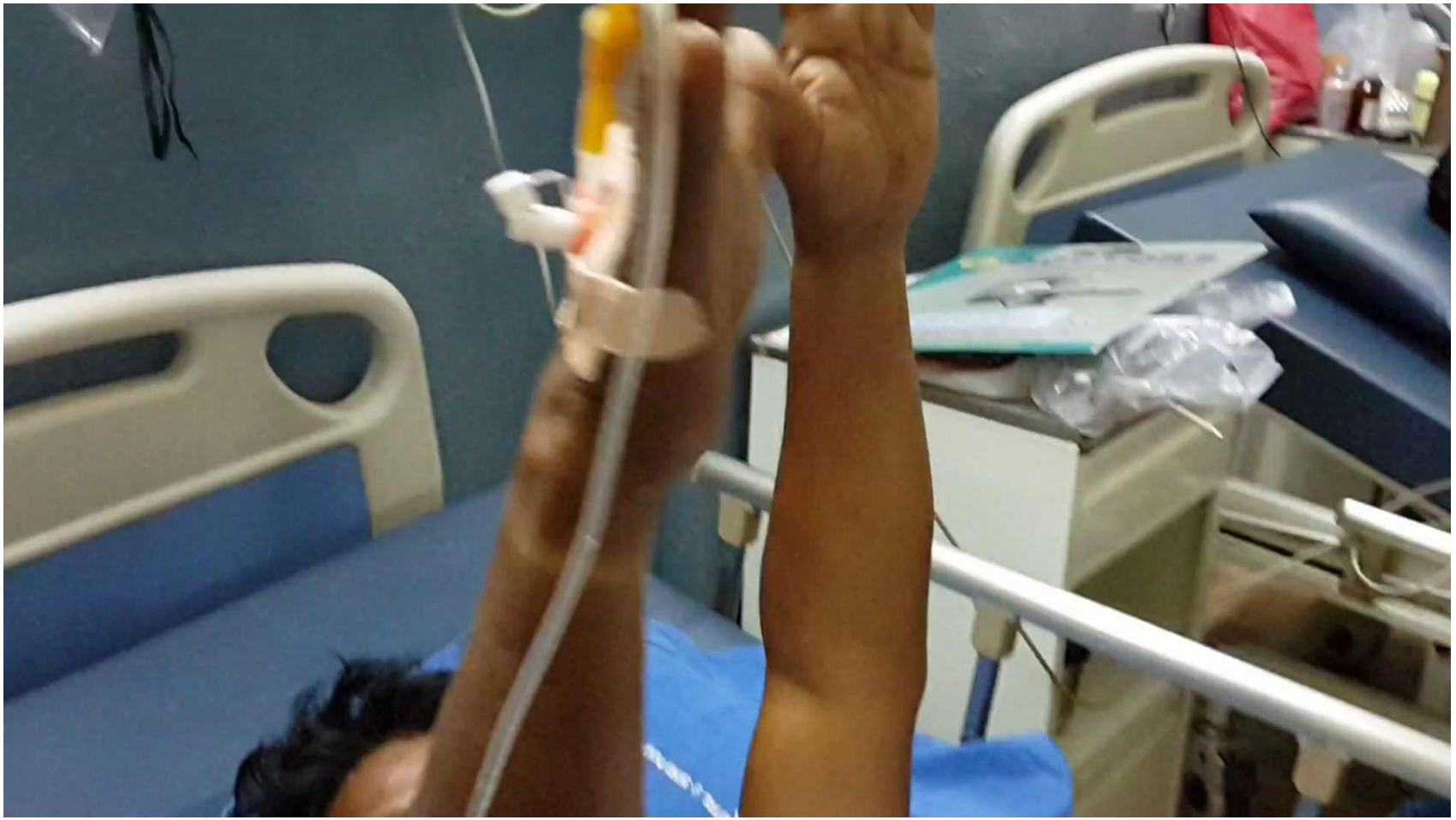
- Asterixis is characterized by intermittent loss of muscle tone in antigravity muscles
- Nearly always present once sensorial clouding appears; it is sensitive, early, reliable indication of UE
- It is almost always bilateral; unilateral asterixis (or any asymmetric response) suggests a structural lesion
- Upper limbs
- Lower limbs
- Stupor or coma



-Neurological Complications of Renal Failure Neil H. Raskin Chapter:16; 1995 Neurology and general medicine: the neurological aspects of medical disorders Editor: M. J. Aminoff
-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; last updated: Agust 9, 2013.

ASTERIXIS

MYOCLONUS

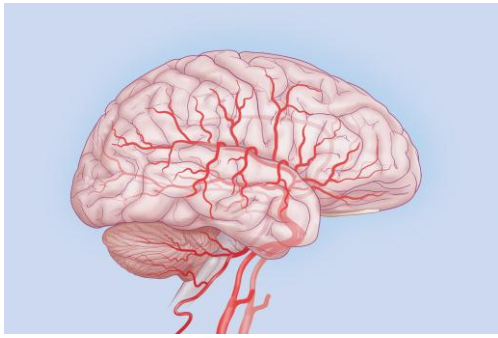


Motor examination

- With the progression of the illness, muscle tone increases further, opisthotonus may occur
- In severely obtunded subjects, decorticate and decerebrate posturing can occur

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; last updated: Agust 9, 2013.

Hemiparesis



- Rarely, focal signs such as hemiparesis or reflex asymmetry may occur

- Such focal signs tend to be transient, alternate from side to side, and resolve with hemodialysis

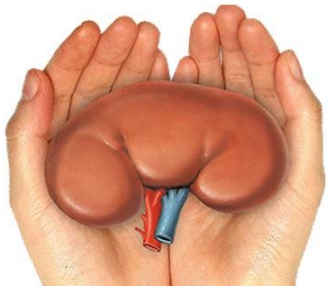
Source:
Schiefer, Wilhelm, Hart (Eds.). Clinical Neuro-Ophthalmology - A Practical Guide. Springer, Berlin/Heidelberg/New York, 2007.

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.

