The Differential Diagnosis of Rapidly Progressive and Rare Dementias

Harvard CME Course
Dementia – A Comprehensive Update
June 9th 2016
Boston, MA

Jeremy D. Schmahmann, M.D.
Ataxia Unit, Cognitive/Behavioral Neurology Unit
Laboratory for Neuroanatomy and Cerebellar Neurobiology
Massachusetts General Hospital and
Harvard Medical School
jschmahmann@partners.org

@MINDlinkFound  MINDlinkFndtn
Disclosures

• Book Publishers
  – Academic Press
  – Elsevier
  – Oxford University Press
  – MacKeith Press
  – Springer

• Licensing
  – BARS, BARSc, CCAS-Test Battery, CNRS, with MGH

• Consulting
  – Takeda; Ataxion; Biohaven
28th Annual Meeting
American Neuropsychiatric Association

Atlanta
The Westin Buckhead Atlanta
March 8-11, 2017

Save the Date!
The American Neuropsychiatric Association

28th Annual Meeting -- March 8-11, 2017

The Westin Buckhead Atlanta

Atlanta, Georgia
Some speakers and symposium chairs from the world of Behavioral Neurology and Cognitive Neuroscience over the past 6 years of ANPA meetings:

• David Amaral
• Al Anderson
• Alireza Atri
• Helen Barbas
• Deborah Black
• Tiffany Chow
• Josep Dalmau
• Antonio Damasio
• Martha Denckla
• Brad Dickerson
• Karl Deisseroth
• Chris Filley
• Yonas Geda
• Ann Graybiel
• Ken Heilman
• Dan Kaufer
• Helen Mayberg
• Mario Mendez
• Marsel Mesulam
• Bruce Miller
• Stephen Nadeau
• Michael Okun
• VS Ramachandran
• Jeremy Schmahmann
• Dennis Selkoe
• David Silbersweig
• Robert Stern
• Robert Stickgold
• Don Stuss
• Helen Tager-Flusberg
• Michael Trimble
Some topics central to Behavioral Neurology over the past 5 years of ANPA meetings:

Atypical Alzheimer’s disease
Autism
Autoimmune encephalitis
Cerebellar Cognition and Neuropsychiatry
Chronic Traumatic Encephalopathy
Closed Head Trauma and Post traumatic Stress Disorder
Cognition in Parkinson’s Disease
Legacy of Norman Geschwind
Neurobehavior of Frontal-Subcortical Circuits
Neurobehavior of Sleep
Neurobehavior of temporo-parieto-occipital injury
Neurobiology of Depression
Neuroimmunology
Neuromodulation in Behavioral Neurology and Neuropsychiatry
Neuropsychiatry of Epilepsy
Neuroscience of Humor
Neuroanatomy and Behavioral Neurology of Subcortical Systems

Jeremy D. Schmahmann and Deepak N. Pandya

The Differential Diagnosis of Rapidly Progressive and Rare Dementias

A Clinical Approach

Jeremy D. Schmahmann

Acute confusional state (Delirium; encephalopathy)

Minutes to Hours

Confusional state = medical emergency

Mental state characterized by waxing and waning level of arousal and attention

Meningitis, encephalitis, intracranial hemorrhage, stroke, acute toxic / metabolic, seizure (convulsive or non-convulsive)
Subacute Dementia

Weeks to Months

The time course is THE MAJOR consideration, and limits the differential diagnosis.
Neurodegenerative dementias

Months to Years

The clinical differential diagnosis is highly determined by the pattern of elementary deficits and the nature of the cognitive decline (the domains of cognition affected)
UCSF: Diagnoses in 178 patients initially suspected of having CJD

- Sporadic CJD: 46.9%
- Acquired CJD: 1.7%
- Genetic Prion: 13.6%
- Non-prion RPD: 38%

N = 67
UCSF Non-prion diagnoses in 67 patients initially suspected of having CJD

- **Neurodegenerative**  N=26; 39%
  - CBD 8, FTD 7, DLB 4, AD 5, PSP 2
- **Autoimmune**  N = 15, 22%
  - Hashimoto 4, MS 1, Antibody mediated 9
- **Unknown**  N = 8; 12%
- **Infectious**  N = 4; 6%
- **Psychiatric**  N = 4; 6%
- **Malignancy**  N = 4; 6%
- **Toxic/metabolic**  N = 3; 4%
- **Vascular**  N = 3; 4%

Subacute Dementia

- **Weeks to Months**
- The time course is **THE MAJOR consideration**, and limits the differential diagnosis.
- Consider neurodegenerative disorders in this category only **after** other identifiable conditions have been excluded
What **ELS** do you need to know to make the diagnosis?

