Potential Conflicts of Interest

- Director of Medical Education and 25% owner of Lighthouse Learning, LLC, a for-profit medical curriculum development company
- Spouse, Susan F. Pioli, V.P. for Faculty Development and 25% owner, Lighthouse Learning, LLC
- Co-Author, Adams and Victor’s Principles of Neurology
- Co-Editor-in-Chief, Samuels’s Manual of Neurologic Therapeutics
- Co-Editor, Office Practice of Neurology
- Founding Editor-in-Chief, emeritus, Journal Watch Neurology
- Co-Author, Shared Care in Neurology
- Editor, Hospitalist Neurology

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders
Immune Mediate Disorders
- Lupus
  - Lupus "cerebritis"
  - Lupus "vasculitis"
  - Steroid encephalopathy
- Sjögren syndrome
- Anti-phospholipid antibody syndrome
- Brain disease (Hashimoto encephalopathy)
- Paraneoplastic syndromes
  - Intracellular antigens
  - Cell surface antigens
  - No known antigens (e.g. Ophelia syndrome)
- Benign auto-antibody mediated syndromes
  - Voltage gated potassium channel
  - NMDA
- Vasculitis of the Central Nervous System
  - Primary CNS (Isolated Angitis of the Nervous System)
  - Secondary to systemic vasculitis (perianteritis, Chung-Strauss, etc)
  - Secondary to infections (TB, aspergillus, mucormycosis)
  - Secondary to tumors (intravascular lymphoma)

Inflammation
Some inflammation is an example of neurovisceral control and provides a link to hypercoagulability.

Traditional Inflammation Definition
A localized protective response elicited by injury or destruction of tissues that serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue, characterized in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), and swelling (tumor), and histologically involving a complex series of events, including dilatation of arterioles, capillaries and venules, with increased permeability and blood flow, exudation of fluids, including plasma proteins, and leukocyte migration into the inflammatory focus.

Tumor Necrosis Factor-α
- 17,000 dalton cytokine
- Released from activated macrophages
- Induces calor, dolor, rubor and tumor
- Induces mononuclear cells to release other cytokines (interleukin 1, interleukin 18, high mobility group B1) as well as nitric oxide and oxygen free radicals
- The net effect is prolonged inflammation and ongoing tissue damage with induction of thrombosis and capillary leakage
Infliximab

- A monoclonal antibody directed against TNF-α
- Useful in disorders in which there is evidence of chronic pathologic elevation of TNF-α (e.g. fistulizing Crohn, rheumatoid arthritis)

Controlling the Effects of TNF-α

- Fragments of TNF-α receptors, released from immune cells, bind and inactivate TNF-α
- Adrenal glucocorticoids, epinephrine and α-melanocyte stimulating hormone inhibit cytokine synthesis and/or interfere with signal transduction
- The nervous system provides a critical link between the afferent inflammatory signals and the efferent anti-inflammatory response

The Inflammatory Reflex

- The sensory (afferent) limb
  - Humoral system via circumventricular organs
  - Neural system in afferent fibers in the Vagus (X) nerve
- The motor (efferent limb)
  - Humoral system via the hypothamic-pituitary-adrenal axis
  - Neural system in efferent fibers in the Vagus (X) nerve

Mechanism of the Efferent Limb of the Inflammatory Reflex

- Vagal firing results in release of acetylcholine into all visceral organs including those in the reticulo-endothelial system
- Acetylcholine activates a nicotinic α-bungarotoxin-sensitive macrophage acetylcholine receptor
- Activity of this receptor inhibits the release of TNF-α, IL-1, and IL-18
Relationship Among Inflammation, Atherosclerosis and Hypercoagulability

- Inflammation is found at the site of plaque rupture
- Some inflammatory markers predict MI and Stroke
- Statin drugs may be anti-inflammatory
- Heparin may be anti-inflammatory

Inflammatory/Hypercoagulability Markers

**Arterial Side**
- Fibrinogen
- Factor VII
- Von Willebrand factor
- tPA
- Lipoprotein a
- TNF-α
- IL-6
- Serum amyloid A
- C-reactive protein
- Homocysteine
- D-dimer

**Venous Side**
- Factor V Leiden
- Prothrombin gene mutation
- Factor VIII
- Protein C
- Protein S
- Homocysteine
- D-dimer

Neuro-Inflammatory Diseases?

**Old ideas**
- Meningoencephalitis
- Multiple sclerosis
- AIDP and CIDP
- Polymyositis
- Abscess
- Mycotic aneurysm
- Neuropsych lupus
- Sjogren syndrome
- CNS vasculitis
- RA/JRA/Still disease

**New ideas**
- Migraine
- Stroke
- Alzheimer disease
- Epilepsy
- Parkinson disease
- ALS
- TRAPS (TNFα related antibody periodic syndromes)

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- *Endocrine Disorders*
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders
Endocrine Disorders

- Hypothyroidism & myxedema-ataxic encephalopathy
- Hyperthyroidism and thyroid storm
- Pituitary apoplexy- headache→ panhypopituitarism
- Cushing disease and syndrome
  - Steroid induced encephalopathy
  - Primary or Secondary
- Pancreatic encephalopathy (questionable entity)
- Hypoglycemia – must be severe (< 30)
  - Acute
  - Chronic recurrent
- Hyperosmolarity (usually related to hyperglycemia, hypernatremia or iatrogenic)

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
  - Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders

Neoplastic Disorders

- Glioma and gliomatosis
- Lymphoma, including intravascular lymphoma (primary and secondary)
- Metastases
- Chemotherapy induced neurotoxicity
- Radiation induced neurotoxicity
- Malnutrition

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies
Vitamin Deficiencies

- Vitamin B1 (thiamine)
  - Alcoholism
  - Cancer and cancer Rx induced malnutrition
  - Bariatric surgery

- Vitamin B12 (cobalamin)
  - Autoimmune gastritis
  - Enzymatic blockade (nitrous oxide)
  - Parasitic (D. Latum)
  - Malnutrition

- Others are very rare in developed countries

Intoxications

- Alcohols
  - Ethyl
  - Methyl
  - Ethylene glycol
- Carbon monoxide
- Toluene
- Acetylcholinesterase Inhibitors
- Opioids
- Barbiturates
- Stimulants
- Anticholinergics
- Salicylates
- Aluminum
- Lead
- Mercury
- Thallium
- Calcineurin Inhibitors
  - Cyclosporine
  - FK 506 Derivatives (tacrolimus, sirolimus, etc)

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders
Renal and Electrolyte Disorders

• Acid-Base Disorders
  – Metabolic acidosis and alkalosis
  – Respiratory acidosis and alkalosis
• Uremia
• Dialysis encephalopathy (dementia)
  – Aluminum toxicity
  – Spongiform (prion-like) pathology
• Osmolarity disorders
  – Hyperosmolar states
  – Hypo-osmolar states
• Osmotic demyelination
  – Central pontine myelinolysis
  – Extrapontine myelinolysis

Brain MRI showed a T2 hyperintense lesion in the central pons.

Brain MRI showed T2/FLAIR hyperintense lesions in the bilateral thalami and basal ganglia.