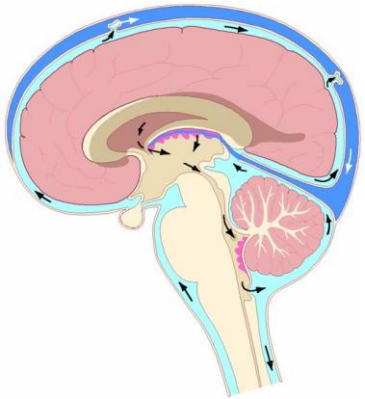
Convulsions

- Convulsions are relatively uncommon in other metabolic encephalopathies
- Epileptic seizures occur in up to 15-30% of all uremic patients
- Usually generalized tonic-clonic, but sometimes focal, multifocal, and partial complex
- In some patients, seizures are subtle, without overt motor manifestations, and require EEG monitoring for their detection

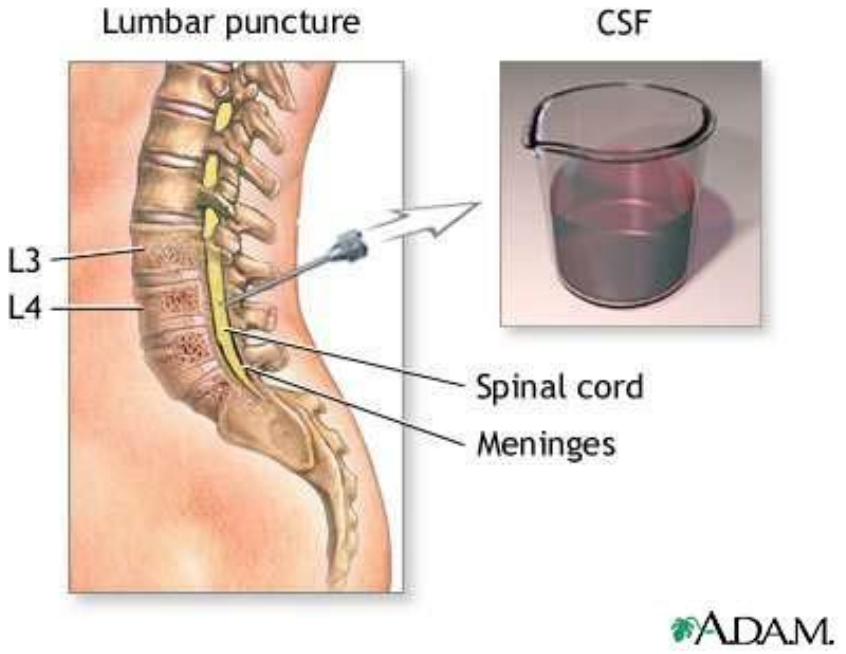
-Neurological Complications of Renal Failure Neil H. Raskin Chapter:16; 1995 Neurology and general medicine: the neurological aspects of medical disorders Editor: M. J. Aminoff
-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; last updated: Agust 9, 2013.
-Neurology in Clinical Practice 4th Edition; P. 1682



Meningeal signs and CSF



- Nuchal rigidity
- Alteration of the blood-CSF barrier
- CSF pleocytosis (usually <25 cells/mm^3)
- CSF increased protein (usually <100 mg/ dl)



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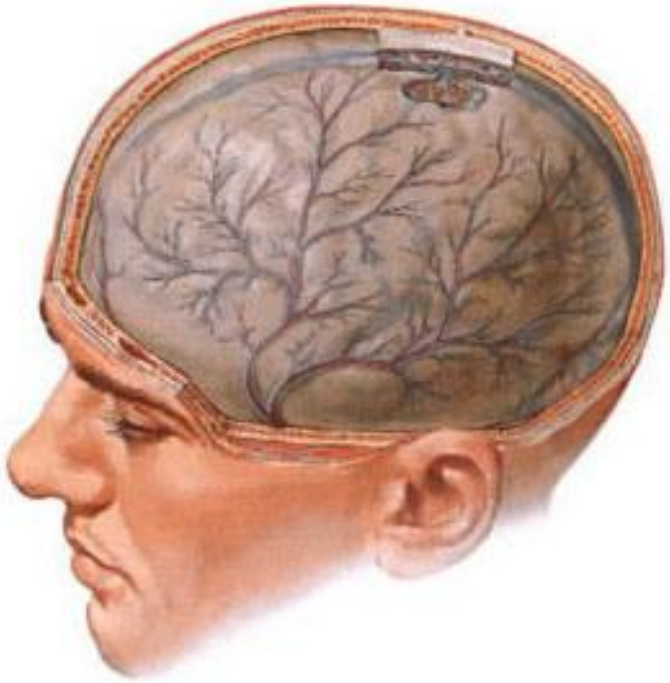
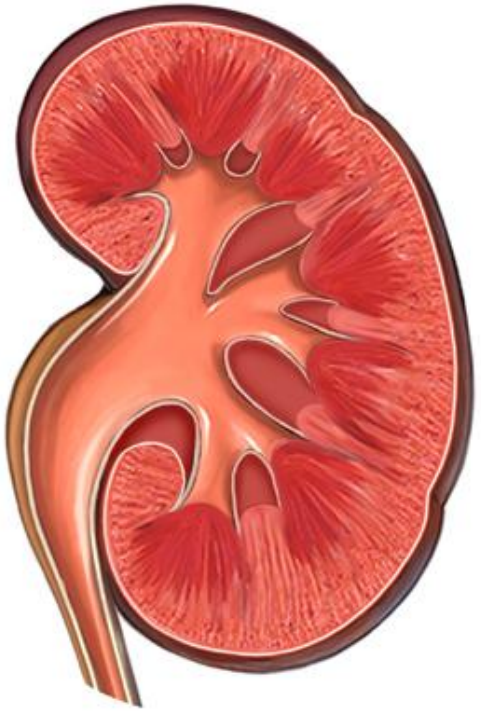
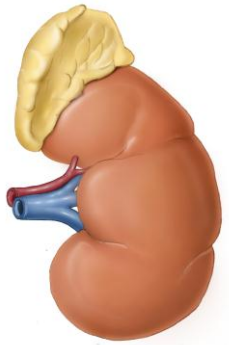




UREMIC ENCEPHALOPATHY PATHOPHYSIOLOGY



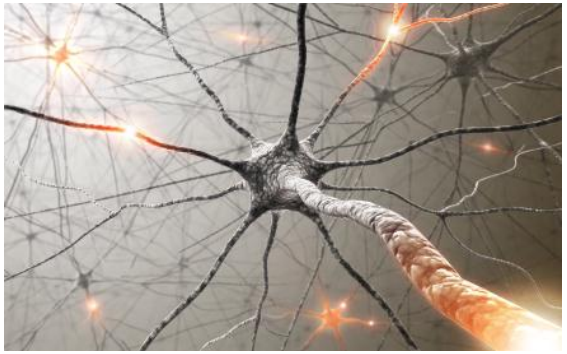
- The dialyzable toxins responsible for UE have not been identified clearly

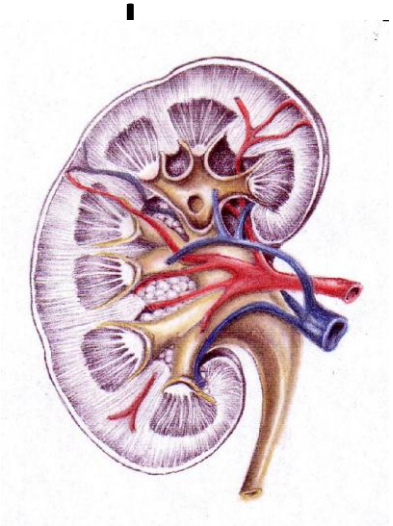
- The degree of azotemia correlates poorly with the presence or degree of encephalopathy

