LESSONS FROM A NEUROLOGY CONSULT: PART 1
From the American Academy of Neurology’s 65th AAN Annual Meeting, San Diego, CA, March 16-23, 2013
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Osmolar Demyelination
Case example: patient with acute and chronic alcoholism became stuporous with rigidly flexed arms and bilateral Babinski signs; had respiratory alkalosis; later became acidic and less hypoxic; later decompensated and required intubation; osmolar gap of 70 on previous admission dropped to 10

Hypermolar states: often seen in critically ill patients; usually associated with volume depletion; possibly caused by external osmoles (eg, mannitol, glycerol) used to treat patients with increased intracranial pressure and cerebral edema

Management: address primary metabolic abnormality; medications, poisons, and nutritional status often provide clues; determine whether volume problem exists by physical examination; calculate free water deficit; add ongoing free water losses; add insensible losses on basis of body temperature; replete

Osmotic demyelination (central pontine myelinolysis): seen in alcoholics; not limited to pons; characteristically distributed in posterior limb of capsule, basal ganglia, and line in cortex producing pseudolaminar necrosis; considered iatrogenic and caused by inappropriately rapid correction of hyponatremia, ie, increasing osmoles too rapidly; patients who survived had spastic tetraparesis, hyporeflexia, and dysarthria; spectrum of symptoms may occur; completely reversible by adjustment of osmolality; all hypertonicity associated with hyponatremia, but not all hyponatremia hypotonic; serum urea nitrogen (BUN) has little effect on osmolality because it diffuses freely; sodium has large effect, as does glucose

Hyponatremia: important to measure osmolality to determine type; isotonic type artifactual (caused by lipid or protein taking up space); hypervolemic type caused by external osmoles; hypotonic — hypervolemic type (edematous) caused by liver, renal, or heart failure; hypovolemic type caused by diuretics or salt wasting (including cerebral); isotonic type commonly caused by inappropriate secretion of antidiuretic hormone; patient in case example hyperosmolar with normal electrolytes (sodium, glucose, and BUN)

Management: isotonic — not treated; hypervolemic — remove external osmoles if possible; hypotonic — if hypervolemic, treat with sodium restriction; if hypovolemic, administer volume (including sodium); if euclidean, determine whether acute or chronic; acute — onset <48 hr; treat immediately with hypertonic saline because of risk for cerebral edema and rapid death; chronic — brain can maintain volume by extruding osmoles if serum sodium decreases gradually; if hypotonic or normal saline administered under these conditions, brain shrinks, causing osmotic demyelination; during shrinking, myelin possibly squeezed in places where crossing and descending fibers form tight net (eg, pons, posterior limb of capsule, subcortical region); appropriate rate of correction of hyponatremia depends on rate of development; if acute, use hypertonic saline; if chronic (solute has been extruded over days, weeks, or months), rapid correction causes brain shrinkage, and hypertonic saline contraindicated; treat gently by restricting water

Case example: patient had been drinking Listerine; after cessation, suffered from cerebral edema caused by rapidly dropping osmolality; if patient under treatment to correct osmolality and signs of osmotic demyelination begin, possible to reverse by treatment with osmoles

Antibiotic Encephalopathy
Case example: patient with lupus, acute myelogenous leukemia, nephropathy, and change in mental status received induction chemotherapy; patient showed polymyoclonus and asterixis with no seizures; new medications included cefepime

Antibiotic neurotoxicity: cephalosporins — toxicity reported with cefepime and ceftazidime; considered γ-aminobutyric acid (GABA) agonists; cross blood-brain barrier poorly, but small amounts that enter cerebral spinal fluid (CSF) not well removed in context of renal failure; imidazole and antifungals (eg, metronidazole) — toxicity easily recognized with cerebellar signs and bright olive on diffusion imaging; fluoroquinolones — may cause seizures with slight changes in renal function

Myeloma-induced Portosystemic Encephalopathy
Case examples: patient with newly diagnosed multiple myeloma; treated with standard regimen; developed acute encephalopathy with asymmetrical asterixis; electroencephalography (EEG) results slow with triphasic waves; ammonia level 115 µg/dL; second patient with IgG kappa multiple myeloma had same treatment regimen, similar EEG results, and elevated ammonia