The central pontine lesion is quite striking on T1 sequences as well.
### Hyponatremia: General Principles

All hypotonicity is associated with hyponatremia, but not all hyponatremia is hypotonic

- **Hypertonic**: external osmoles (e.g., mannitol)
- **Hypotonic**
  - Hypervolemic: edematous (e.g., liver, renal, heart failure)
  - Hypovolemic: diuretics; blood loss; Salt wasting nephropathy including cerebral form; Addison disease
- **Isotonic**: pseudo-hyponatremia (e.g., lipid; protein)
  - Isovolemic: osmotic (e.g., hyperglycemia; reset osmostat; spinal cord injury; hypothyroidism; massive polydipsia; SIADH (lung, CNS, or inflammatory disease, such as Guillain-Barre syndrome)

### Management of Hyponatremia

- **Isotonic**: no treatment
- **Hypertonic**: remove external osmoles, if possible
- **Hypotonic**
  - Hypervolemic: sodium restriction and Rx of disease
  - Hypovolemic: volume (including Na) admin.
  - Euvolemic
    - Acute (less than 48 hours): hypertonic (3%) saline
    - Chronic (longer than 48 hours): water restriction; loop diuretics; demeclocycline or lithium; arginine vasopressin (ADH) antagonist, conivaptan (Vaprisol)

### Rate of Correction of Hyponatremia

Depends on Rate of Its Development

- In acutely developing (less than 48 hours) hyponatremia, the brain cells will swell, causing increased intracranial pressure that can be life threatening.
- In chronically developing hyponatremia, the brain is the only organ that compensates by extruding osmoles. If, upon this compensated substrate, a hyperosmolar fluid is administered (even normal saline), then the brain cells will rapidly shrink, causing osmotic demyelination (formally known as central pontine myelinolysis).

### Acute vs Chronic Hyponatremia

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>A few hours</td>
<td>Day, weeks or months</td>
</tr>
<tr>
<td>No time for compensation</td>
<td>Solute extruded</td>
</tr>
<tr>
<td>Brain edema is problem</td>
<td>Rapid correction causes brain shrinkage</td>
</tr>
<tr>
<td>Hypertonic saline required</td>
<td>Hypertonic saline is contraindicated</td>
</tr>
</tbody>
</table>
Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders

Hematologic Disorders

- Iron Deficiency (Ekbom syndrome)
- Hypercoagulability (Trousseau syndrome)
- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated Intravascular Coagulation (DIC)
- Hyperviscosity
- Bing-Neel Syndrome (the encephalopathy of Waldenstrom disease)
- Bleeding diathesis
- Hemoglobinopathies with moy-a-moya
- Extramedullary hematopoiesis

Hemophilia

Acute Promyelocytic Leukemia with Subcortical Hemorrhages
Platelet count was 20K
Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- **Hepatic Diseases**
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders

---

Hepatic Disorders

- Acute Hepatic Encephalopathy
- Complications of Hepatic Transplantation
- Chronic Portosystemic Encephalopathy
  - Wilson disease
  - Non-Wilsonian hepatocerebral degeneration
- Porphyria
### The Hepato-Cerebral Syndromes

- Acute hepatic encephalopathy
- Recurrent, reversible hepatic encephalopathy
- Chronic progressive irreversible hepatic encephalopathy
  - Hereditary hepato-lenticular (Wilson, 1912)
  - Acquired hepato-cerebral (van Woerkom, 1914)

### Hepatic Encephalopathy is due to Porto-systemic shunts

- Porto-systemic encephalopathy (PSE) can be seen with no liver disease
- Porto-systemic shunting may be intra-hepatic (as in some hepatic tumors) or extra-hepatic (as with Eck’s portocaval fistulas)
- Severe liver disease without porto-systemic shunts may produce no neurological disorder and no characteristic pathology

### Clinical Features of PSE

- Mental disorder (confusion to coma)
- Postural and goal directed action tremors
- Asterixis/myoclonus
- Dysarthria
- Dystonia
- Supranuclear pyramidal disorder characterized by spastic leg weakness, hyper-reflexia and Babinski signs (hepatic paraplegia)
Laboratory Features of PSE

- Hyperammonemia (poor correlation with signs)
- Hypoxemia is common
- Respiratory alkalosis
- Elevated CSF glutamine
- EEG triphasic waves (insensitive and non-specific)
- MRI T1 hyperintensity in basal ganglia

Potential Causes of PSE that have not panned out

- Decreased cerebral oxygen uptake
- Decreased cerebral blood flow
- Increased alpha-keto acids in the blood
- Increased blood lactate
- Respiratory alkalosis (due to intra-pulmonary shunts)
- Hypoglycemia
- Hypokalemia
- Octopamine & phenylethenolamine as false transmitters
- Mercaptans (the substances that produce fetor)

The Major Theories

- The Ammonia Hypothesis
  - Ammonia exposure in cirrhatics causes confusion
  - Dietary protein and GI bleeding exacerbates PSE
  - Inherited hyper-ammonemia causes same neuropathology
  - Low ammonia helps patients (diet, neomycin, lactulose)
- The GABA-Benzodiazepine Hypothesis
  - Benzos found in pre-Librium parafin embedded brains
  - Flumazanil, a benzodiazepine receptor antagonist, helps somewhat
  - GABA receptor is modulated allosterically by benzos, barbiturates and endogenous peptides derived from the diazepam binding inhibitor (DBI)
Unifying Hypothesis of PSE

- Ammonia is a neurotoxin
- Ammonia is metabolized in glial cells using the glutamate glutamine detoxification system
- Alzheimer II glia are a manifestation of the up-regulation of this system under conditions of high ammonia
- When the system is saturated, glial cells fail, leading to ammonia toxicity, cerebral edema and neurotransmitter imbalance with activation of the GABA receptor
Treatment of PSE

• In liver failure, await recovery or replace the liver
• Repair or remove intra- or extra-hepatic shunts
• Symptomatic therapy
  – Lactulose (a synthetic disaccharide)
  – Dietary protein restriction
  – Prevent or treat GI bleeding (protein load)
  – Flumazenil
  – Dopamine agonists, mainly for hepatic paraparesis

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

• Immune Mediated Disorders
• Endocrine Disorders
• Neoplastic Disorders
• Vitamin Deficiencies
• Intoxications
• Renal and Electrolyte Disorders
• Hematologic Disorders
• Hepatic Diseases
  • Gastrointestinal Disorders
• Infectious Diseases
• Cardiovascular Disorders
• Ob/Gyn disorders
• Pulmonary Diseases
• Hydrocephalus
• Psychiatric illnesses
• Thermal control disorders

Gastrointestinal Diseases

• Celiac disease (ataxic encephalopathy)
• Complications of bariatric surgery
• Pancreatic encephalopathy (doubtful)
• Autoimmune gastritis (pernicious anemia)
### Infectious Diseases

- Endocarditis
- HIV encephalitis
- Chronic meningoencephalitis
- Prion diseases
- Neuro-Borreliosis (Lyme Disease)
- Neuro-Erlichiosis
- Neuro-Babesiosis
- Neuro-Cysticercosis
  - Intraparenchymal
  - Recemose

### Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders

### Cardiovascular Diseases

- Left Atrial Myxoma
- Cardiac Tumors
- Non-bacterial Endocarditis
- Hypertensive encephalopathy
  - Acute
  - Subacute
  - Chronic
- Heart failure encephalopathy

### Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders
Ob/Gyn Diseases

- Toxemia of Pregnancy
- Cortical Vein and Dural Sinus Thrombosis
- Ovarian Teratoma anti-NMDA Disease

The Unifying Hypothesis of Reversible Posterior Leukoencephalopathy (RPLE) aka Posterior Reversible Encephalopathy Syndrome (PRES)