-Chen, R, Young, GB. Metabolic Encephalopathies. In: Bolton, CF, Young, GB, (Eds), Baillere's Clinical Neurology, Balliere Tindall, London 1996. p.577.
-Brenner and Rectors the Kidney 9th Edition; 2012; Section: 8, p. 2146

UE-Pathophysiology

1. accumulation of metabolites,
2. an imbalance of excitatory and inhibitory neurotransmitters in the brain
3. hormonal disturbances,
4. altered intermediate metabolism,

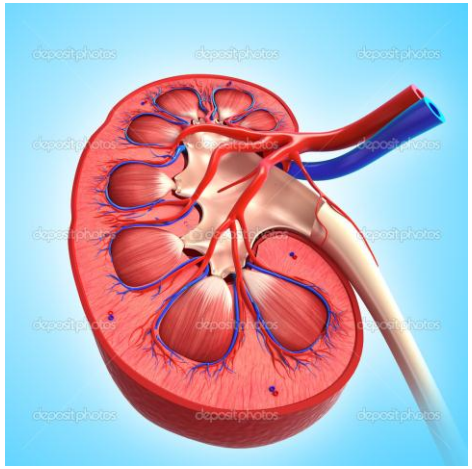


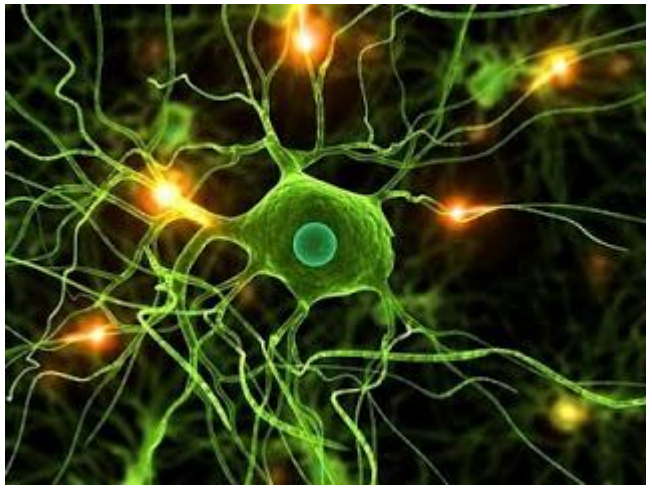


Roles of organic anion/cation transporters at the blood–brain and blood–cerebrospinal fluid barriers involving uremic toxins. Clin Exp Nephrol (2011) 15:478–485

Pathophysiology

- an increase in brain inflammation
- an increase in vascular permeability
- brain edema

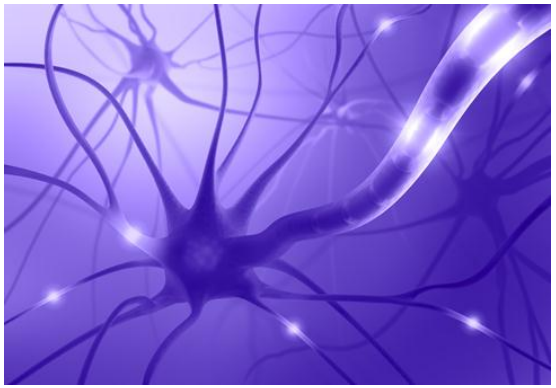


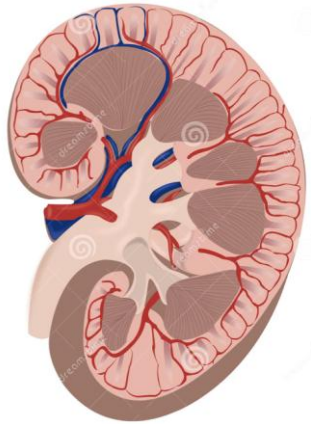


Brenner and Rectors the Kidney 9th Edition; 2012; Section: 8, p. 2146

Impaired Brain amino acid metabolism

- an imbalance between excitatory and inhibitory neurotransmitters
- the accumulation of false neurotransmitters such as methylguanidine and "**middle molecules**”





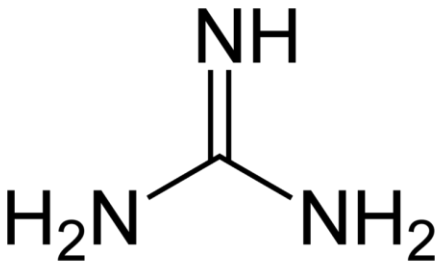
-Raymond Vanholder. Uremic toxins. Uptodate. Last updated: July 24, 2013
-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.

What are "middle molecules”?

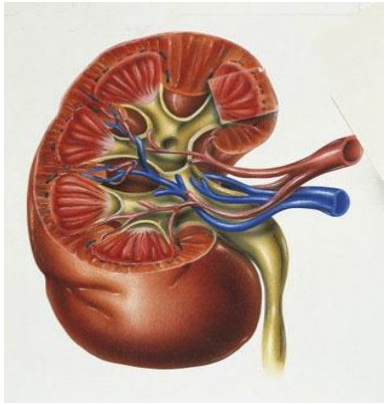
- Uremic toxins can be subdivided into three major groups based upon their chemical and physical characteristics:

1. Small, water-soluble, non-protein-bound compounds, such as ***urea***
2. Small, lipid-soluble and/or protein-bound compounds, such as the ***phenols***
3. Larger so-called middle-molecules (> 20 compounds)

Raymond Vanholder. Uremic toxins. Uptodate. Last updated: July 24, 2013



Guanidines

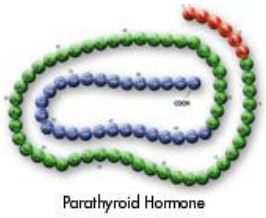


The guanidines are a large group of structural metabolites of ***arginine***

Guanidino succinic acid,
Gamma-guanidinobutyric acid,
Methylguanidine,
Homoarginine, and
Creatine

induce **seizures** after systemic and/or cerebroventricular administration in animals

-Raymond Vanholder. Uremic toxins. Uptodate. Last updated: July 24, 2013
-Guanidino compounds that are increased in cerebrospinal fluid and brain of uremic patients inhibit GABA and glycine responses on mouse neurons in cell culture. De Deyn PP, Macdonald RL. Ann Neurol. 1990;28(5):627

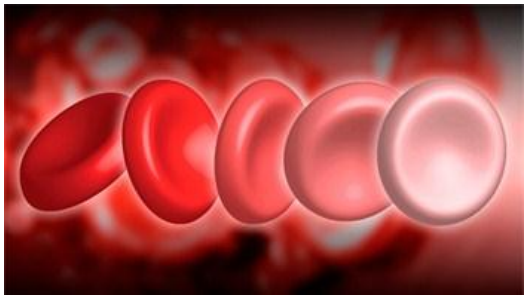


Parathyroid hormone (PTH)

- A middle molecule with a MW of ≃ 9000 D
- In animal models of uremia, infusion of parathyroid hormone reproduces both the clinical and the EEG findings of UE
- Increased cellular calcium may play a role in neuroexcitation