Portosystemic encephalopathy (PSE): tumor lysis syndrome not unusual in patients undergoing induction chemotherapy for

Educational Objectives
The goal of this program is to improve the diagnosis and treatment of various neurologic disorders. After hearing and assimilating this program, the clinician will be better able to:
1. Diagnose and treat osmotic demyelination.
2. Recognize the features of antibiotic neurotoxicity.
3. Diagnose hepatic encephalopathies in patients with and without portosystemic shunts.
4. Elaborate on the features and probable etiology of portosystemic encephalopathy and ammonia toxicity in patients with myeloma.
5. Diagnose and treat lupus with Sjögren syndrome manifesting as a neurologic disorder.

Faculty Disclosure
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myeloma; characterized by elevated serum ammonia produced by lysis of plasma cells; liver failure not necessary

**Hepatic cerebrovascular syndromes:** acute hepatic encephalopathy; recurrent reversible hepatic encephalopathy — may occur in patients with liver disease who suffer lysis of red cells, eg, gastrointestinal (GI) bleeding; condition worsens, then returns to baseline

Chronic progressive irreversible hepatic encephalopathy: patients become spastic in legs, show hypertreflexia, and have various movement disorders; may respond to L-dopa; types — hereditary hepatolenticular (Wilson disease); acquired hepatocerebral degeneration

**Hepatic encephalopathy:** often caused by portosystemic shunts (not required); PSE can occur without liver disease; portosystemic shunting possibly intrahepatic, eg, with some hepatic tumors or arteriovenous (AV) malformations of liver, or extrahepatic, eg, with Eck fistulas caused either spontaneously by trauma or during surgery to relieve portal hypertension and esophageal varices; many patients with severe liver disease do not have portosystemic shunts, neurologic abnormalities, asterixis, or triphasic waves; metabolic diseases also cause excess ammonia that produces identical syndrome

**Clinical features of PSE:** confusion and rapidly developing unresponsiveness; postural and goal directed action tremors; asterixis and myoclonus (nearly always present); progressing forms show severe irreversible dysarthria with dystonia; hepatic paraplegia; originally considered myelopathy, but no primary disease of spinal cord present; focal encephalopathy (longest axon affected first by metabolic disease) with stiffness of legs, up-turned toes, and spasticity with little bladder or bowel disturbance; condition resembles primary lateral sclerosis; only source of ammonia or portosystemic shunts required to produce syndrome

**Laboratory features:** usually hyperammonemia; level of ammonia correlates well with syndrome within given patient but not from patient to patient; hypoxemia and respiratory alkalosis common; CSF levels of false neurotransmitters, eg, glutamine and octopamine elevated (not causal); triphasic waves not specific but characteristic; T1 hyperintensity seen in basal ganglia on magnetic resonance imaging (MRI)

**Ammonia hypothesis:** supporting facts — exposure to ammonia in ciirrhotics causes confusion; dietary protein and GI bleeding exacerbate PSE; inherited hyperammonemias cause same neuropathology (pseudolaminar necrosis and Alzheimer type 2 glial cells); low-ammonia diet, neomycin, lactulose (artificial disaccharide that facilitates removal of ammonium in stool), or glial cells fail, blood-brain barrier fails and leaks, causing abnormalities seen on MRI; previously, children exposed to aspirin developed acute PSE with massive brain edema

**GABA-benzodiazepine hypothesis:** benzodiazepine receptors found in paraffin-embedded brains before introduction of chlordiazepoxide (eg, Librium, Mitran, Poxi) suggest existence of natural benzodiazepines; treatment with benzodiazepine-receptor antagonist flumazenil helpful; GABA receptor modulated allosterically by benzodiazepines, barbiturates, and endogenous peptides (diazepam binding inhibitor)

**Unifying hypothesis:** brain does not have urea (ornithine-arginine-citrulline) cycle to detoxify ammonia; instead, uses conversion of glutamate to glutamine; disease affects astrocytes, not neurons; astrocytes important for detoxification; astrocyte foot processes produce blood-brain barrier; ammonia acts as neurotoxin; metabolized in glial cells by glutamate-glutamine detoxification system; when ammonia levels elevated (from, eg, lysis of plasma cells, metabolic disorders, consumption of external ammonia, liver disease, portosystemic shunts), cells upregulate and prevent failure of neurons; if system saturated, glial cells fail, blood-brain barrier fails and leaks, causing abnormalities seen on MRI; previously, children exposed to aspirin developed acute PSE with massive brain edema