- Causes are:
  - Toxemia and HELLP
  - Hypertension
  - Cyclosporine and FK drugs (calcineurin inhibitors)
  - TTP and hemolytic uremic syndrome

- Common features are:
  - Hypomagnesemia
  - Endothelial damage
  - Relative cerebral hypertension

- Endothelial dysfunction is caused by:
  - Physical damage (barotrauma)
  - Toxic damage
  - Immune mediated damage
Endothelial Diseases
(sometimes called reversible posterior leukencephalopathy or posterior reversible encephalopathy syndrome)

- Toxemia of Pregnancy
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Hemolytic anemia with elevated liver function tests and low platelets (HELLP) syndrome
- Hypertensive encephalopathy
- Post-carotid endarterectomy hemisphere syndrome
- Calcineurin inhibitor toxicity (cyclosporine & FK drugs)
- Hypomagnesemia
Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
  - Pulmonary Diseases
  - Hydrocephalus
  - Psychiatric illnesses
  - Thermal control disorders

Pulmonary Diseases

- Chronic hypoxia and hypercarbia

- Lung Cancer Associated Neurologic Disorders
Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
  - Hydrocephalus
  - Psychiatric illnesses
  - Thermal control disorders

Hydrocephalus

- “Normal Pressure” Hydrocephalus
- High Pressure Hydrocephalus

Psychiatric Disorders

- Depression and Bipolar Disease
- Ganser Syndrome (approximate answers)
- Hysteria
- Schizophrenia
- Anxiety and phobias
- Malingering and Factitious illness
Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric Illnesses
- Thermal control disorders

Thermal Control Disorders

- Neuroleptic Malignant Syndrome
- Serotonin Syndrome
- Malignant Hyperthermia
- Hyperthermia
  - Heat exhaustion
  - Heat shock
  - Heat stroke
- Hypothermia
  - Exogenous
  - Hypothalamic disease

Initial Evaluation of Subacute Encephalopathy to Exclude Medical Causes

- Careful history for potential drugs and toxins
- General physical examination
- CBC, Differential, RBC Indices
- HIV
- ESR, CRP, ANA, RF, SSA, SSB
- SPEP and Immunofixation
- TSH, FBS, Hemoglobin 1c
- LFT’s, RFT’s, Electrolytes, Calcium
- MRI brain
- EEG
- CSF for cells, protein, oligoclonal bands
- Toxic Screen (add lead, mercury if suspected)
- Cobalamin level

Cases
36 Year Old Woman

- 36 year-old woman with a PMHx of asthma and hypothyroidism, TBI at age 3 with subsequent cognitive deficits but no seizures (apparently in coma for several days) admitted following several days of headache, unsteady gait and falls. She had a witnessed generalized tonic-clonic seizure, and was taken to an ED. Seizure with reported head and eye deviation to the right. Reports also of significant bilateral intermittent tremor, worse with held postures.

- CSF showed a normal glucose, elevated protein, 9 WBCs (lymphocytic). Head CT revealed no acute process. She was intubated in the emergency department and transferred to the neurology service.

36 Year Old Woman

- Repeat LP showed a markedly elevated protein, and mildly elevated WBCs (lymphocytic). MRI revealed no convincing evidence of encephalitis, stroke, or mass. Initial impression was that of aseptic meningitis, thus pt was started on acyclovir for presumed HSV encephalitis, ultimately PCR negative.

- Neurology consult service felt that viral meningo-encephalitis was still the most likely etiology.
- Continued supportive care with daily improvement in her mental status.
- At the time of discharge she was back to her mental status baseline.
- Discharge was delayed by continued headaches which were worsened by LP and treated by both IV caffeine and eventual blood patch.

- Ultimately it was thought that the patient likely had a viral meningitis which led to a seizure in the context of an abnormal brain substrate s/p TBI.
- Phenytoin taper was planned as an outpatient per the Neurology consult service.

36 Year Old Woman

- Readmitted one month later to Neuro ICU (intubated at OSH) for GTC seizure, again with right head/eye deviation. Course tremors in UE persisted after discharge. CSF showing 9 WBCs lymphocyte predominant, culture and viral studies negative. A CT, MRI/MRA/MRV were negative.

- She was afebrile, without leukocytosis, and was hemodynamically stable. LFTs WNL.

36 Year Old Woman

- Hospital course: (+) hallucinations. Waxing and waning mental status and aphasia.
- After 2-3 days, was appropriately interactive with mental status findings (impaired memory and attention) consistent with her baseline.
- Minimal tremor evident with intention only and minimal gait instability.
- EEG: no epileptiform d/cs. Lab and imaging w/u negative.
- Diagnosis: ongoing subacute aseptic meningoencephalitis since her last admission in 7/07 with similar CSF findings suggestive of aseptic picture and ongoing seizure tendency suggestive of meningoencephalitis.
- Continued phenytoin, discharged home, clinically stable.
36 Year Old Woman

- HIV NEGATIVE
- ESR 30, TSH 3.30
- Lactic acid 2.0
- ANA, HIV, Bartonella, WNV, Malaria, Babesia, serum RPR were all negative. Porphyria screen negative. CSF 7/22—WBC 13 (lymphs), TP 114
- Ceruloplasmin was normal, copper level normal.

36 Year Old Woman

- CSF: Glucose 96, Total Protein 109, RBC 1, WBC 9 lymphocytic. culture negative, VZV, EBV, CMV, HSV negative. EEE, WNV negative, VDRL negative, crypto negative.
- Tox screens negative
- Urine heavy metals negative
- Porphyrins negative

36 Year Old Woman

- Readmitted again 5 days after discharge for persistent altered mental status. More confused, often aphasic or answering in 1-2 word phrases. Myoclonic jerking vs asterixis on exam. Gait unsteady at home. LFTs elevated to ~ 100 from 20s. No new seizures.
- CSF: WBC 3, TP 116, GS/culture negative, HSV/EBV/CMV/VZV negative, crypto negative.
- Chest CT mild bilat hilar lymphadenopathy, Abd CT negative.
- Serum anti-thyroperoxidase AB > 1000

36 Year Old Woman

- Diagnosis: Hashimoto’s Encephalopathy
  (Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis)
- Started methylprednisilone IV 1 g X 5 days with plan to do very slow PO taper. Mental status vastly improved, brighter, back to baseline per family, no speech deficit.
- Discharged to f/u for steroid management, repeat EEG
- Returned to normal; steroids slowly tapered
Brain Disease

Lord Brain:
Distinguished British Neurologist, prolific writer

Described first case of episodic encephalopathy associated with Hashimoto’s Thyroiditis in 1966

Brain Disease

In the following case-report, however, the apparent onset of Hashimoto’s disease itself led to hospital investigations, and was followed within a few weeks by an extraordinary and puzzling neurological illness which waxed and waned for over a year. No neurological illnesses other than myasthenia gravis (Daly and Jackson 1964, Simpson 1964, Singer and Sahay 1966) have been hitherto reported in association with Hashimoto’s disease, though one of us has seen Hashimoto’s disease associated with exophthalmic ophthalmoplegia.