-Julian Lawrence Seifter, Martin A. Samuels . Neurologic Complications of Chronic Kidney Disease . Chapter 82· Comprehensive Clinical Nephrology; 2010
-Bolton, CF, Young, GB. Uremic encephalopathy. In: Bolton, CF, Young, GB, (Eds), Neurological Complications of Renal Disease, Buttersworth, Stoneham 1990. p.44

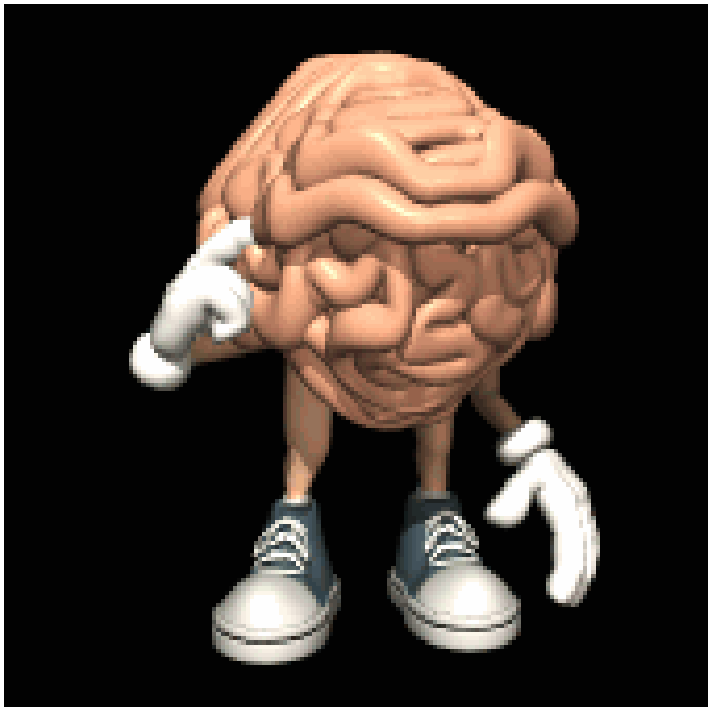
UE and anemia



- Epidemiologic studies link anemia with impaired cognitive function in persons with ESRD

- In uncontrolled short-term studies, administration of erythropoietin improves performance on cognitive function and electrophysiological testing

Brenner and Rectors the Kidney 9th Edition; 2012; Section: 8, p. 2146



DIFFERENTIAL DIAGNOSIS
-UE IS A DIAGNOSIS OF EXCLUSION-

Encephalopathy in renal failure

Encephalopathy	(Presumed) pathophysiology	Therapeutic or preventive measures
Uremic encephalopathy	Accumulation neurotoxins Disturbance intermediary metabolism Hormonal disturbances	Dialysis or kidney transplantation
Wernicke's encephalopathy	Thiamine deficiency	Thiamine administration
Dialysis encephalopathy/dementia	Aluminium accumulation	Use of aluminium free dialysate Avoid aluminium-based phosphate binders Administration of deferoxamine
Rejection encephalopathy	Cytokine production due to rejection process	↑ Immunosuppression
Hypertensive encephalopathy	Cerebral vasogenic edema	Antihypertensive treatment
Dysequilibrium syndrome	Reverse urea effect Intracellular acidosis in cerbral cortex	Self-limited
Fluid and electrolyte disturbances	↑ Calcium, magnesium, natrium, osmolality ↓ Natrium, osmolality	Correction of electrolyte imbalance
Drug toxicity	Drugs metabolised or excreted by kidney Immunosuppressive drugs	Dose reduction or cessation

Neurological complications in renal failure: a review. Clinical Neurology and Neurosurgery 107 (2004) 1–16

Wernicke's encephalopathy

is due to dysfunction of central gray structures surrounding the third and fourth ventricles secondary to thiamine deficiency

fasting	being fed after a period of starvation,
receiving parenteral nutrition	undergoing hemodialysis
recovering from gastrointestinal surgery	advanced cancer

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.

Wernicke's encephalopathy

- is characterized by a triad of confusion, ataxia, and ophthalmoplegia
- **Ocular signs** are the **hallmark** of the disease, including horizontal nystagmus, bilateral abducens palsy, complete ophthalmoplegia, and pupillary abnormalities

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.
Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. N Engl J Med 1985; 312:1035

Acute Rejection encephalopathy

- is characterized by headache, confusion, seizures, and papilledema
- CSF opening pressure may be increased, and CT reveals diffuse cerebral edema
- The EEG shows diffuse slowing in all cases and focal slowing in 25 percent of cases
- The syndrome is ascribed to release of soluble immune mediators

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate;
Last updated: Agust 9, 2013.

Cohen JA, Raps EC. Critical neurologic illness in the immunocompromised patient. Neurol Clin 1995; 13:659.

Dialysis disequilibrium syndrome (DDS)

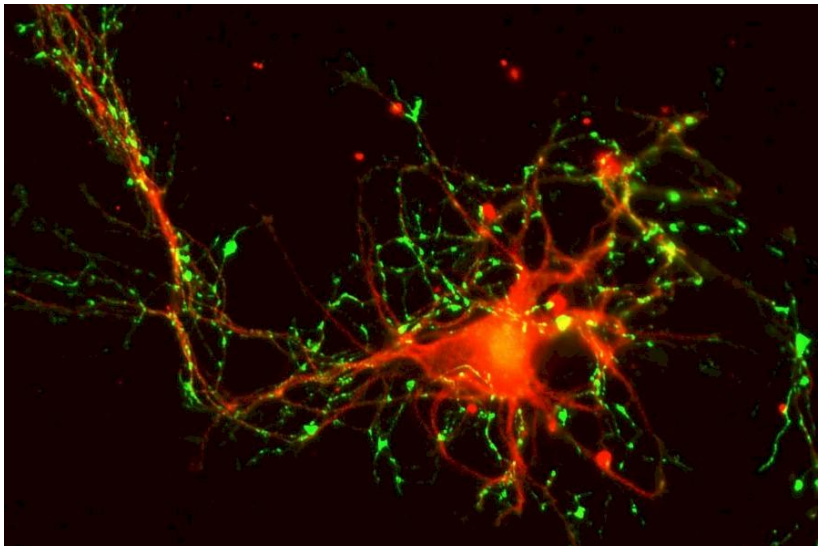
- DDS are caused by water movement into the brain, leading to cerebral edema
- Classic DDS develops **during or immediately after hemodialysis**, particularly when they are first started on hemodialysis
- DDS is characterized by neurologic symptoms related to cerebral edema
- Stop Dialysis