**EXAM**
- Time course
- Nature of the progression
- Medical / Elementary neurologic features
- Cognitive profile

**LAB**
- Blood, urine, CXR, LP when indicated

**SCAN**
- MRI, CT, as indicated
• Something obvious
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – Metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – Imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• Something not so obvious – if you don’t think of it you won’t diagnose it
  – DON’T MISS THIS BECAUSE:
    • A) Your patient may die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

– First line labs are fine
– Imaging is normal, not clearly abnormal, non-specific, or missed
– **THE BIG FOUR:** Drugs / toxins / metabolic / infectious
  Limbic encephalitis (paraneoplastic / immune mediated)
  Hashimoto encephalopathy
  Creutzfeld-Jakob disease
EVERYTHING ELSE
Here’s how this really works…

• **Something obvious**
  - Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - Metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  - Imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious – if you don’t think of it you won’t diagnose it**
  - DON’T MISS THIS BECAUSE:
    • A) Your patient may die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  - First line labs are fine
  - Imaging is normal, not clearly abnormal, non-specific, or missed
  - THE BIG FOUR: Drugs / toxins / metabolic / infectious
    - Limbic encephalitis (paraneoplastic / immune mediated)
    - Hashimoto encephalopathy
    - Creutzfeld-Jakob disease
  - EVERYTHING ELSE
Something not so obvious – if you don’t think of it you won’t diagnose it

DON’T MISS THIS BECAUSE:

A) Your patient may die if you miss it, because it’s lethal and treatable

or

B) Patients and families need to know the diagnosis, even though you may not be able to cure it
Here’s how this really works…

- **Something obvious**
  - Exam diagnostic
    - Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - Metabolic derangement on first line labs
    - Na, Ca, UTI, pneumonia, pO2…
  - Imaging diagnostically abnormal and easy
    - stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    - NPH, MELAS, ADEM, stroke that didn’t make sense until now

- **Something not so obvious** – if you don’t think of it you won’t diagnose it
  - **DON’T MISS THIS BECAUSE:**
    - A) Your patient may die if you miss it, because it’s lethal and treatable, or
    - B) Patients and families need to know the diagnosis, even though you may not be able to cure it

- First line labs are fine
- Imaging is normal, not clearly abnormal, non-specific, or missed
- **THE BIG FOUR:** Drugs / toxins / metabolic / infectious
  - Limbic encephalitis (paraneoplastic / immune mediated)
  - Hashimoto encephalopathy
  - Creutzfeld-Jakob disease
- EVERYTHING ELSE
Drugs / toxins / metabolic derangements

- **Medications**
  - Benzodiazepines – use or withdrawal
  - Anticonvulsants – keppra in the elderly
  - Dopaminergic agents – sinemet confusion
  - Neuroleptics
  - Anticholinergics
  - Polypharmacy

- **Alcohol**
  - Acute
  - Chronic (Korsakoff, Marchiafava-Bignami)
Wernicke encephalopathy (B1, thiamine)
(If it’s Korsakoff, it’s probably too late)
  Confusion, ataxia, nystagmus, extraocular nerve palsy
    – VI most common

Vitamin B12 deficiency
  Dementia +/- pernicious anemia, myelopathy
    (subacute combined degeneration of the spinal cord)

Vitamin B3 deficiency (nicotinic, niacin)
  Pellagra – dementia +/- dermatitis, diarrhea
Pellagra encephalopathy

- Rapidly progressive dementia
- Fluctuating cognition, frontal disinhibition, release phenomena
- Startle myoclonus, decreased arousal
- Cerebellar motor syndrome
- Hyperreflexia
- Peripheral neuropathy
- Autonomic dysfunction
- Cranial neuropathies
- In the alcoholic patient, differentiate alcohol withdrawal from the acute and persistent confusional state, disorientation, agitation, irritability, paranoia, and hallucinations of pellagra.

Ishii and Nishihara, 1981
In, Schmahmann, 2014
Drugs / toxins / metabolic derangements

Hypothroid
Myxedema madness († Relationship to Hashimoto)

Adrenal insufficiency
Addison's disease

Vitamin E deficiency
Encephalopathy with neuropathy, ataxia
Drugs / toxins / metabolic derangements

Carbon monoxide, cyanide – globus pallidus lesions
Marijuana psychosis
Heroin – intravenous drug use
  “Chasing the Dragon” leukoencephalopathy
Phencyclidine (PCP)
Mescaline
Heavy metals: lead, mercury, arsenic
Herpes simplex encephalitis

Fever, confusion, often with aphasia
Herpes simplex encephalitis

The Big Four:
- Drugs / toxins / metabolic / infectious
- Limbic encephalitis
- Hashimoto
- Creutzfeld
Limbic Encephalitis