Brain Disease

• Brain’s Case study of a 40 year-old male “coachbuilder” with seizures, disorientation, frequent alternating hemiparesis
  - Transient episodes, associated with elevated total protein in CSF and transient EEG abnormalities. 12 episodes total, complete recovery.
  - (+) clinical hypothyroidism, (+) antithyroid antibodies, (-) antibrain antibodies, receiving adequate thyroxine therapy
  - “Antibodies studies in future cases of unexplained encephalopathy should show whether we have described a syndrome or a coincidence.”
Brain Disease

- 1953: Found lying "deeply unconscious" with lacerated scalp, admitted to 2 different hospitals, slow but complete recovery, CSF with TP 50, WBC 6. Presumed unobserved head injury. Remained well for next 7 years
- 1960: While undergoing negative evaluation for slight hemoptysis, found to be "sleepy, podgy, sensitive to cold...goiter, puffy face." Clinical dx of Hashimoto's Thyroiditis, confirmed by positive thyroid antibodies, started Thyroxine.

Brain Disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (mg. per 100 ml.)</td>
<td>100</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>190</td>
<td>100</td>
<td>240</td>
<td>50</td>
</tr>
<tr>
<td>Cells (mononuclear per c.m.m.)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>4</td>
<td>8</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Lange colloidal gold</td>
<td>11110000</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
<td>2233321</td>
<td>0*</td>
<td>0*</td>
<td>0*</td>
</tr>
</tbody>
</table>

Brain Disease

- Terminology
  - Hashimoto's Encephalopathy
  - Steroid-Responsive Encephalopathy
    Associated with Autoimmune Thyroiditis (SREAT)
- > 100 cases now reported since 1966
Brain Disease

- Thyroid function usually normal/treated, or subclinical hypothyroidism
- EEG abnormal, MRI usually normal, CSF with increased protein and minimal if any leukocytosis and other infectious/inflammatory tests negative
- No relationship between severity of thyroid/lab abnormality and severity of neurologic syndrome
- Endocrinologists: “No proof for a direct relationship between thyroid autoimmunity with antithyroid Abs and pathogenesis of the encephalopathy—Thyroid autoimmunity does not necessarily CAUSE the encephalopathy.
  - No proof that these particular autoantibodies react against antigens in the brain.


Brain Disease

- SREAT should be considered in any patient with elevated anti-thyroperoxidase antibodies in the serum with clinical evidence of fluctuating, otherwise unexplained encephalopathy. Euthyroid vs hypothyroid should not influence these considerations—no correlation.

Castillo et. al. Steroid-Responsive Encephalopathy Associated With Autoimmune Thyroiditis. ARCH NEUROL/VOL 63, FEB 2006

Brain Disease

Take-Home Message

Brain disease (steroid responsive encephalopathy) is one of many inflammatory, presumably immune mediated illnesses, that are associated with a number of markers of auto-immunity (e.g. Anti-thyroperoxidase, Anti-Nuclear, Rheumatoid factor, Sjögren specific, Anti-mitochondrial, etc). Steroid responsiveness is usually striking.

80 Year Old Man

An 80 year old man, previously healthy except for a CABG eight years earlier, got lost twice while driving. He had the presence of mind to use his GPS to find his way home from ordinarily familiar locations. His family thought there was a subtle loss of memory that had become evident over the past month.
80 Year Old Man

His neurological examination showed only very mild memory impairment. The geographical disorientation, noted by history, was not demonstrable by exam. There was no aphasia, agnosia or apraxia and his cranial nerve, motor, sensory, coordination and reflex exam were all normal. His general physical exam revealed a 6cm non-tender mass in the right buttock. He believed it had been then for some time.

Biopsy of the gluteal mass revealed a B cell lymphoma
80 Year Old Man

The hematologists stated that the lymphoma was of sufficiently low grade that they would ordinarily not treat it were it not for the brain lesion.

80 Year Old Man

Another diagnostic test was obtained.

Glioblastoma Multiforme

Lessons from the 80 Year Old man

• The parsimony of nature only goes so far

• The appearance of the brain lesion by MRI and the neurological history are so characteristic of GBM that the low grade systemic lymphoma should have been considered a separate problem
An Anesthesiologist

A 55 year old right handed man noticed the gradual onset of paresthesias in both hands accompanied by awkwardness in carrying out tasks that required fine motor skills. After several months of symptoms, he reported the problem to his primary care physician who diagnosed carpal tunnel syndrome and sent him to an occupational therapist for cock-up splints.

Anesthesiologist continued

Despite using the splints fairly regularly, the symptoms slowly worsened so he was referred to an orthopedic hand surgeon for consideration of carpal tunnel releases. The orthopedic surgeon obtained a cervical spine MRI that demonstrated multilevel cervical spondylosis worst at C4-5 with increased signal in the cord, interpreted as evidence of significant compression. The orthopedic surgeon referred the patient to a spine neurosurgeon who felt that the cervical spondylosis was the cause of some or all of the hand symptoms.

The Anesthesiologist’s MRI

An anterior decompression and fusion was performed without apparent difficulty, but in the recovery room the patient was nearly tetraplegic; very weak in all four extremities but without a sensory level on the trunk. A repeat MRI showed no hemorrhage but the patient was returned to the operating room for exploration of the site where a very small amount of epidural blood was found.
Anesthesiologist continued

Post-operatively the patient partially recovered but was left with some weakness in all four extremities, a sensory ataxia and spasticity in his legs that was sufficiently severe so that he could not work effectively. He complained that, in addition to his awkwardness, he had developed bradypnea. He developed a very painful tongue, which he and his doctors believed was a herpes virus infection. He became depressed.

Anesthesiologist continued

Because of progressive worsening he was advised to have a repeat cervical spine exploration. After admission, the neurosurgical resident, who had just completed her rotation on neurology, was not satisfied with the diagnosis and obtained a neurology consultation. A neurological examination revealed the following.
A diagnostic test was performed
**Structure of Cobalamin**

**Cobalamin Biology**
- cobalamin is a true vitamin (a pyrole) made by microbes.
- ingested in meat, liver, fish, eggs, milk.
- four forms: hydroxycobalamin, cyanocobalamin, adenosylcobalamin, and methylcobalamin.
- Separated from food with amylase in acid environment.
- bound to intrinsic factor in stomach (parietal cells produce both acid and intrinsic factor).
- IF-CBL complex absorbed in ilium.
- carried by transcobalamins.

**Causes of Cobalamin Deficiency**
- Defective diet (vegans) – difficult to accomplish.
- Defective Absorption:
  - intrinsic factor deficiency (PA, gastrectomy, ageing).
  - intestinal disease (Crohn, sprue, tapeworm).
- Increased metabolic requirement:
  - thyrotoxicosis.
  - pregnancy.
  - neoplasia.
- Enzymatic deficiency or inhibition:
  - inherited.
  - acquired (e.g. nitrous oxide inhibition of methyl transferase).

