UREMIC ENCEPHALOPATHY
(UE)
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ATATURK UNIVERSITY MEDICAL FACULTY,
ERZURUM
DEPARTMENT OF EMERGENCY
Saturday, May, 2014

33 yo M, complaint: nausea, 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
- HCO₃⁻: 15
- pCO₂: 22
- pO₂: 81
- Lac: 1.8
- CBC: N
- Ammonia: N
- ECG: sinus tach
- Chest x-ray: N
Brain MRI
• Consultations: Neurology and Nephrology
• Neurologist → Uremic Encephalopathy
• Nephrologist → Hypertensive 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

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

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

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

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.
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

- Julio A Chalela, Scott E Kasner, Acute toxic-metabolic encephalopathy in adults; Uptodate; last updated: Augst 9,12013.
- 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/mm³)
- CSF increased protein (usually <100 mg/dl)

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

-Brenner and Rectors the Kidney 9th Edition; 2012; Section: 8, p. 2146
1. accumulation of metabolites,
2. an imbalance of excitatory and inhibitory neurotransmitters in the brain
3. hormonal disturbances,
4. altered intermediate metabolism,

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"

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)
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.

-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 \( \approx 9000 \) 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

-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-
<table>
<thead>
<tr>
<th>Encephalopathy</th>
<th>(Presumed) pathophysiology</th>
<th>Therapeutic or preventive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic encephalopathy</td>
<td>Accumulation neurotoxins&lt;br&gt;Disturbance intermediary metabolism&lt;br&gt;Hormonal disturbances</td>
<td>Dialysis or kidney transplantation</td>
</tr>
<tr>
<td>Wernicke’s encephalopathy</td>
<td>Thiamine deficiency</td>
<td>Thiamine administration</td>
</tr>
<tr>
<td>Dialysis encephalopathy/dementia</td>
<td>Aluminium accumulation</td>
<td>Use of aluminium free dialysate&lt;br&gt;Avoid aluminium-based phosphate binders&lt;br&gt;Administration of deferoxamine</td>
</tr>
<tr>
<td>Rejection encephalopathy</td>
<td>Cytokine production due to rejection process</td>
<td>↑ Immunosuppression</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Cerebral vasogenic edema</td>
<td>Antihypertensive treatment</td>
</tr>
<tr>
<td>Dysequilibrium syndrome</td>
<td>Reverse urea effect&lt;br&gt;Intracellular acidosis in cerbral cortex</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Fluid and electrolyte disturbances</td>
<td>↑ Calcium, magnesium, natrium, osmolality&lt;br&gt;↓ Natrium, osmolality</td>
<td>Correction of electrolyte imbalance</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Drugs metabolised or excreted by kidney&lt;br&gt;Immunosuppressive drugs</td>
<td>Dose reduction or cessation</td>
</tr>
</tbody>
</table>
Wernicke's encephalopathy is due to dysfunction of central gray structures surrounding the third and fourth ventricles secondary to thiamine deficiency.

<table>
<thead>
<tr>
<th>fasting</th>
<th>being fed after a period of starvation,</th>
</tr>
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<tbody>
<tr>
<td>receiving parenteral nutrition</td>
<td>undergoing hemodialysis</td>
</tr>
<tr>
<td>recovering from gastrointestinal surgery</td>
<td>advanced cancer</td>
</tr>
</tbody>
</table>
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.
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: August 9, 2013.
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
Hypertensive encephalopathy

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

• Aphasia and **cortical blindness** are far more common in HTE
**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. Garcia\(^a\)

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

- first described in 1996 by Hinchey et al
- typical symptoms → headache, convulsion, 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


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%)
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).

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)**.
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.
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<td>Complete blood count</td>
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<td>Coagulation studies</td>
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<td>Electrolyte panel including calcium, magnesium, phosphate</td>
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<tr>
<td>Blood urea nitrogen, creatinine</td>
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<tr>
<td>Bilirubin, liver enzymes, ammonia</td>
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<td>Serum osmolality</td>
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<td>Arterial blood gases</td>
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<td>Toxicologic screening for suspected intoxications</td>
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<td>Thyroid function tests</td>
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<td>Vitamin B12</td>
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<td>Serum cortisol concentrations</td>
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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
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
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?