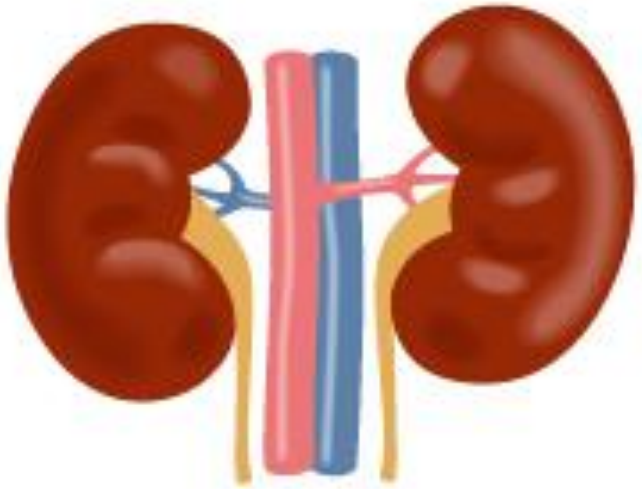
Lionel U Mailloux. Dialysis disequilibrium syndrome. Uptodate. Last updated: No v 21, 2013

Hypertansive encepahlopathy

- **Papil edema** is a major sign that **distinguishes**

- Aphasia and cortical blindness are far more common in HTE





Diagnostic and Interventional Imaging (2013) 94, 45—52

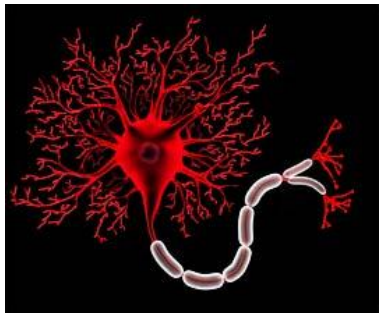
ICONOGRAPHIC REVIEW / *Neurology*

Posterior reversible encephalopathy syndrome (PRES): Features on CT and MR imaging

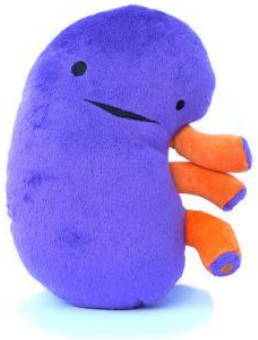
E. Hugonnet[a], D. Da Ines[a,*], H. Boby[b], B. Claise[c], V. Petitcolin[a], V. Lannareix[a], J.-M. Garcier[a]

Table 1 Clinical features of patients with posterior reversible encephalopathy syndrome (PRES).

Settings in which PRES may be likely to develop	Clinical presentations
Arterial hypertension	Headaches
Pre-eclampsia	Confusion
Transplant: allogeneic bone marrow transplant or solid organ transplant	Nausea, vomiting
Immunosuppressant medication: ciclosporin, tacrolimus, etc.	Generalised seizures, sometimes with status epilepticus
Septicaemia, severe infections, often with a state of shock and multiple organ dysfunction syndrome	Cerebellar syndrome
Autoimmune disease: systemic lupus erythematosus, scleroderma, Wegener's granulomatosis	Cortical blindness, hemianopia, blurred vision
Cancer chemotherapy: cisplatin, etc.	Hemiparesis
Chronic renal failure and dialysis	Coma



PRES

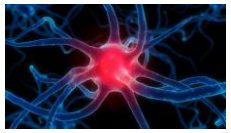


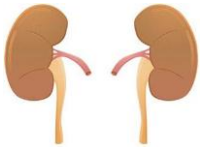
- first described in 1996 by Hinchey et al
- typical symptoms → **headache, <u>convulsion</u>, visual disturbances** (including formed visual hallucinations and visual field cuts) and altered mentation
- M/F = 1/1
- Hypertension the most common risk factor: 68-80% of cases

Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al: A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996; 334:494 –500

Posterior Reversible Encephalopathy Syndrome . Journal of Clinical Neuroscience 18 (2011) 406–409

Posterior reversible encephalopathy syndrome (PRES)





- The typical appearance is of diffuse cortical, subcortical and deep lesions
- It is usually the posterior regions that are affected: the parietal or **occipital lobes** are involved in **98%** of cases
- The lesions can also affect the frontal lobes (68%), the temporal lobes (40%) and the cerebellar hemispheres (30%)

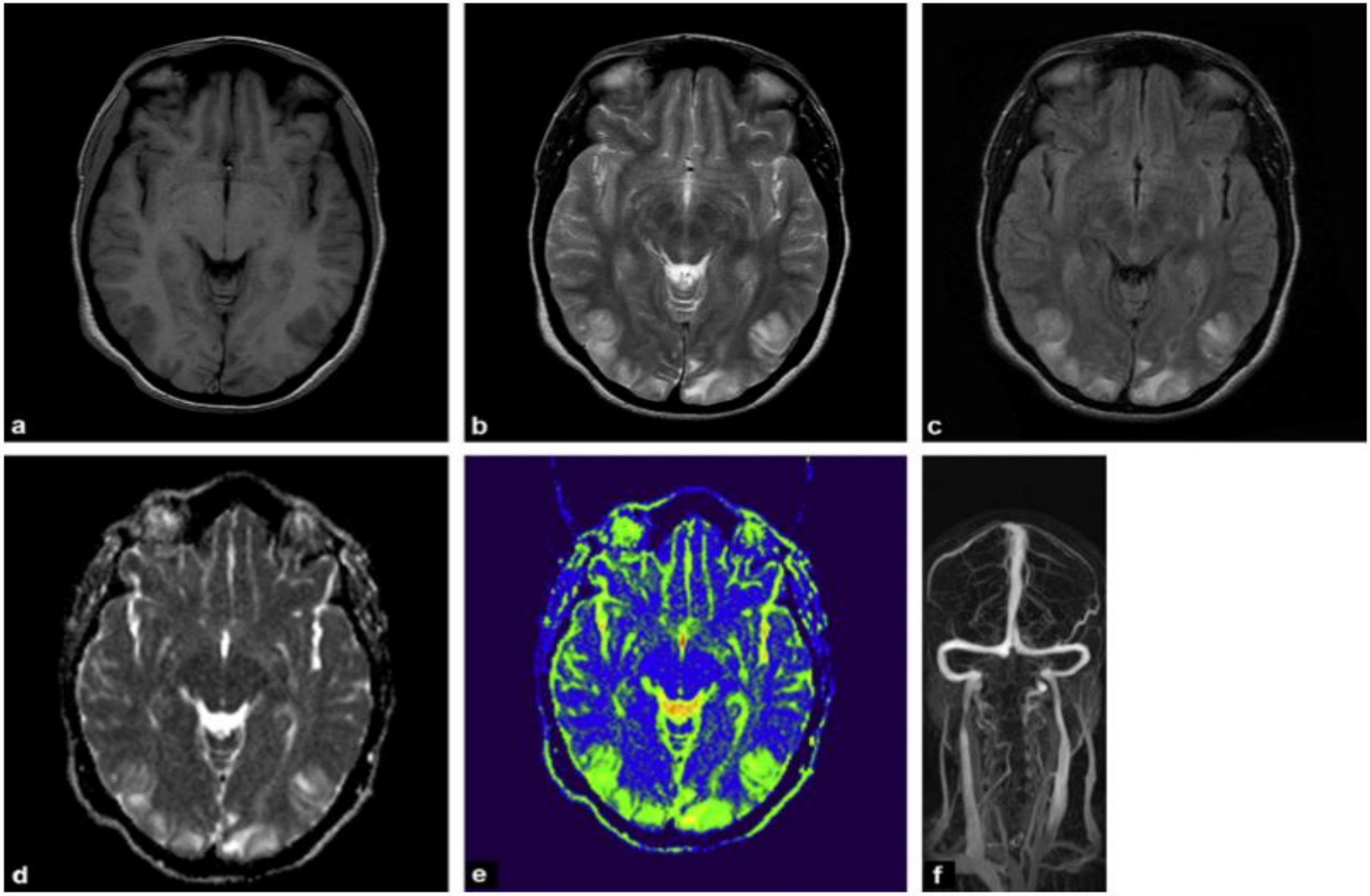
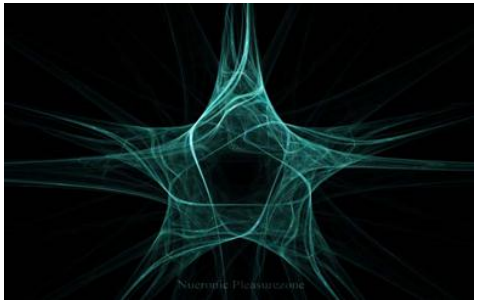