**Pathogenesis of Cobalamin Deficiency Clinical Syndromes**
- Methylcobalamin (methyltransferase) system:
  - hematologic and GI manifestations.
  - oligodendrocyte function.
  - cyanide toxicity.
  - inhibited by nitrous oxide.
- Adenosylcobalamin (methylmalonyl CoA) system:
  - abnormal fatty acid synthesis.
  - cyanide toxicity.
  - ? inhibited by nitrous oxide.
**Methylcobalamin Enzyme System**

**Adenosylcobalamin Enzyme System**

Valine, Isoleucine, Methionine, Threonine and Odd chain fatty acids

- Propyl-CoA
- Biotin
- Methylmalonyl-CoA
- Vitamin B12
- Succinyl-CoA
- TCA Cycle

**Saturated Long Chain Fatty Acid Synthesis**

**Synthesis of Long Chain Fatty Acids**

1. $\text{Acetyl-CoA}[2] + \text{CO}_2[1] \rightarrow \text{Malonyl-CoA}[3]
2. $\text{Malonyl-CoA}[3] + \text{Acetyl-CoA}[2] - \text{CO}_2[1] \rightarrow \text{Butyryl-CoA}[4]

number of carbon atoms in brackets
Subacute Combined Disease

- Myelinopathy
- Myelopathy (lower cervical at first)
- Peripheral neuropathy late and mild
- Optic neuropathy
- Encephalopathy

Spongy Myelopathy Reminiscent of Retroviral Myelopathy
Diagnosis of Cbl Deficiency

- Blood smear
  - Macrocytosis
  - Hypersegmentation of PMLs
- Radioimmunoassay
  - Cbl ≤ 100 likely
  - Cbl 100-250 possible
  - Cbl ≥ 250 unlikely
- Methylmalonic acid for possible cases
- Microbiological assay (gold standard)
- Schilling test to determine the cause
- Antibodies in probable auto-immune cases
  - Anti-intrinsic factor (specific but insensitive)
  - Anti-parietal cell (sensitive but nonspecific)

Laboratory Studies on the Anesthesiologist

- Hct = 39% (was 41% at first operation)
- MCV = 110
- Cobalamin = 100
- Methylmalonic acid = 3 (n=0-.41)
- Homocysteine = 85 (n=5-14)
- Folate = 17 (n=5-10)
- EMG/NCV: no significant neuropathy

Anesthesiologist continued

- He was treated with cobalamin, parenterally for 10 days followed by orally
- One month later the neurological examination showed the following.
Rather than enlarge further upon the details and results of the treatment of pernicious anemia, I shall now present, with your permission, a motion picture, which will illustrate many points more clearly than I could discuss them here.

Nobel Prizes Related to Cobalamin

- 1934: Whipple, Minot, Murphy – liver cure
- 1964: Hodgkin – x-ray crystallography
- 1965: Woodward – organosynthesis
Anesthesiologist conclusions

• Pernicious anemia (auto-immune gastritis)

• Superimposed nitrous oxide toxicity

• Anesthesia paresthetica

Dementia and Gait Disorder

42 y/o African American teacher became rapidly demented and unable to walk over a two month period. She had a remote history of thyroiditis. A brain biopsy had been suggested by a neurologist. Exam showed severe abulia and inability to walk because of spasticity and proprioceptive problems. Vision was untestable, but discs were pale. She had vitiligo and a horizontal scar on the neck.

Lab Studies in the Teacher

• Hct = 20
• MCV = 115
• Cobalamin = 0  (repeat = 0)
• Folate = 20
• Methylmalonic acid = 4.0
• Homocysteine = 68
• Anti-intrinsic factor antibodies  1:128
• Anti-parietal cell antibodies  1:64
• EMG/NCV: no significant neuropathy

Diagnosis in The Teacher

• Pernicious anemia (auto-immune gastritis)
• Associated other auto-immune conditions
  − Vitiligo
  − Thyroiditis
Treatment and Follow-up on The Teacher

- Treated with parenteral cobalamin for two weeks followed by oral therapy
- Back to work in three months “better than ever”

The Epidemic

- In the 1990’s an epidemic occurred in the western hemisphere
- Over five years 20,000 people were affected by an illness characterized by
  - Progressive blindness
  - Progressive spastic ataxia
  - Progressive deafness

Cuba

The New York Times

May 21, 1993

26,000 Cubans Partly Blinded; Cause Is Unclear

By LAWRENCE K. ALTMAN

A disease that isasts vision and affects the nerves has struck almost 26,000 Cubans, predominantly adult men, health officials in Havana say. The Government has invited foreign experts to investigate.

A neurologist from Columbus University’s medical school who has examined patients in Cuba said the epidemic was apparently caused by a nutritional deficiency, probably a lack of vitamin B1, thiamine.

The Deputy Health Minister of Cuba, Jorge Antoco, has told the World Health Organization that the epidemic began in January 1992, amid harsh economic conditions and natural disasters.

Dr. Astcon said the 30-year trade embargo imposed on Cuba by the United States has been aggravated by an abrupt decline in trade with the former Soviet Union and its allies. Cuba also suffered heavy agricultural and industrial devastation from a tropical storm, “Sustained” the year before.

The epidemic is different from any ever reported, Dr. Astcon said, adding, “We cannot rule out the hand of the enemy in the origins of this disease as long as the cruel and heartless economic embargo remains in effect.”

But American experts said the evidence seemed to point to a vitamin B1 deficiency known as Scurran syndrome, described by a British health officer, Dr. H. Sturman, in Jamaica in 1885.
Cause of The Epidemic
The Strachan Syndrome

- Impoverished diet, poor in B vitamins
- Cyanide toxicity from cigar smoke and cassava
- Alcohol use
- The alcohol-tobacco amblyopia
- Strachan syndrome (William Henry Williams Strachan (1874-1921) describe in WWI starving prisoners of war

Follow up on The Epidemic

A widespread public health program was initiated consisting of oral administration of oral B vitamins (folate, cobalamin, thiamine and pyridoxine). Within six months the epidemic ended and no new cases occurred.

75 Year Old Man

- 75 year old, very active man; ran ranch for children with disabilities; up at 6 am
- Gradual loss of energy, drive, and clarity of thinking; unable to get started in am; (“brain fog”);
  - Self-acknowledged “depression” for 9 months
  - “The depression is fierce”; “A black cloud hanging over my head”; “I don’t take enjoyment in anything”
- No family history of dementia, suicides or depression

75 Year Old Man

- Normal general physical examination
- Normal orientation, trail making, short-term memory, language, praxis, Luria but all slow
- Normal somatic neurological and general exam
- Absent bradykinesia and tremor; normal limb tone
- No grasping; normal walking; toes flexor; no Romberg sign
75 Year Old Man

- Diagnosed with Late Life Depression
  - Escitalopram of minimal help in testiness and multitasking but no change in emotional state

- So a consultation to a psychiatrist is obtained

75 Year Old Man

- Psychiatrist indicated that it was unusual for this degree of depression and asthenia to arise late in life without prior episodes of depression or recent history of major life events (no recent deaths, losses, business reversals, spousal or family difficulties; no alcohol, drugs)

- Psychiatrist colleague orders lab tests:
  - Normal lead and arsenic levels
  - Whole blood mercury level=47 µg/L (Nat. Acad. Sci. recommended level <5)

- Normal levels in wife

75 Year Old Man

- Mercury intoxication is considered very unlikely

- Several antidepressant medications are tried

- Despite this, over the next 6 months, the patient worsens to a slowed, hypoactive state, still with no bradykinesia

75 Year Old Man

- Chelation therapy is begun, and the patient’s symptoms resolved entirely over 6 weeks

- The patient later admitted to using massive amounts (about a pint/day) of over the counter fish oil “to enhance his health and reduce the risk of heart disease”

- His wife did not use these products and was unaware of the amount used by the patient
A 21 year old engineering student is brought to the emergency department by his friends because of staggering gait, lethargy, weakness and slurred speech. The people who brought him to the ED disappeared before any questions could be asked and no past medical history is obtainable.

**Initial Evaluation**
BP = 88/50; HR = 132 (regular)
Heart: a midsystolic click is heard
Lungs: diffuse wheezing
Abdomen: diffusely tender without rebound
Skin: a facial vesicular rash was noted
Neurological exam: awake but confused; could not retain any of three objects in memory for 5 minutes; no aphasia. Reflexes were average in amplitude and equal bilaterally; no Babinski signs.