Voltage-gated K⁺ channel antibody syndrome (VGKC-Ab)

Memory loss, confusion, seizures; low serum sodium

Treat with immune modulation (steroids, plasmapheresis, IVIG)

THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld
THE BIG FOUR:
Drugs / toxins / metabolic / infectious; **Limbic encephalitis**; Hashimoto; Creutzfeld

**TABLE 15.4** Well-Characterized Onconeural Antibodies and Paraneoplastic Neurological Syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Predominant Tumors</th>
<th>Most Common PNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu (ANNA1)</td>
<td>SCLC</td>
<td>Encephalomyelitis, limbic encephalitis, brainstem encephalitis, PCD; sensory neuronopathy, gastrointestinal pseudoobstruction</td>
</tr>
<tr>
<td>CV2 (CRMP5)</td>
<td>SCLC, thymoma</td>
<td>Same as Hu, and chorea, optic neuropathy, isolated myelopathy, and mixed neuropathies</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Breast SCLC</td>
<td>Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis, sensory neuronopathy</td>
</tr>
<tr>
<td>Ri (ANNA2)</td>
<td>Breast, SCLC</td>
<td>Brainstem encephalitis, opsonoclonus myoclonus</td>
</tr>
<tr>
<td>Yo (PCA 1)</td>
<td>Ovary, breast</td>
<td>PCD</td>
</tr>
<tr>
<td>Ma2</td>
<td>Testicular</td>
<td>Limbic and brainstem encephalitis</td>
</tr>
<tr>
<td>Tr</td>
<td>Hodgkin’s</td>
<td>PCD</td>
</tr>
</tbody>
</table>

PCD, paraneoplastic cerebellar degeneration; PNS, paraneoplastic neurological syndromes; SCLC, small-cell lung cancer. *Source:* From Graus and Dalmau (2012); reproduced with permission.

**TABLE 15.5** Antibodies Against Cell Surface or Synaptic Antigens Associated With Paraneoplastic Neurological Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;3&lt;/sub&gt;R</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>CASPR2</td>
<td>Morvan’s syndrome</td>
</tr>
<tr>
<td>AMPAR</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>VGCC</td>
<td>PCD</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Limbic encephalitis</td>
</tr>
</tbody>
</table>

AMPAR, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein 2; GABA<sub>3</sub>R, γ-aminobutyric acid-B receptor; mGluR5, metabotropic glutamate receptor type 5; NMDAR, N-methyl-D-aspartate receptor; PCD, paraneoplastic cerebellar degeneration; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel. *Source:* From Graus and Dalmau (2012); reproduced with permission.
Hashimoto encephalopathy

Roma origin. Grade 3 education. Grew up “in the carnival”.
Active housewife, sociable, respectful and aware of social conventions.

Age 47, dizziness, tiredness, anxiety, intermittent shaking of hands and legs, episodes of slurring of speech and confusion.
Age 48, over 3 months, change in personality with decreased conversation, not following the thread of conversation.
Personality change - inconsiderate of other people’s feelings, "talking dirty", reporting she was smelling bad things, restriction of her activities, refused to shower, spent much of her day sleeping, did not brush her teeth, liberal with profanities.

Thyroid problem began 15 years ago. On levothyroxine
Thyroid peroxidase (TPO) 301 (0-34 IU/mL)
Thyroglobulin Ab >3,000 (<40 IU/mL)
Hashimoto encephalopathy

Elementary exam unremarkable

Fluent language
Unable to learn words
Cannot repeat 3 numbers forwards, or understand reverse digit span
Confabulates. Frequent profanities. Utilization behavior
Asked to draw a picture – produces female nude
Perseverates with Luria diagram, and copying 2-loop diagram
Draw-to-stimulus with copying 2-D figure
THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; **Hashimoto**; Creutzfeld

**Hashimoto encephalopathy**

9/2010

9/2014

48 year-old woman. Confusion, profound disinhibition, aphasia.
65 yr woman. 4 months of unsteady gait, lethargy, confusion, forgetfulness

THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld

Creutzfeld-Jakob disease
Ataxia, dementia, myoclonus

DWI -MRI
Creutzfeld-Jakob disease

54-yr woman. 6 week history. Vertigo, unsteady gait, cortical visual loss, alexia, agraphia, apraxia, aphasia (output > comprehension), amnesia, confusion
Sporadic CJD

- **Dementia**
  - concentration, memory, judgment, personality, depression/disinhibition

- **Ataxia**
  - impaired gait (not necessarily typically cerebellar)

- **Myoclonus**
  - with startle in 90%

- Also: extrapyramidal, corticospinal (40 – 80%), cerebellar, occipital (Heidenhein), thalamic, basal ganglia
EEG in CJD
Periodic triphasic waves

67 – 95% of cases
Sensitivity 67%
Specificity 86%

THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld
• **CSF in CJD**
  - 14-3-3 protein
    - Sensitivity 53 to 85%, Specificity 95%
  - RT-QuIC (Real-time quaking-induced conversion: amplify, detect, and quantify prion protein)

• **CJD Pathology** – spongiform encephalopathy

Courtesy Matthew Frosch, MD, PhD
Here’s how this really works...