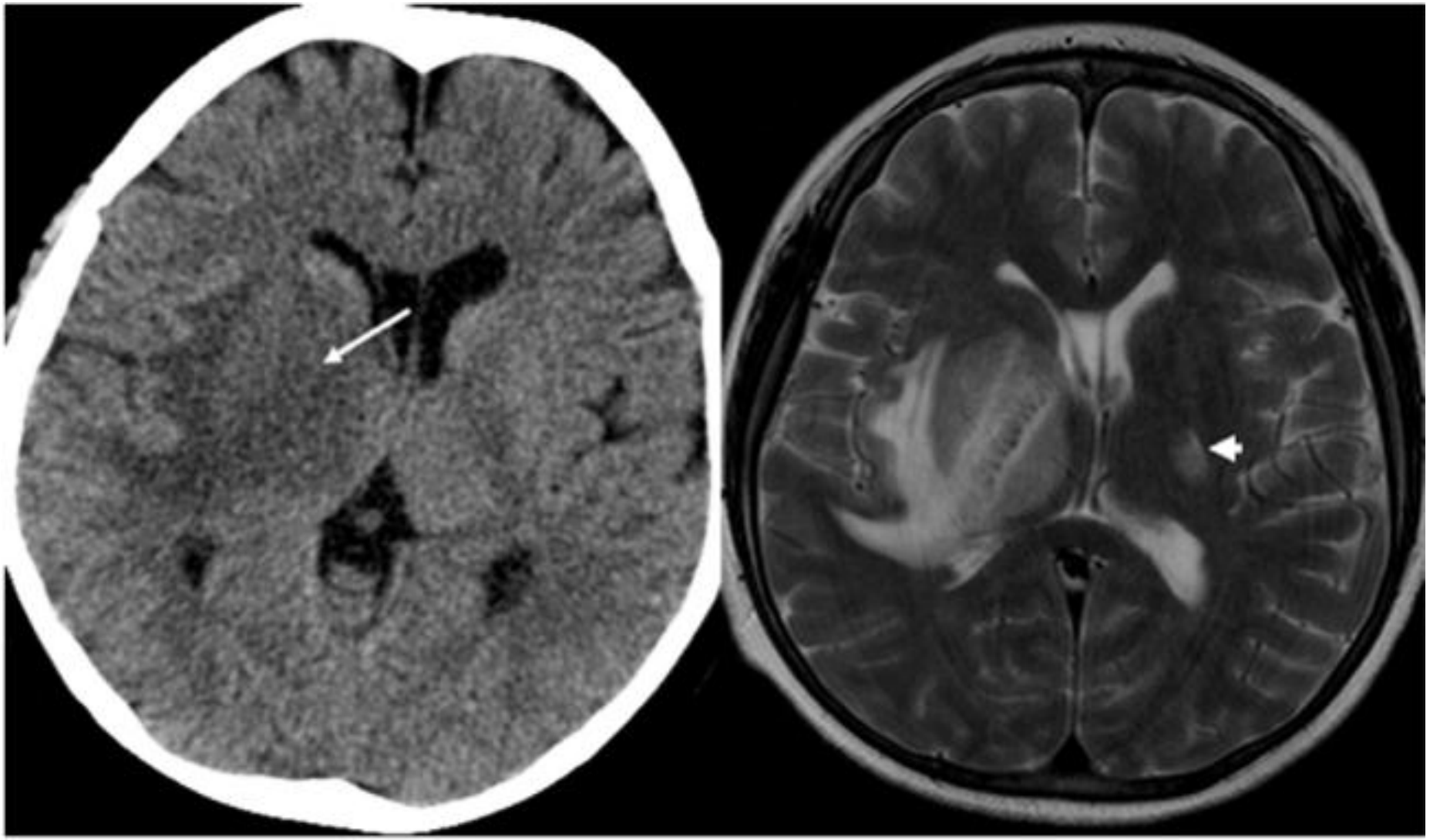
Figure 2. Female aged 31, on dialysis, who had presented with her first partial epileptic seizure against a background of hypertension (systolic blood pressure of 230 mmHg). The MRI showed characteristic diffuse, bilateral, posterior lesions. The neurological signs quickly disappeared after anti-hypertensive treatment: a: T1-weighted axial view: low signal intensity occipital lesions; b: T2-weighted axial view: high signal intensity occipital lesions; c: axial view on FLAIR sequence: high signal intensity occipital lesions; d and e: axial views — diffusion-weighted sequence: the apparent diffusion coefficient mapping in grey and in colour shows high signal intensity from the lesions pointing to a raised diffusion coefficient; f: 3D MR angiography: eliminates the differential diagnosis of cerebral thrombophlebitis by demonstrating that the venous sinuses are patent.