**Relevant Laboratory Studies**
- Na = 127
- K = 2.0
- Cl = 113
- HCO3 = 4
- BUN = 53
- Creatinine = 1.7
- Calcium = 10.7
- PO4 = 1.4
- Uric acid = 2.3
- Mg = 1.8
- Glucose = 98
- ALT = 65
- AST = 32
- LDH = 201
- Alkaline phosphatase = 78
- Urine Na = 25
- Urine K = 10
- Urine creatinine = 185
- pH = 6.97
- pCO2 = 43
- pO2 = 54

**Which of the Following Would Your Recommend?**
- 0.9% saline
- 0.45% saline with 66 meq/L NaHCO3
- Albuterol
- CT, LP, EEG and MRI
- Plasma hippurate level
- Ethanol infusion and acute hemodialysis
- Skin biopsy with Tzanck preparation
21 Year Old Engineering Student
Acid Base Status

- pH = 6.97 (severe acidosis)
- HCO3 = 4 (metabolic acidosis)
- Anion gap = Na – (Cl + HCO3) = 127 – 117 – 10
- Therefore, this is a severe hyperchloremic non-anion gap metabolic acidosis

21 Year Old Engineering Student
Calculating the A-a Gradient

- A-a = (150-pCO2/0.8) – pCO2
- A-a = (150 – 43/0.8) – 54 = 96 – 54 = 42
- Normal for a 21 year old = 21/4 + 4 = 9
- Therefore, there is a huge A-a gradient probably reflecting lung that is perfused but not well ventilated (diffuse wheezing)

21 Year Old Engineering Student
Pathogenesis

- Toluene inhalation causes a metabolic acidosis which causes an encephalopathy
- Toluene inhalation causes bronchospasm which leads to hypoxemia with a large A-a gradient, which aggravates the encephalopathy
- Hyponatremia and hyokalemia are due to excretion of sodium and potassium hippurate
21 Year Old Engineering Student Toluene Poisoning

- Non-anion gap metabolic acidosis with hyponatremia and hypokalemia
- May be due to direct toxicity-induced distal renal tubular acidosis
- An alternative explanation is overproduction of hippurate, a major toluene metabolite, which drags Na and K into the urine when excreted
- Toluene is inhaled, often producing a vesicular rash around the nostrils

21 Year Old Engineering Student Pathogenesis

- Toluene inhalation causes a metabolic acidosis which causes an encephalopathy
- Toluene inhalation causes bronchospasm which leads to hypoxemia with a large A-a gradient, which aggravates the encephalopathy
- Hyponatremia and hypokalemia are due to excretion of sodium and potassium hippurate

Which of the Following Would Your Recommend?

- 0.9% saline
- 0.45% saline with 66 meq/L NaHCO3
- Albuterol
- CT, LP, EEG and MRI
- **Plasma hippurate level**
- Ethanol infusion and acute hemodialysis
- Skin biopsy with Tzanck preparation

21 Year Old Engineering Student Management

- Urine hippurate level to document the cause
- Sodium bicarbonate for acidosis
- Respiratory support as necessary
62 Year Old Man

- A 62 year old man complained to his PCP of relatively recent onset of insomnia. The cause was a combination of a “crawling sensation” in his legs at night and “thoughts which he couldn’t get out of his mind.” He believed he was going “crazy.”
- PCP diagnosed depression and tried an SSRI, which made symptoms worse

62 Year Old Man

- He was referred to a neurologist who immediately recognized the problem as the ..........

62 Year Old Man with Restless Legs Syndrome

- A trial of clonazepam worked very well, but after about 3 months, the benefits wore off and he was noticing morning confusion
- A trial of pramipexole was met with even more obsessional intrusive thoughts

62 Year Old Man

- A diagnostic test was obtained
Neurological Effects of Iron Deficiency
- Increased viscosity of rigid red blood cells
- Obsessive-compulsive-like disorders
  - Restless legs
  - Pica behaviors (amylophagia, geophagia, pagophagia)
- Ekbom syndrome: OCD behaviors in iron deficiency
- May explain the unusual eating habits in pregnancy
- Appears to be another dopamine deficiency syndrome
- Treatment is dopamine agonists and benzodiazepines
- Mechanism is not fully elucidated, but could be:
  - Fe is a co-enzyme for tyrosine hydroxylase
  - Fe deficiency may change iron content of basal ganglia

Patient Follow Up
- Six months later he developed hematochezia
- Endoscopy revealed a cecal carcinoma
- Surgery was performed but there were hepatic metastases from which he died

Subacute Weakness, Ataxia and Altered Mental Status
68 year old man; July began making financial mistakes; August became unsteady on his feet; September developed intermittent giving out of the legs and paresthesias in the calves; generally fatigued and admitted in early October. Angioplasty 5 years ago; 2 ppd smoker; screening colonoscopy in June negative. He was from Brazil and was there in the past year but was not ill as far as he knew.
68 year old man continued

Neuro exam: confused (inattentive); no cranial nerve abnormalities; slightly weak distally; no sensory loss identified; equally unsteady with eyes open or closed; gait very abnormal requiring full assistance; reflexes brisk except absent AJs; bilateral Babinski signs.

Relevant Laboratory Studies

- Hct = 39.8
- C-reactive protein = 8.1
- ESR = 63
- Blood viscosity = normal
- Cobalamin = 841
- Folate = 14
- ANA = 1:640 (homogeneous)
- SPEP = M component
- CXR = normal
- SIEP = IgM lambda 958
- B-2-microglobulin = 4391
- Cryoglobulin = absent
- CH50 < 10
- Anti-Hu = negative
- Anti-MAG = negative
- CSF protein = 67
- CSF cells = 13 rbcs; 2 lymphs
- CSF cytology = negative
- CSF oligoclonal bands = absent
- MRI/A = non-specific white matter disease

68 year old man continued

Over the next two weeks, he became rapidly weaker and more encephalopathic. EMG/NCV suggested axonal neuropathy; Bone marrow biopsy: average cellularity with scattered abnormal appearing plasma cells averaging 10-15% of the nucleated cells; sequential MRIs showed rapid accumulation of ischemic lesions in the end arterial territories bilaterally; TEE negative; blood cultures negative; Hct fell to 23.7; ANA rose to 1:1280; LDH rose to 531; Anti-MAG=2635; viscosity=1.1 (normal)

Ten Days Later
Key Features of this Case
• Rapidly developing anemia (Hgb dropped from 12 to 7 in 2 wks)
• ESR high: 63
• Very low total complement: CH50 is less than 10
• C-reactive protein high: 8.1
• Auto-antibodies
  – ANA (homogeneous) 1:640 and 1:1280
  – Anti-MAG at high titer: 2635
• Moderate sized IgM lambda monoclonal (almost 1 gm/dL)
• β-2 Microglobulin very high (4391)
• LDH high (395 and 531)
• Bone marrow: too many (abnormal) plasma cells (>15%)
• Developing brain lesions in “borderzones” (end arterial terr.)
• CSF Protein mildly elevated (67)
• Post-colonoscopy urinary retention; worsening over time
• “Dizziness” and fainting spells (? Orthostatic intolerance)

Key Negatives in this Case
• RPR
• Hepatitis B/C
• Anti-cardiolipin antibody
• HIV
• Lyme
• SSA/SSB
• Cryoglobulins absent
• Serum viscosity 1.1 (only measured once)
• Urine immunoelectrophoresis: no Bence-Jones