• **Something obvious**
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious – if you don’t think of it you won’t diagnose it**
  – DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it
  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed
  – **THE BIG FOUR: Drugs / toxins / metabolic / infectious**
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
  – EVERYTHING ELSE
Here’s how this really works…

• **Something obvious**
  - Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  - imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious** – if you don’t think of it you won’t diagnose it
  - DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

• First line labs are fine
• Imaging is normal, not clearly abnormal, non-specific, or missed
• THE BIG FOUR: Drugs / toxins / metabolic / infectious
  - Limbic encephalitis (paraneoplastic / immune mediated)
  - Hashimoto encephalopathy
  - Creutzfeld-Jakob disease
EVERYTHING ELSE
Here’s how this really works…

• **Something obvious**
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious – if you don’t think of it you won’t diagnose it**
  – DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed
  – **THE BIG FOUR:** Drugs / toxins / metabolic / infectious
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
  – EVERYTHING ELSE
Anterior Cerebral Artery Infarct

Watershed infarction
(Triple borderzone)
Anomia, verbal memory impairment, hemianopsia - the “silent confusional state” from LEFT occipitotemporal infarction
Prosopagnosia and visual disorientation from RIGHT medial temporal lobe (and thalamic) stroke
Posterior reversible encephalopathy syndrome (PRES)

hypertensive encephalopathy, eclampsia, cyclosporin, uremia
Here’s how this really works…

- **Something obvious**
  - Exam diagnostic
    - Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - metabolic derangement on first line labs
    - Na, Ca, UTI, pneumonia, pO2…
  - imaging diagnostically abnormal and easy
    - stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    - NPH, MELAS, ADEM, stroke that didn’t make sense until now

- **Something not so obvious – if you don’t think of it you won’t diagnose it**
  - DON’T MISS THIS BECAUSE:
    - A) Your patient will die if you miss it, because it’s lethal and treatable, or
    - B) Patients and families need to know the diagnosis, even though you may not be able to cure it

- First line labs are fine
- Imaging is normal, not clearly abnormal, non-specific, or missed
- **THE BIG FOUR: Drugs / toxins / metabolic / infectious**
  - Limbic encephalitis (paraneoplastic / immune mediated)
  - Hashimoto encephalopathy
  - Creutzfeld-Jakob disease
  - EVERYTHING ELSE
Amyloid angiopathy - dementia and lobar hemorrhage
Cerebral amyloid angiopathy and ischemic leukoencephalopathy

Smith et al Neurology 2002;59:193
Here’s how this really works…

• **Something obvious**
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious – if you don’t think of it you won’t diagnose it**
  – DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed
  – **THE BIG FOUR: Drugs / toxins / metabolic / infectious**
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
    EVERYTHING ELSE
Solitary lung metastasis

Gliomatosis cerebri

Solitary splenium metastasis causing amnesia
Intraventricular tumor resection. Delayed post-surgery seizure, with amnesia, and transient DWI signal hyperintensity in splenium.
Here’s how this really works…

- **Something obvious**
  - Exam diagnostic
    - Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - metabolic derangement on first line labs
    - Na, Ca, UTI, pneumonia, pO2…
  - imaging diagnostically abnormal and easy
    - stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    - NPH, MELAS, ADEM, stroke that didn’t make sense until now

- **Something not so obvious – if you don’t think of it you won’t diagnose it**
  - DON’T MISS THIS BECAUSE:
    - A) Your patient will die if you miss it, because it’s lethal and treatable, or
    - B) Patients and families need to know the diagnosis, even though you may not be able to cure it

- First line labs are fine
- Imaging is normal, not clearly abnormal, non-specific, or missed
- THE BIG FOUR: Drugs / toxins / metabolic / infectious
  - Limbic encephalitis (paraneoplastic / immune mediated)
  - Hashimoto encephalopathy
  - Creutzfeld-Jakob disease