**Treatment:** in liver failure, replace liver or wait for recovery (transplantation completely reverses syndrome); repair or remove any extrahepatic shunts; treat symptoms

Ammonia toxicity in myeloma (Nott et al, 2007): plasma cells rich source of ammonia; toxicity may occur in untreated myeloma; seen more often after lysis of plasma cells by acute therapy with monoclonal antibody and cytotoxic drugs; treat with lactulose; serum ammonia drops and symptoms disappear

**Lupus with Sjögren Syndrome Plus Malnutrition**

Case example: African woman bitten on foot by cat; developed burning pain and weakness in leg; later, developed weakness in other leg and gradually in arms; no facial or respiratory involvement; also cooked with cassava

**Presentation:** severe cachexia despite no loss of appetite; muscle wasting and contractures in all 4 limbs; no abnormalities above neck; tetraparesis (legs worse than arms) with flaccidity; loss of vibration and position sense in all 4 limbs; no change in sensation at any level on trunk; reflexes absent

**Serum analysis:** albumin 1.8 g/dL, iron 16 μg/dL, total iron binding capacity (TIBC) 149 μg/dL, ferritin 1224 ng/mL; vitamin B₁₂ normal (cobalamin deficiency requires >4 yr of starvation); folate 6.8 ng/mL; copper normal; zinc slightly low; sedimentation rate 111 mm/hr; C-reactive protein 171.9 mg/L (patient had active abscesses in both buttocks); white blood cell count 6.45/μL; anemia; platelets 315,000/μL

**CSF analysis:** glucose 29 mg/100 mL; protein slightly elevated; 2 white cells/μL

Other findings: all cultures negative; all microbiology tests negative; abscesses disappeared after treatment with antibiotics; pericardial effusion (with tamponade) developed

**Electroencephalography-direct conduction studies:** revealed no sensory or motor responses in median (bilaterally), ulnar, or sural nerves; results on nerve conduction interpreted as abnormal because of inability to record sensory or motor responses except for left radial; results of electromyography considered abnormal for fibrillation potentials and decreased interference; concluded severe polyneuropathy present with distal degeneration of sensory and motor axons (myelopathy not excluded)

**Imaging:** spine — longitudinal extensive intramedullary signal seen beginning at C2 and extending entire length of cord; column strikingly posterior; brain — bilateral lesions seen in globus pallidus; symmetrical T2 prolongation of globus pallidus bilaterally. Orally seen in CO toxicity, disorders of oxygen metabolism, or other toxicity, eg, cyanide

**Immunology results:** antinuclear antibody (ANA) 1:2560; double-stranded DNA value greater than limit of assay; extremely high anti-Ro and anti-La (Sjögren-specific antibodies A and B); elevated anticardiolipin IgG (16 IgG phospholipid units) and IgM (44 IgM phospholipid units); low values for C3 and C4; elevated anticardiolipin IgG (16 IgG phospholipid units) and IgM (44 IgM phospholipid units); low values for C3 and C4; negative results for antibodies against Smith antigen, ribonucleoprotein, antineutrophil cytoplasmic antibodies, antibodies against rheumatoid factor, and neuropeptidin optica (NMO) IgG

**Results of renal biopsy:** showed active immune-complex renal disease characteristic of lupus with Sjögren syndrome

**Outcome:** condition diagnosed as lupus with Sjögren syndrome, severe malnutrition, and probable intoxication with cassava; Sjögren often considered syndrome of dry eyes and mouth (sicca syndrome) by rheumatologists; double-stranded DNA test not sensitive but highly specific for lupus; Sjögren syndrome seen as idiopathic, cryptogenic disease and as complication of or in association with lupus; patient suffered from ganglionopathy (secondary degeneration of bipolar axon belonging to dorsal root ganglion cell) with myelopathy secondary to ganglionopathy; encephalopathy also possible, although not present in case example; patient also had nephropathy and pericardio-
Manifestations of Sjögren syndrome: may or may not include dry eyes and mouth (sicca syndrome); possible to diagnose Sjögren syndrome of nervous system on basis of antibody tests and clinical picture; patients may have numbness of face; often have numerous other antibodies, eg, ANA, anti-SSA, anti-SSB, NMO-IgG, antithyroid antibody

