Chief Complaint

- 67-year-old right-handed female with about 15 year history of urinary incontinence and 10 year history of a gait disturbance referred for evaluation of 5 year history of progressive memory and cognitive decline.

History of Present Illness

Urinary Incontinence

- Initially characterized by stress and urge incontinence with increased frequency, but over time lost control of bladder completely.
- Extensive workup 3 years prior led to diagnosis of detrusor overactivity causing moderately severe obstruction. A detrusor muscle biopsy showed axonless schwann cells.
History of Present Illness

Gait Disturbance
- Characterized by mild shuffling and difficulty walking up inclines.
- Has very slowly progressed to feeling constantly unsteady, especially when walks down stairs.
- Occasionally trips over an uneven floor, but has not fallen.

History of Present Illness

Cognitive Decline
- Symptoms first noted in setting of febrile illness when she was described as going into a confusional state.
- Began to show progressive problems with memory including forgetting things such as conversations, events, and appointments.
- Initially forgot things occurring greater than 24 hours before, but progressed until was forgetting events shortly after they occurred.

History of Present Illness

Cognitive Decline
- Remembering a sequence of events is particularly confusing, frequently mixing up the day’s scheduled activities.
- Memory loss has been insidious with small slow steps, not sudden drops.
- Has begun to fill in memory gaps with “logical false memories,” which she later finds difficult to differentiate from the truth.

History of Present Illness

Cognitive Decline
- Frequently gets confused with directions and navigational skills have dramatically declined.
- Would get lost driving and no longer drives.
- Stopped paying the bills approximately 1 year ago.
History of Present Illness

Cognitive Decline
- Still fluent in five languages, very good at recalling words and names of people, particularly old movie actors.
- Maintains piano playing ability, and is able to still paint and write.
- Personality and social skills are intact.
- Increased fatigue and less active, watches more TV, takes more naps.

---

Discussion

2 bladder functions

Emptying:
- external sphincter relaxes
- bladder wall contracts
  (by parasympathetic discharges through the pelvic nerve to the pelvic ganglion)

Storage: Both sphincters need to contract
- internal sphincter (bladder neck smooth muscle)
  (contracted at rest, mediated by sympathetic tone from the inferior mesenteric ganglion to the hypogastric nerve)
- external sphincter (somatic muscle)
  (under voluntary cortical control through the pudendal nerve)
- Inhibition of parasympathetic tone to bladder wall
3 Micturition Centers

- Orbitofrontal cortex
  - inhibits sacral MC

- Pontine micturition centers
  - coordination of relaxation of external sphincter and contraction of bladder
  - 1 each for storage and voiding phases

- Sacral micturition center
  - bladder contraction

Micturition and the Soul

Gert Holstege
Department of Anatomy and Embryology, University Medical Center, University of Groningen, The Netherlands

The Journal of Comparative Neurology 493:15-20 (2005)

Activation of pontine micturition center at small volumes (it responds as bladder fills, not just during emptying)

At large volumes the orbitofrontal cortex becomes increasingly involved (more so in normals (top) than in those with poor bladder control (bottom))

Role of the Orbitofrontal Cortex
2 Types of Incontinence

- Stress Incontinence
  - Inability of internal sphincter to remain closed in response to coughing/sneezing
  - Lack of SNS tone or weakness of pelvic floor

- Urge Incontinence
  - Due to instability or hypermotility of bladder wall, leading to spontaneous contractions

1st Urological Phenomenon

Detrusor overactivity

- "detrusor hyper-reflexia" (involuntary contractions)
- spontaneous increase in bladder pressure at volumes below normal capacity
- incontinence is likely, especially if sphincter is weak
- manifests as urinary frequency and progressively increasing urge to urinate
- bladder wall does not become spastic

Bladder outlet obstruction

- associated with changes in detrusor structure
- excessive deposits of elastic fibers (hyper-elastosis) between widely separated muscle cells and in interstitium
- probable structural basis for increased bladder distensibility and chronic retention
- superimposed degeneration of muscle cells and axons


Two interesting conclusions

1. Bladder obstruction from any cause → overactive bladder
2. Detrusor muscle biopsy significance
Detrusor muscle biopsy significance

- 15 female/31 males, aged 7-96, hyperactive bladder for 1-43 years

<table>
<thead>
<tr>
<th></th>
<th>Meningomyelocele</th>
<th>Spinal cord injury</th>
<th>Brain Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td># biopsies</td>
<td>9</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Normal axons</td>
<td>6 (33%)</td>
<td>20 (80%)</td>
<td>9 (88%)</td>
</tr>
<tr>
<td>Axon degeneration</td>
<td>9</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Axon Sprouting</td>
<td>2</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

- It is unclear that they clearly differ UMN vs LMN in their groups of meningomyelocele and spinal cord injury
- “Conclusion: Combined degeneration and regeneration is the characteristic change in intrinsic nerves of the detrusor in UMN neurogenic bladder dysfunction”
- Axonal degeneration observed in 44/45 biopsies


2nd Urological Phenomenon

Detrusor-Sphincter Dyssynergia

- Synergy between relaxation of the internal and external sphincters and contraction of the bladder is key
- Results if connection is affected between pontine micturition center and sacral micturition center
- Bladder contracts at same time sphincter contracts
- This may cause:
  - Small capacity, hyperactive bladder often seen in spinal cord disease
  - Non-relaxing sphincter leading to incomplete bladder emptying and eventually possibly upper urinary tract dilatation