EVERYTHING ELSE
Toxoplasmosis with trophozoites
• **Something obvious**
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious – if you don’t think of it you won’t diagnose it**
  – DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it
  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed
  – **THE BIG FOUR: Drugs / toxins / metabolic / infectious**
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
  – EVERYTHING ELSE
Normal Pressure Hydrocephalus

Before VP shunt

After VP shunt

Schwartzschild M, Rordorf G, Bekken K, Buonanno F, Schmahmann JD.
Normal Pressure Hydrocephalus with Misleading Features of Irreversible Dementias. A Case Report.
Normal Pressure Hydrocephalus

Axial views

Coronal views
Normal Pressure Hydrocephalus

Acute callosal angle at the level of the posterior commissure
Normal pressure hydrocephalus
Following intraparenchymal hemorrhage
MELAS (Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes)

Lactate in serum and on MR spectroscopy, muscle biopsy, A3243G mutation or others on gene testing
Acute disseminated encephalomyelitis

2007 - Height of illness

2009 - Recovered following treatment with IVIG
Progressive Multifocal Leukoencephalopathy
(JC virus attacks oligodendroglia)
Cerebral Autosomal Dominant Arteriopathy with Stroke-like episodes and Ischemic Leukoencephalopathy

CADASIL

52 yr. man with progressive cognitive decline
Left hemineglect from infarct in genu of right internal capsule

Schmahmann, 1984
• Fluctuating arousal and orientation
• Impaired learning, memory, autobiographical memory
• Personality changes, apathy, abulia
• Executive failure, perseveration
• True to hemisphere – language if VL involved on left; hemispatial neglect if right sided
• Emotional facial, acalculia, apraxia

Paramedian artery territory infarction

- Decreased arousal (coma vigil if bilateral)
- Impaired learning and memory, confabulation, temporal disorientation, poor autobiographical memory
- Altered social skills and personality, including apathy, aggression, agitation
- Aphasia if left sided, spatial deficits if right sided

Cerebellar Cognitive Affective Syndrome

23-yr woman post gangioglioma resection

I am a young girl
who is twenty-three.
The young girl went into her closet.

62-yr man

Schmahmann and Sherman 1998
Binswanger disease – progressive subcortical ischemic leukoencephalopathy
Intravascular lymphoma
HIV encephalitis

Multinucleated giant cell

Microglial nodule
Methotrexate leukoencephalopathy
Chasing the Dragon –
Inhaled heroin leukoencephalopathy

Kriegstein et al. 1999
Hippocampal involvement due to heroin inhalation—“Chasing the Dragon”

Gupta, Krishnan, Sudhara
Clin Neurol Neurosurg 2009; 111: 278-281
21 year-old woman
Recovering addict ~ 1 year
Heroin relapse. Developed confusion, repeating questions, agitation.

Exam:
**Profound anterograde amnesia**
Preserved autobiographical memory, relatively preserved long term recall

Impaired reverse digit span (3), unable to spell WORLD backwards

Normal:
Attention span (DSF 8), language, drawing,copying, praxis, abstract reasoning, calculation, affect
Heroin
Delayed post-hypoxic leukoencephalopathy

2010 - At start of illness; 3 weeks after initiating event

2012 - Stable, chronically disabled
Here’s how this really works…

• **Something obvious**
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious** – if you don’t think of it you won’t diagnose it
  – DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed

• **The Big Four:** Drugs / toxins / metabolic / infectious
  – Limbic encephalitis (paraneoplastic / immune mediated)
  – Hashimoto encephalopathy
  – Creutzfeld-Jakob disease

EVERYTHING ELSE
Subacute Dementia: A broad approach to differential diagnosis by category and disease

- TRAUMA
- INFLAMMATION/INFECTION
- NEOPLASTIC
- METABOLIC
- VASCULAR
- AUTOIMMUNE
- DRUGS/TOXINS
- DEMYELINATING
- OBSTRUCTIVE
- DEGENERATIVE
TRAUMA

• Diffuse axonal injury, hemorrhage
• Chronic subdural hematoma
• Post-concussion syndrome
• Chronic traumatic encephalopathy
INFLAMMATION / INFECTION

- Creutzfeld-Jakob disease
- post-Herpes simplex encephalitis
- HIV dementia, and opportunistic infections
- focal cerebritis/abscess (including toxoplasma)
- Progressive multifocal leukoencephalopathy
- Lyme encephalopathy (with or without meningitis)
- Chronic meningitis (TB, cryptococcus, cysticercosis)
- Syphilis (GPI, gumma, vasculitic)
- Parenchymal sarcoidosis
- Subacute sclerosing panencephalitis
- Whipple’s disease of the brain
NEOPLASTIC