Plasma Cell Disorders
Definition
Neoplastic diseases involving proliferation of a single clone of plasma cells producing a homogeneous (monoclonal) immunoglobulin protein (M protein) that can be identified as a spike on electrophoresis of serum or urine

Types of Plasma Cell Disorders
• Myeloma
  – Multiple
  – Osteosclerotic (plasmacytoma)
• Plasma cell leukemia
• Waldenstrom macroglobuliemia
• Immunoglobulin-related amyloidosis
• Monoclonal gammopathy of unknown significance (MGUS)
Peripheral Nervous System Disorders In Patients with Plasma Cell Disorders

- MGUS neuropathy (IgM=60%; IgG=30%; IgA=10%)
- Polyradiculopathy caused by epidural disease (neuropathomyomatosis)
- Sensory motor demyelinating neuropathy
  - Anti-MAG present; often IgM MGUS related
  - Anti-MAG absent; often IgG & IgA MGUS related
  - Waldenstrom macroglobulinemia
- Sensory motor axonal neuropathy
  - Cryoglobulinemia with demyelinating & axonal features
  - Related to chemotherapeutic agents
- Motor sensory demyelinating neuropathy
  - Osteosclerotic myeloma and Castleman disease
  - POEMS syndrome
- Sensory motor neuropathy with dysautonomia
  - Amyloidosis

Central Nervous System Disorders In Patients with Plasma Cell Disorders

- Epidural spinal cord compression
  - Back pain, paralysis, sensory loss, bowel-bladder
- Leptomeningeal infiltration
  - Multiple cranial nerves, headache, hydrocephalus
- Paraneoplastic disorders
  - Cerebellar degeneration, motor neuron disease
- Hyperviscosity syndrome
  - Headache, vertigo, ataxia, hearing loss, confusion, strokes
- Hypercalcemia
  - Headache, weakness, seizures, lethargy confusion, coma
- Bing-Neel syndrome
  - Leukoencephalopathy with seizures, paralysis, confusion

Waldenstrom Macroglobulinemia

- Described by Jan Waldenstrom described in 1944
- Rare illness (about 10% as common as myeloma)
- Lymphplasmacytoid lymphoma/immunocytoma
- Monoclonal IgM (kappa or lambda)
Clinical Manifestations of Waldenstrom Macroglobulinemia

- Direct tumor infiltration
  - Always involves bone marrow
  - Organomegaly in 30%
  - Brain infiltration rare
- Amount and properties of IgM
  - Hyperviscosity usually when measured at over 5cp
  - IgM usually above 3gms/dL for hyperviscosity
  - Cryoglobulinemia (Type I monoclonal)
  - Cold agglutinins: cold reactive antibody
- Deposition of IgM
  - Polyneuropathy
  - Renal precipitation of IgM, immune complexes or amyloid
  - Skin deposits: urticarial (Schnitzler syndrome) or diffuse
  - Gut deposits of monoclonal IgM causing diarrhea/malabsorption

Intravascular Lymphoma of the Brain

Diagnosis: The Bing Neel Syndrome

- Lymphoplasmacytic lymphoma/Immunocytoma secreting IgM lambda (Waldenstrom macroglobulinemia)

- Angiocentric (intravascular) lymphoplasmacytic lymphoma

Status Epilepticus

A 50 year old woman with known adenocarcinoma of the colon resected two years earlier and treated with 5FU began to develop multifocal seizures. Despite aggressive anti-epileptic drug management the seizures developed into status epilepticus from which she died. Before death a diagnostic test was performed.
Renal Infarction

Multiple Cerebral Infarctions

Nonbacterial (marantic) Endocarditis (NBTE)

Nonbacterial (marantic) Endocarditis (NBTE)
Encephalopathy and a Rash

A 38 y/o woman has had two days of confusion, fever and a rash. In the ED she is noted to have a mild left hemiparesis and is intermittently seizing on the right side. There is a purpuric rash on the trunk and extremities which does not blanch. Her platelet count is 58,000; Hct=21; BUN=64.

A diagnostic procedure is performed.
A 44 year old woman has had several attacks of TTP. On each occasion, her blood smear was severely microangiopathic. Treatments have included plasma pheresis and intermittent oral steroids. She developed multifocal seizures which were resistant to all therapeutic efforts and she died in status epilepticus. ADAMPT 13 was less than 10% of normal. A diagnostic test was performed.
76 Year Old Woman

- 76 yo woman developed R weakness (unable to dial phone) which progressed over a month
- PMH: COPD, arthritis, GERD
- Home meds: hydroxychloroquin, spiriva, raloxifene, omeprazole, albuterol
- Exam: T 98.7F, petechiae on shins
- Neuro: fluent aphasia, acalculia, right-sided neglect, left-right confusion, left gaze preference, right hemiplegia

- Hct 27, Plt 25 (2 weeks prior: Hct 34, Plt 214), WBC 9.7
- Na 138, K 3.9, Cl 106, HCO3 26, BUN 9, Crea 0.8 (baseline 0.8-1.1)
- PT 13.9, PTT 25.2, Fibrinogen 404, D-Dimer 1726
- LDH 576, haptoglobin < 8
- ALT 22, AST 27, Tbilii 0.9
- ESR 56, TSH 1.7
- UA: + blood, no RBCs
- Peripheral smear: true thrombocytopenia w/o giant platelets or artifactual clumping, frequent target cells, average of 5-6 schistocytes/HPF (range 2-9), unremarkable morphology and distribution of leukocytes

→ Microangiopathic hemolytic process
76 Year Old Woman

Blood smear showing microangiopathic hemolytic process

helmet cells (small black arrows), other fragmented red cells (large black arrow); large platelet (red arrow)

76 Year Old Woman

Diagnostic Possibilities

- TTP:
  - Hemolytic anemia
  - Thrombocytopenia
  - MS changes
  - Fever
  - Renal failure
- DIC (chronic)
  - Bleeding/microangiopathy
  - Thromboembolism/NBTE
- HIT
  - Recent heparin exposure
- Hypercoagulable state/consumptive process
  - Endocarditis
  - APLA syndrome
- Medication induced thrombocytopenia
  - Hydroxychloroquine
  -Raloxifene
- ITP
  - Bleeding (thrombocytopenia)
  - No hemolysis

76 Year Old Woman

- Protein C/S, ATIII, β2MG wnl, ANA, RF neg.
- Lupus anticoagulant, APLA (IgG, IgM) negative, HCV neg.
- Trop I 3.74, CK 143, CKMB 7.0
- ADAMTS 13 – pending…..
- TTE: EF 50%, trace MR, no PFO
- TEE: EF 65%, no LA thrombus, no shunt, no valvular vegetations; protruding but nonmobile atheroma noted in the ascending aorta
- CT chest: thickening of the upper esophagus. One 1 cm pretracheal lymph node, several subcentimeter hilar and mediastinal lymph nodes
- Bone marrow: normocellular; no lymphoma
76 Year Old Woman

- Received 2 U PRBC and 1 pack plts (for TEE)
- plts stable 50-60 over next two days
- Started plasmapheresis
- Clinical course: no bleeding events, fading petechiae on shins, patient remains aphasic and with right hemiplegia

Patient’s son (HCP) finds more medication bottles in the patient’s apartment….