Questions and answers: reason for rapid onset — extremely rapid onset seen in this case not unusual for lupus; speaker considers illness in similar category to ovarian teratoma, eg, benign autoimmunity; role of lip biopsy — if condition suggests Sjögren syndrome and other methods of diagnosis inconclusive, speaker recommends biopsy of minor salivary gland; biopsy results usually not specific enough to diagnose Sjögren syndrome in absence of positive results for anti-SSA and anti-SSB

Acknowledgements

Dr. Samuels spoke at the American Academy of Neurology’s 65th AAN Annual Meeting, held March 16-23, 2013, in San Diego, CA, and presented by the American Academy of Neurology. The AAN’s Annual Meeting is available as a comprehensive digital library of content with more than 550 hours of presentations, including access to syllabus materials and audio presentations that are synchronized with the slides presented at the meeting. For more information, or to order your copy, visit www.audiodigest.org/aan13. For information on AAN’s 2014 Annual Meeting, scheduled for April 26 to May 3, 2014, in Philadelphia, please visit www.aan.com/cme-and-moc.

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- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes

Suggested Reading

1. Which of the following is the cause of osmotic demyelination?
   (A) Alcohol toxicity  
   (B) High levels of serum urea nitrogen (BUN)  
   (C) High levels of blood glucose  
   (D) Iatrogenic

2. Choose the correct statements about hyponatremia.
   1. Isotonic hyponatremia is artifactual and does not require treatment
   2. Hypertonic hyponatremia is caused by the presence of external osmoles
   3. Hypervolemic hyponatremia is caused by diuretics or salt wasting
   4. Hypovolemic hyponatremia is caused by liver, renal, or heart failure
   5. Isovolemic hyponatremia is commonly caused by inappropriate secretion of antidiuretic hormone
      (A) 1,2,3  
      (B) 2,3,4  
      (C) 1,2,5  
      (D) 1,2,3,4,5

3. Which of the following is the appropriate treatment of chronic hyponatremia of >48 hr duration?
   (A) Treat with water restriction  
   (B) Treat immediately with hypertonic saline because of risk for cerebral edema and rapid death
   (C) Treat immediately with normal saline
   (D) None of the above

4. Cefepime and ceftazidime may cause antibiotic neurotoxicity despite low permeability across the blood-brain barrier.
   (A) True  
   (B) False

5. Choose the most likely diagnosis for a patient with myeloma who has undergone chemotherapy, has normal liver function,
   and has developed acute encephalopathy with asymmetrical asterixis, triphasic waves on electroencephalography (EEG),
   and hyperammonemia.
   (A) Antibiotic encephalopathy  
   (B) Portosystemic encephalopathy  
   (C) Osmotic demyelination  
   (D) Infectious encephalopathy

6. Portosystemic encephalopathy is caused by elevated levels of octopamine in the cerebral spinal fluid.
   (A) True  
   (B) False

7. All the following are appropriate treatments for portosystemic encephalopathy, except:
   (A) Transplantation of a failed liver  
   (B) Removal of any extrahepatic shunts  
   (C) Prescription of a high-protein diet  
   (D) Administration of dietary lactulose

8. The double-stranded DNA test has ______ for lupus.
   (A) High sensitivity and high specificity  
   (B) High sensitivity and low specificity  
   (C) Low sensitivity and high specificity  
   (D) Low sensitivity and low specificity

9. All the following are typical manifestations of Sjögren syndrome, except:
   (A) Dry eyes and mouth  
   (B) Numbness of the face  
   (C) Pericardopathy  
   (D) Symmetrical T2 prolongation of the globus pallidus on imaging

10. Rapid onset of neurologic symptoms is not unusual for which of the following disorders?
    (A) Systemic lupus erythematosus  
    (B) Sjögren syndrome  
    (C) Cobalamin deficiency  
    (D) All the above

Answers to Audio-Digest Neurology Volume 04, Issue 19: 1-D, 2-A, 3-B, 4-B, 5-A, 6-C, 7-A, 8-C, 9-A, 10-B

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