Imaging in UE

- Imaging in UE is frequently normal
- Patients with abnormal imaging findings typically have bilateral symmetrical or asymmetrical involvement of the **basal ganglia**, internal and external capsules
- At CT, these usually appear as areas of decreased attenuation
- At MRI, these appear as regions of T1 and T2 prolongation

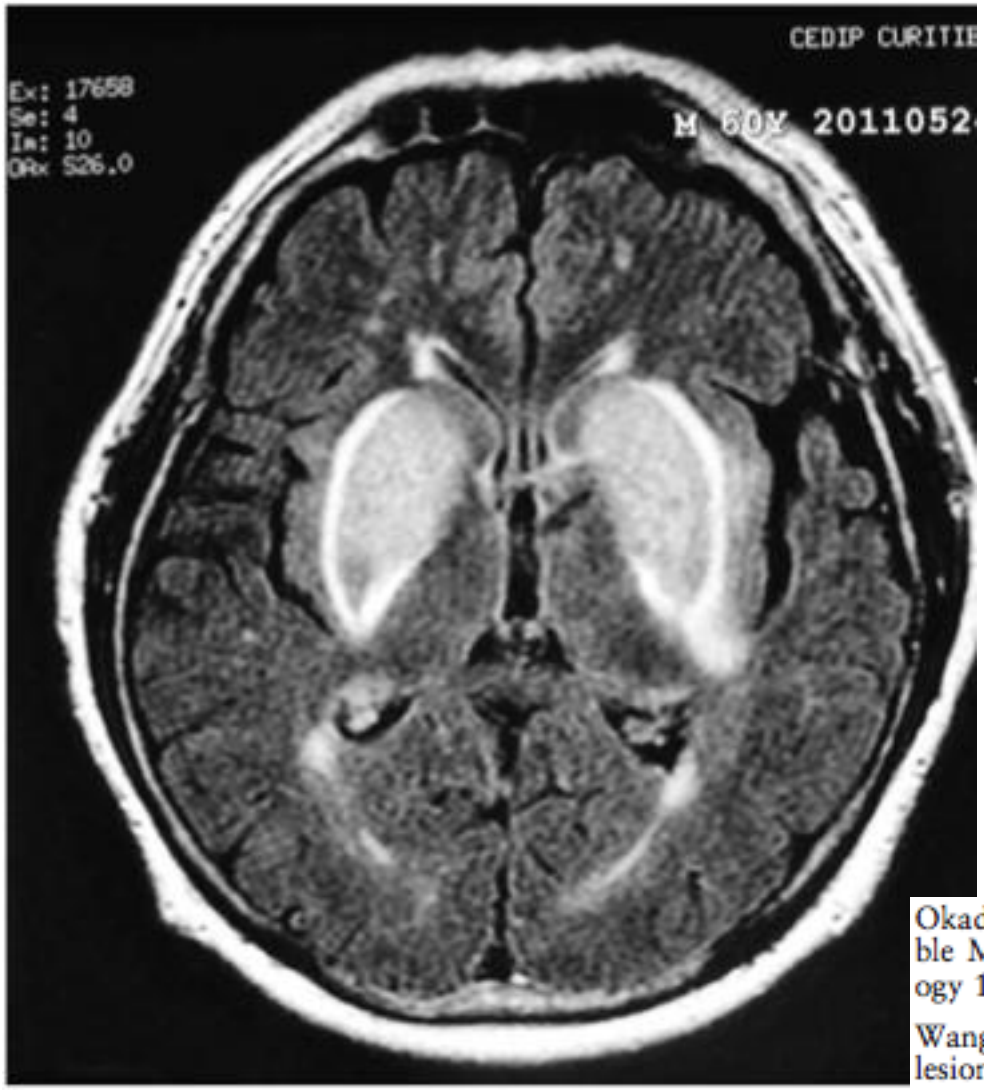
Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.



Hypodense right basal ganglia, internal capsule and thalamus are illustrated on the CT image . The aforementioned abnormal areas are noted to be hyperintense on axial T2-weighted MRI. Involvement of the left internal capsule is better depicted on MRI (arrowhead).

Bathla G, Hegde AN. MRI and CT appearances in metabolic encephalopathies due to systemic diseases in adults. Clin Radiol. 2013 Jun;68(6):545-54.

a fork-like structure formed by the bright hyperintense rim that delineates the lentiform nucleus; this finding is known as the **Lentiform fork sign (LFS)**



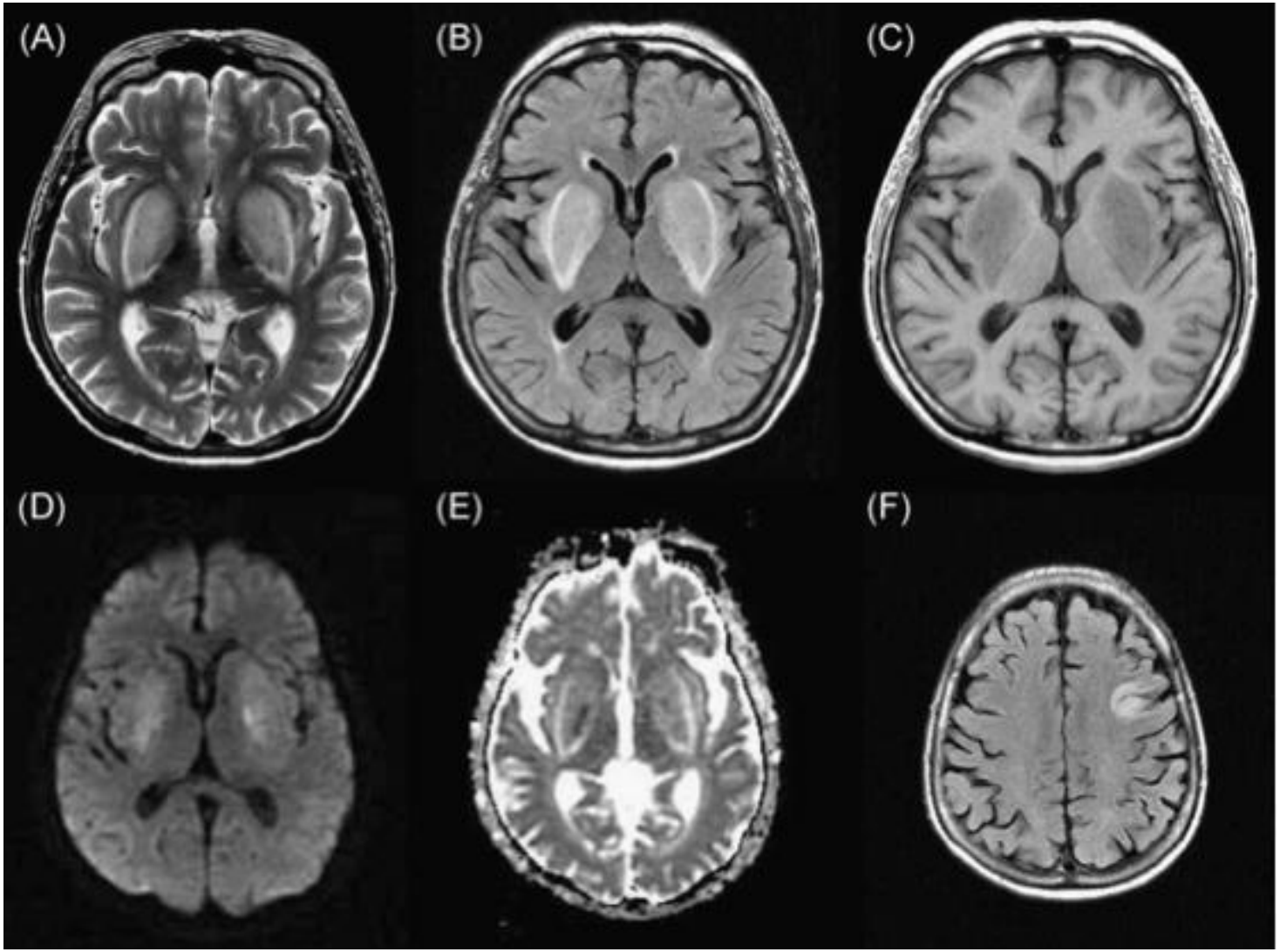
Lentiform Fork Sign and Fluctuating, Reversible Parkinsonism in a Patient With Uremic Encephalopathy

Movement Disorders

Volume 28, Issue 8, page 1053, 2013

Okada J, Yoshikawa K, Matsuo H, Kanno K, Oouchi M. Reversible MRI and CT findings in uremic encephalopathy. Neuroradiology 1991;33:524–526.