- Tumor - benign (frontal meningioma, clivus chordoma invading medial temporal structures)
- Tumor - malignant, 1º / 2 º
  - presentation depends on location
  - e.g., tumor in splenium of corpus callosum causing amnesia
- Paraneoplastic limbic encephalitis (small cell lung cancer, gynecologic, breast, testis, other – including colon, hematologic)
  Note - there may be NO tumor
  - Hu (SCLC), Ri, CV2, Ma2 (testicular), NMDA (teratoma), AMPA
  - Morvan syndrome
  - VGKC with neuromyotonia (100%), neuropsychiatric features (insomnia 89.7%, confusion 65.5%, amnesia 55.6%, hallucinations 51.9%), dysautonomia (hyperhidrosis 86.2%, cardiovascular 48.3%), neuropathic pain (62.1%). CASPR2 antibodies > LGI1 antibodies, associated with thymoma.
- Radiation necrosis
- Cancer chemotherapy “chemobrain”
- Intravascular lymphoma
VASCULAR

- Multi-infarct dementia
- Binswanger's encephalopathy
- Amyloid dementia
- Focal vascular syndrome (thalamic, inferotemporal, frontal)
- Triple borderzone watershed infarction (post - cardiac bypass)
- Diffuse hypoxic / ischemic injury
- Posterior reversible encephalopathy syndrome (PRES)
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, migraine)
- Mitochondrial disease (Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, MELAS)
AUTOIMMUNE

- Non-paraneoplastic limbic encephalitis
  - VGKC Ab
- Systemic lupus erythematosus
- Isolated angiitis of the nervous system
- Temporal arteritis
- Wegener's granulomatosis
- Polyarteritis nodosa
- Hashimoto encephalopathy (Steroid responsive encephalopathy syndrome [SREAT] – may need IVIG)
- Susac Syndrome
DRUGS / TOXINS

- **Medications:** neuroleptics, benzodiazepines, anticonvulsants, dopaminergic agents, antidepressants, beta blockers, histamine / dopamine blockade, methotrexate
- **Substances of abuse:**
  - Alcohol (Korsakoff, Marchiafava-Bignami)
  - PCP
  - Heroin: “Chasing the Dragon” leukencephalopathy
  - mescaline
  - marijuana psychosis
- **Toxins:** lead, mercury, arsenic
- **Carbon monoxide, cyanide:** globus pallidus lesions
DEMYELINATING

- Multiple sclerosis, Schilder's, Balo's sclerosis
- Acute disseminated encephalomyelitis (ADEM)
- Delayed post-hypoxic leukoencephalopathy
- Leukodystrophy with axonal spheroids (myelin and axons)
- Adrenoleukodystrophy
- Metachromatic leukodystrophy
- Electricity-induced demyelination
- Decompression sickness demyelination
OBSTRUCTIVE (or mechanical)

- Normal pressure hydrocephalus
- Obstructive hydrocephalus
- Sagging Brain Syndrome
Some uncommon - but not vanishingly rare - degenerative disorders that cause dementia

Huntington's disease
Fragile X Tremor Ataxia Syndrome
Gordon Holmes Syndrome
Spinocerebellar Ataxias
  SCA 1 – cortical, subcortical as well as cerebellar
  SCA 2 – can resemble PD
  SCA 3 (Machado-Joseph Disease)
  SCA 17 – resembles HD
  And others
Langerhans cell histiocytosis
Niemann-Pick Type C
Case Study Examples
Chronic Traumatic Encephalopathy

McKee, 2009
Subacute sclerosing panencephalitis
(late complication of measles virus)

Pregnant 20-yr woman. 2 weeks of dizziness, emesis, weak left side, impaired gait. Progressed to being combative, confused, short-term memory loss, disorientation. Over 1 month became mute with minimal reaction to environment. EEG with FIRDA.
CNS Whipple’s Disease
(Tropheryma whippelli)

Dementia/psychiatric, vertical gaze palsy, hypothalamic-autonomic, rhythmic movements of face and eyes (oculomasticatory myorhythmia)
Susac syndrome - Autoimmune arteriopathy
Branch retinal artery occlusion, sensorineural hearing loss, encephalopathy
Sagging Brain Syndrome – mimics frontotemporal dementia

Scharff, Buchbinder, Schmahmann, unpublished
<table>
<thead>
<tr>
<th>X-ALD</th>
<th>MLD</th>
<th>GLD</th>
<th>VWMD</th>
</tr>
</thead>
</table>

Adrenoleukodystrophy
Metachromatic Leukodystrophy
Globoid Cell Leukodystrophy
Vanishing White Matter Disease