Patient took quinine medication, prescribed by a neurologist, for leg cramps (OTC) for past 4 weeks prior to admission

76 Year Old Woman

- Plasmapheresis x 8 sessions
- Labs: platelets > 150 after plasmapheresis #4, fibrinogen and coags remained wnl, LDH normalized, Crea/BUN remained wnl
- ADAMTS 13 activity – 51% (normal > 67%)
- Secondary TTP provoked by quinine

76 Year Old Woman

TTP-HUS

- Moschowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. Arch Int Med 1925
  - reviewed all 271 published cases and defined pentad of TTP (thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms/signs, renal dysfunction, fever)
- Epidemiology: suspected TTP-HUS: 11/million/yr, more female and black
- Idiopathic (37%), drug-associated (13%), autoimmune (13%), infection (9%), pregnancy/postpartum (7%)
76 Year Old Woman

TTP-HUS

Pathogenesis:

• larger multimers of vWF attach to vW receptor → platelet aggregation
• Reason: ADAMTS13 deficiency – vWF cleaving metalloproteinase (ADisintegrin-like And Metalloproteinase with ThromboSpondin type 1 repeats)
• Hereditary (genetic mutations) or acquired (autoantibodies)
• ADAMTS13 absent or severely deficient during acute episode, normal after recovery; inhibitor IgG in 48-80%

Labs: anemia, thrombocytopenia, reticulocytosis, schistocytes (>1% ->2/HPF); ↑ LDH, normal PT/PTT/fibrinogen/fibrin degradation products; ADAMTS13 - prognostic value (relapse rare w/o severe deficiency)

Moderate reduction of ADAMTS13 in DIC, ITP, cancer chemotherapy, sepsis, SLE, HIT, leukemia, cirrhosis, uremia or in normal individuals

76 Year Old Woman

TTP

• Quinine induced thrombocytopenia: antibody production against platelet glycoprotein complexes
• Quinine induced TTP: cross-reaction of antibodies with quinine altered glycoprotein molecules on endothelial cell membranes; not dose dependent; more common in women
• DDx: Quinine induced DIC: onset typically within hours of taking the drug, 80% GI symptoms, renal failure common; 16 cases reported since 1969, 80% female
• Treatment: plasma exchange until plt count normalized and hemolysis ceased
• Pt transfusion dangerous as may precipitate new or expanding thrombi as the infused plt are consumed

Endothelial Diseases

(sometimes incorrectly called posterior reversible leukencephalopathy or posterior reversible encephalopathy syndrome)

• Toxemia of Pregnancy
• Thrombotic thrombocytopenic purpura (TTP)
• Hemolytic uremic syndrome (HUS)
• Hemolytic anemia with elevated liver function tests and low platelets (HELLP) syndrome
• Hypertensive encephalopathy
• Post-carotid endarterectomy hemisphere syndrome
• Calcineurin inhibitor toxicity (FK drugs)
• Cyclosporine toxicity
• Hypomagnesemia

Depression and Strokes

63 y/o woman has a one year history of depression, progressive slowness of thinking and vague nondescript back pain. Two months earlier she developed a painful thrombosed vein at the site of a venapuncture in the antecubital fossa. She suddenly becomes confused and is brought to the ED where she is found to have a left homonymous hemianopsia. While under treatment she develops untreatable hypotension, suffers a cardiac arrest and resuscitation attempts fail.
Endogenous Anticoagulation Systems

- Thrombomodulin-thrombin activation of protein C/S
- Heparin-like substances – AT III
- Generation of plasmin (fibrinolysis)
- Tissue factor pathway inhibitor

Primary Hypercoagulable States
Disorders of the Four endogenous anticoagulant systems

Anti thrombin III deficiency
1/2000 incidence; AD or acquired

Protein C/S deficiency
rarer than AT III deficiency; AD or acquired

Fibrinolytic disorders
tPA deficiency; fibrinogen gene mutation

Deficiency of a contact (intrinsic pathway) factor
factor V Leiden mutation
Secondary Hypercoagulable States

- Platelet Abnormalities
  - Myeloproliferative diseases; thrombocytosis; PNH; hyperlipidemia; hyper-β-lipoproteinemia; diabetes mellitus; heparin induced thrombocytopenia (HIT)
- Blood Vessel and rheological abnormalities
  - Venous stasis; immobilization, artificial surfaces, obesity, vasculitis, homocysteinemia, hyperviscosity, TTP
- Coagulation and fibrinolytic abnormalities
  - Malignancy (Trousseau’s), pregnancy, nephrotic syndrome, infusion of prothrombin complex concentrates, antiphospholipid antibody syndrome

Antiphospholipid Antibodies

- History
  - Wasserman, 1906
  - Cardiolipin, 1941, accounts for false +VDRL
  - Lupus “anticoagulant”, 1963
- Relationship to Systemic Lupus
  - Verrucous endocarditis (Libman-Sacks)
  - Valvular abnormalities

Antiphospholipid Antibodies

- Antiphospholipid antibodies (aPL) are antibodies that interfere with the phospholipid steps in the coagulation cascade during in vitro testing
- Examples are: cardiolipin; β2-glycoprotein I; phosphatidyl-serine; phosphatidyl-inositol
### Lupus Anticoagulant (LA)

- The lupus “anticoagulant” is a functional inhibitor of the phospholipid steps in the coagulation cascade.
- Diagnosis requires a three step functional process:
  - Screening test (aPTT, aPTT-LA, Russell’s viper venom, plasma clot time)
  - Mixing test (does normal plasma correct the screening test abnormality?)
  - Phospholipid absorption test (e.g. platelet neutralization or hexagonal phase phospholipid test) to determine whether the plasma factor is, in fact, an antiphospholipid antibody.

### Anticardiolipin Antibody (aCL)

- An anticardiolipin antibody is an immunoglobulin (IgG, IgM, IgA) that binds cardiolipin.
- The lab test is a quantifiable enzyme linked immunosorbent assay (ELISA).
- 1 GPL unit is the cardiolipin binding activity of 1 µg/ml of an affinity purified IgG aCL preparation from a standard serum.
- Greater than 20 units is considered pathological and IgG is considered a worse clinical actor than IgM and IgA.

### Primary aCL (Sneddon) Syndrome

- Not secondary to lupus
- Not secondary to drugs (e.g. neuroleptics)
- Migraine
- Spontaneous midterm abortions
- Livedo reticularis
- Thrombosis prone
- Cardiac valvular abnormalities

### Mechanism of Hypercoagulability with aPL

- May inhibit prostacyclin
- May interfere with protein C/S interaction
- May cause platelet stickiness
- Co-factor that normally inhibits cascade may be blocked by aPL
Treatment of aPL

- Controversy still exists
- Warfarin of intermediate intensity (INR 2-3) probably OK
- Use of aspirin may be possible in mild cases or in those who cannot take warfarin
- In resistant or severe cases one may use:
  - Steroids
  - Intravenous IVIG
  - Plasma exchange
  - Methotrexate/cyclophosphamide

Major Categories of Medical Disease That Can Cause Subacute Encephalopathies

- Immune Mediated Disorders
- Endocrine Disorders
- Neoplastic Disorders
- Vitamin Deficiencies
- Intoxications
- Renal and Electrolyte Disorders
- Hematologic Disorders
- Hepatic Diseases
- Gastrointestinal Disorders
- Infectious Diseases
- Cardiovascular Disorders
- Ob/Gyn disorders
- Pulmonary Diseases
- Hydrocephalus
- Psychiatric illnesses
- Thermal control disorders

Subacute Encephalopathies Caused by Medical Diseases

Martin A. Samuels, M.D.
Chair, Department of Neurology
Brigham and Women’s Hospital
Professor of Neurology
Harvard Medical School