Wang HC, Cheng SJ. The syndrome of acute bilateral basal ganglia lesions in diabetic uremic patients. J Neurol 2003;250:948–955.



Bilateral basal ganglia and unilateral cortical involvement in a diabetic uremic patient.
Clinical Neurology and Neurosurgery 111 (2009) 477–479

A B S T R A C T

We report a 57-year-old woman with uremic encephalopathy who presented with dysarthria, dysphagia, hypophonia, and drowsiness. The patient's radiologic findings were rather unusual in that magnetic resonance imaging (MRI) showed abnormal findings involving the basal ganglia bilaterally and frontal cortex unilaterally. After intensified hemodialysis, her symptoms and follow-up brain MRI showed marked improvement. We postulated that the underlying mechanism of uremic encephalopathy based on diffusion-weighted imaging and apparent diffusion coefficient maps.

Laboratory
Complete blood count
Coagulation studies
Electrolyte panel including calcium, magnesium, phosphate
Blood urea nitrogen, creatinine
Bilirubin, liver enzymes, ammonia
Serum osmolality
Arterial blood gases
Toxicologic screening for suspected intoxications
Thyroid function tests
Vitamin B12
Serum cortisol concentrations

Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.

Electroencephalography (EEG)

- The EEG is usually abnormal but non-specific
- Generalized slowing with an excess of delta and theta waves is found
- The EEG in uremia reflects the severity of encephalopathy
- EEG can both confirm global cerebral dysfunction and exclude subclinical seizures

-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.
-Bolton, CF, Young, GB. Uremic encephalopathy. In: Bolton, CF, Young, GB, (Eds), Neurological Complications of Renal Disease, Buttersworth, Stoneham 1990. p.44.

Tx

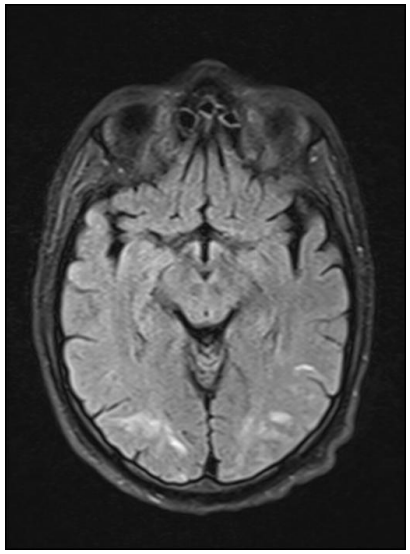
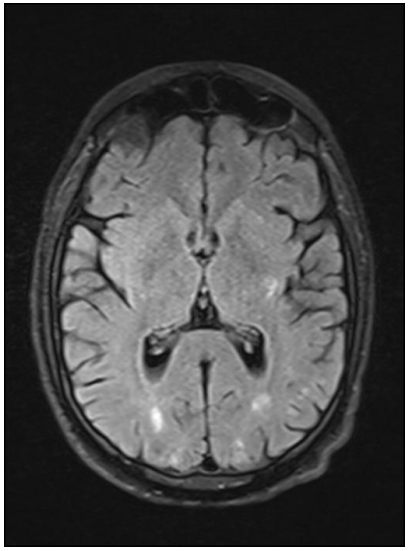
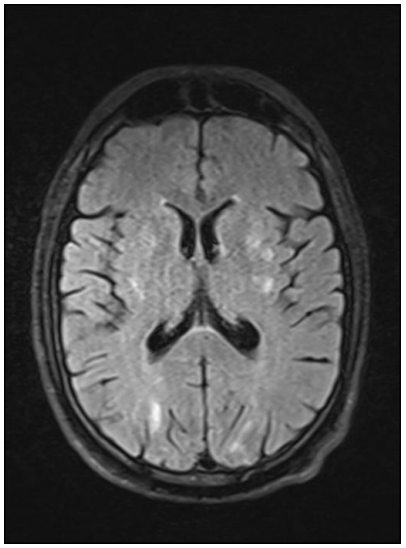
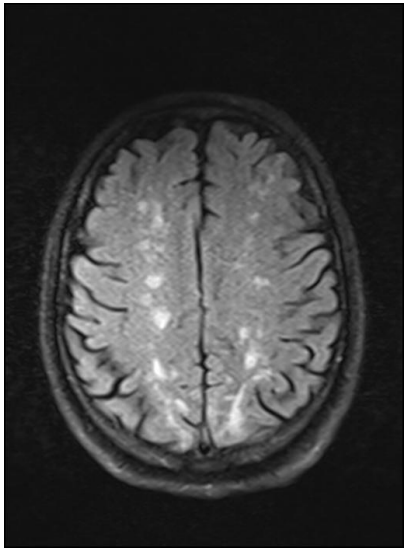
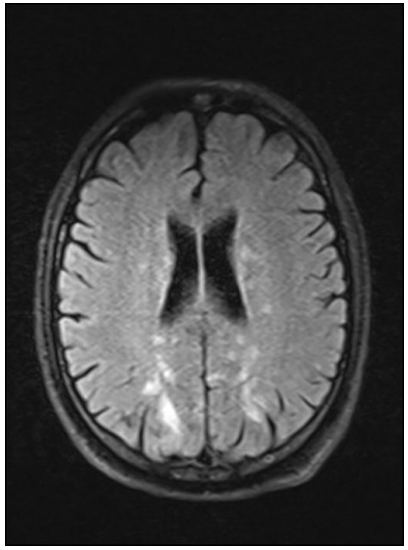
- Renal replacement therapy (**dialysis**) is the primary therapy for UE → Sxs are alleviated by dialysis
- Correction of anemia (i.e., hemoglobin <10 g/dL)
- Dietary protein restriction
- **Failure to improve substantially following dialysis should alert the physician to other possible etiologies of encephalopathy**

-Brenner and Rectors the Kidney 9th Edition; 2012; Section: 8, p. 2146
-Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; Last updated: Agust 9, 2013.

What can we study about UE in ED?

- Multicentric
- Is there a role of anti PTH tx in UE? Animal study
- Role of erythropoietin tx in UE? Exp study
- Role of Erythropoietin receptors in UE? Exp histologic study
- What are physiological differences in acute and chronic renal failure?

Which department for hospitalization?

THANK YOU
ANY QUESTIONS?