42 yr F: Adult Onset Leukodystrophy with Neuroaxonal Spheroids

Huntington’s disease
Movement disorder, cognitive, psychiatric manifestations

COGNITIVE FEATURES

- Slowed learning
- Impaired delayed free recall
- Decreased use of organizational strategies (clustering of semantically related words)
- Difficulty completing multi-step sequences
- Impaired organizational and sequential planning
Fragile X Tremor Ataxia Syndrome

(ataxia, tremor, cognitive failure / dementia, incontinence, ED)
Gordon Holmes Syndrome
(ataxia, hypothalamic hypogonadism, dementia)
Spinocerebellar ataxia type 2
Langerhans cell histiocytosis

Mild ataxia, but prominent impulsivity, aggression, dysexecutive function

Age 8  
Age 25
Cerebellar hemorrhage, age 16
Profound multi-domain cognitive impairment
Subacute Dementia:
A working approach to differential diagnosis

- Structural (multifocal)
- Trauma
- Obstructive
- Paraneoplastic
- Infectious
- Metabolic / Toxic

STOPIM
STOPIM - Structural

• Tumor
  – Primary (focal, multicentric glioma, lymphoma)
  – Metastatic
• Single or multiple strategic strokes
  – (Cortical and / or subcortical – location is critical)
• Multiple small strokes
  – Subacute bacterial endocarditis; vasculitis (may also be large vessel)
• Multifocal abscess or cerebritis
  – toxoplasma, seeded from lung, blood
• ADEM (acute demyelinating encephalomyelopathy); and MS variants
• MELAS (mitochondrial encephalopathy, lactic acidosis, stroke like episodes)
• Subacute or Chronic Subdural Hematoma (weeks to months)

• The concussion that does not resolve – intraparenchymal contusions
STOPIM - Obstructive

- Hydrocephalus
  - Normal pressure hydrocephalus
    - Dementia, ataxia ("frontal" gait impairment), incontinence
  - Obstructive hydrocephalus
STOPIM - Paraneoplastic

- Paraneoplastic limbic encephalitis
  - New learning, remote memory, confusion, psychiatric features
  - Lung, gynecologic, testicular, others

- Non-paraneoplastic limbic encephalitis
  - Voltage gated potassium channel antibodies: VGKC-Ab
  - Others
STOPIM - Infectious

- Prion diseases – CJD, variant
- HIV and complications
- Progressive multifocal leukoencephalopathy (PML)
- Chronic meningoencephalitis
  - TB, syphilis, fungus (crypto), Lyme, sarcoid, lymphocytic choriomeningitis virus, SSPE
- Whipple’s disease of the CNS
STOPIM – Metabolic

• Vitamin B deficiency syndromes:
  – Wernicke’s encephalopathy (B1, thiamine deficiency)
  – Subacute degeneration of spinal cord with dementia (B12 deficiency)
  – Pellagra (B3, niacin deficiency)
• Thyroid deficiency or excess
• Encephalopathy with asterixis
  – Hepatic, renal, hypoxemic encephalopathy
  – Magnesium deficiency
  – Lithium excess
• Hashimoto’s encephalitis with Hashimoto’s thyroiditis
  – Dementia, personality change, myoclonus, ataxia, seizures
  – Antibodies to thyroglobulin, thyroid peroxidase
  – Dramatic recovery with steroids; on occasion, IVIG
• Poisoning (arsenic, lead, mercury, cyanide)
DEGENERATIVE – ADULT
(Can’t stopim…yet!)

• Alzheimer's disease
• Lewy Body Disease
• Corticobasal Degeneration / Syndrome
• Frontotemporal dementia / Pick's disease
• Huntington’s Disease
• Progressive Supranuclear Palsy
• Other less common – e.g., AOLNS, FAXTAS, MELAS, SCA’s, Leukodystrophies, Lysosomal storage, Iron accumulation
The take-home message:
What **ELS** do you need to know to make the diagnosis?

**Exam**
- Time course
- Nature of the progression
- Medical / Elementary neurologic features
- Cognitive profile

**Lab**
- Blood, urine, CXR, LP when indicated

**Scan**
- MRI, CT, as indicated
Here’s how this really works…

• Something obvious
  – Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  – Metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  – Imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  – Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• Something not so obvious – if you don’t think of it you won’t diagnose it
  – DON’T MISS THIS BECAUSE:
    • A) Your patient may die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  – First line labs are fine
  – Imaging is normal, not clearly abnormal, non-specific, or missed
  – THE BIG FOUR: Drugs / toxins / metabolic / infectious
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease

EVERYTHING ELSE
Collaborators

**Neuroanatomy**
Deepak Pandya

**Cerebellar Atlas**
Julien Doyon
Alan Evans
David McDonald
Michael Petrides
Arthur Toga

**Diffusion Imaging**
George Dai
Ellen Grant
Cristina Granziera
Emi Takahashi
Ruopeng Wang
Van Wedeen

**Clinical studies**
Louis Caplan
Milan Chheda
Alice Cronin-Golomb
Maureen Daly
Xavier Guell
Franziska Hoche
Stefanie Freeman
Matthew Frosch
Winthrop Harvey
Tessa Hedley-Whyte
Katherine Hermann
Raquel Gardner
Laura Horton
Richard Lewis
Lisi Levisohn
David Lin
Jason MacMore
Marygrace Neal
Janet Sherman
Christopher Stephen
Mark Vangel
Jeffrey Weilburg

**fMRI, morphometry**
Lino Becerra
David Borsook
Nikos Makris
Eric Moulton
Catherine Stoodley
Eve Valera

**Clinical Consortia**
Cerebellar Research
Consortium for the
Study of Spinocerebellar
Ataxias (CRC-SCA)

**Posterior Fossa Society**
Primate behavior
Ronald Killiany
Tara Moore
Mark Moss
Douglas Rosene

**Cerebellar TMS**
Jennifer Cromer
Asli Demirtas-Tatlidede
Faranak Farzan
Catarina Freitas
Irene Gonsalves
Mark Halko
Dost Ongur
Alvaro Pascual Leone
Laura Safar
Larry Seidman
William Stone

**Cerebellar Atlas**
Julien Doyon
Alan Evans
David McDonald
Michael Petrides
Arthur Toga

**Clinical Consortia**
Cerebellar Research
Consortium for the
Study of Spinocerebellar
Ataxias (CRC-SCA)

**Posterior Fossa Society**
Primate behavior
Ronald Killiany
Tara Moore
Mark Moss
Douglas Rosene

**Funding:**
NIMH, National Ataxia Foundation, Harvard CTSC, AT Children’s Project
Birmingham, MINDLink, and Sidney R. Baer Jr. Foundations

Photo by
Jinny Sagorin
Some references


More on Prion Diseases
Prion Diseases
(Transmissible Spongiform Encephalopathies - TSE)

- **Scrapie** – disease of sheep, described 1732
- **Kuru** (W.T. Brown 1954; Michael Alpers, Carleton Gadjusek 1957)
- **Prions** (Prusiner, 1982)

- **Conformational change**
  - PrPC
    - Alpha helical, transmembrane
    - Normal, encoded by PRNP gene, chromosome 20
  - PrPSc (4 subtypes)
    - beta helical, intracellular
    - protease resistant, polymerizes into fibrils, rods
Human Prion Diseases

- Kuru
- Fatal Familial Insomnia
- Gerstmann-Straussler-Scheinker syndrome (GSS)
- Creutzfeld-Jakob Disease (CJD)

? Mechanism of protein misfolding / conformational change as the basis for a wide range of neurodegenerative diseases
Kuru

- Prototype prion disease
- Fore tribes of Papa, New Guinea, ritual cannibalism
- Tremor (shivering = kuru), myoclonus, ataxia, dementia
- 9 – 24 months
- PrPSc reactive plaques
Fatal Familial Insomnia

- Age 35 – 61. Mean duration 13 months.
- Insomnia, abnormal sleep architecture on EEG
- Confusion, impaired concentration, poor memory, hallucinations
- Myoclonus
- Ataxia
- Spasticity
- Extrapyramidal features
Gerstmann-Straussler-Scheinker

- Extremely rare, autosomal dominant, 5 yr course
- Cerebellar presentation
- Peripheral sensorimotor neuropathy
- Dementia
- No myoclonus
- Kuru-like plaques, with AD-like tangles
Variant CJD

- Younger patients (mean 29 )
- Relatively slower progression (mean 14 months)
- Psychiatric presentation – depression, anxiety, psychosis, followed 4-6 months later by –
  - Ataxia, dysarthria, dementia. Sensory abnormalities, myoclonus in some.

- EEG – slowing, MRI – not definitive
- Tonsil biopsy for PrPSc subtype 4
- Pathology – kuru-like plaques
Creutzfeld-Jakob Disease (CJD)

- **Sporadic** 85 – 95 %
  - 1 per million. Latency 9 – 10 years.
  - Mean duration 4-5 months. Rarely >2 yrs. Mean age early 60’s

- **Familial** 5 – 15 %

- **Iatrogenic** <5 %
  - Human derived pituitary hormone therapy, dural grafts and dural material for embolization, cornea and liver transplants, neurosurgical instruments, depth electrodes)

- **Variant**
  - Human counterpart to Bovine Spongiform Encephalopathy