Interactive Question #1:
Given these 4 symptoms, is it possible that our patient’s incontinence is due to:

A. an upper motor neuron central nervous system lesion
B. a lower motor neuron peripheral nervous system lesion
C. a peripheral autonomic nervous system lesion
D. a structural outflow lesion, especially if she were male (prostate hypertrophy)
E. all of the above (“although I didn’t think so before this CPC”)

Her four urological symptoms:

1. stress and urge incontinence
2. intermittent catheterization; complete loss of control
3. obstruction and detrusor overactivity
4. detrusor muscle biopsy: axonless Schwann cells
Interactive question #2:

The time from onset until diagnosis in idiopathic NPH is usually:

A. from weeks to 6 months
B. from 6 months to 2 years
C. from 2 years to 6 years
D. from 6 to 15 years
E. it varies too much to say

Interactive question #3:

Idiopathic NPH most often evolves:

1. initially incontinence, then gait, then cognitive
2. initially gait, then incontinence, then cognitive
3. initially cognitive, then gait, then incontinence
4. initially incontinence, then cognitive, then gait
5. none of the above reliably

Idiopathic NPH: Time Course

Data:
- No mention in 4 of 5 major texts; Merritt “weeks to months”
- McGirt, 2005:
  - 132 patients treated surgically over 10 years at Hopkins
  - Time 1st symptom until diagnosis = 6 months to 5.5 years
- Stolze, 2000
  - Germany 10 patients treated surgically
  - Time to 1st symptom ranged 1-4 years (average 2.1 years)

Data: Urinary incontinence and NPH

- Major texts:
  - 3 of 5: late development (Noseworthy, Samuels, Adams)
  - 1 of 5 early (Bradley)
  - 1 no mention of order (Merritt)

- Meier and Miethke 2003 (200 pts with NPH seen over 18 yrs in Berlin)
  - but mean age was 52 and most cases were not idiopathic
  - urinary incontinence was a late symptom

Data: Gait Disturbance and NPH

- Major texts:
  - 3 of 5 gait disturbance occurs first (Noseworthy, Samuels, Bradley)
  - 1 of 5 both gait and cognitive changes precede incontinence (Adams)
  - 1 of 5 makes no mention (Merritt)

- McGirt 132 pts with idiopathic NPH does not address this directly but notes:
  - gait impairment seen in 98%, present for 36 +/- 30 months (6 mo to 5.5 yrs) before presentation
  - urinary sx seen in 79% for 30 +/- 28 months (2 mo to just under 5.5 yrs) before presentation
  - cognitive decline seen in 76% for 30 +/- 25 months (5 months to 5 yrs)
  - complete triad was present in 62%
  - most debilitation symptom was the gait difficulty in 82%, cognitive in 12% and urinary in only 6%.

- Stolze 10 with idiopathic NPH
  - gait was at least 1 of the 1st signs all 10 patients
  - Gait was the only 1st sign in 8 of 10
  - in 1 of the 10 1st sign was gait + dementia
  - in 1 of the 10 1st sign was gait + incontinence.

Weaknesses

1. “logical false memories” confabulation
2. loss of navigational skills
3. loss of sequencing
4. order of loss of memories (>24 hrs, then a few hrs, finally even less)

Strengths

1. preserved fluency in 5 languages
2. preserved musical ability
3. excellent personality and social skills
4. names of old actors
Interactive question #4:

This patient’s dementia fits best into the category:

A. cortical dementia  
B. subcortical dementia  
C. mixed cortical/subcortical dementia  
D. I don’t use the dementia terms ‘cortical’ and ‘subcortical’!

Subcortical

- lesser memory loss
- relative perseveration of vocabulary and naming
- slower thought processes
- lack of initiative
- depression

Cortical

- more severe memory loss
- language difficulty
- calculation difficulty
- apraxia and agnosia
- impaired abstract thought
Confabulation

- False statements that are not made to deceive and are more coherent than delusional thought (Johnson, 1991)
- Categories:
  - ‘momentary’ or neutral
  - ‘fantastic’ or personal

- How anatomically localizing?
- How pathologically specific?

Papez circuit

Basolateral Circuit

Prefrontal cortex
Dorsomedial thalamus
Perirhinal cortex
Amygdala

Weakness
Confabulation
orbital and ventromedial frontal, R>L

Localization
<table>
<thead>
<tr>
<th>Weakness</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confabulation</td>
<td>orbital and ventromedial frontal, R&gt;L</td>
</tr>
<tr>
<td>Loss of navigation</td>
<td>parietal lobe and medial occipital temporal cortex, R&gt;L</td>
</tr>
<tr>
<td>Loss of sequencing</td>
<td>patchy dorsolateral prefrontal cortex and/or connections</td>
</tr>
<tr>
<td>Memory loss order</td>
<td>hippocampus/hippocampal formation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weakness</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confabulation</td>
<td>orbital and ventromedial frontal, R&gt;L</td>
</tr>
<tr>
<td>Loss of navigation</td>
<td>parietal lobe and medial occipital temporal cortex, R&gt;L</td>
</tr>
<tr>
<td>Loss of sequencing</td>
<td>patchy dorsolateral prefrontal cortex and/or connections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluency in 5 languages</td>
<td>left temporal cortex</td>
</tr>
<tr>
<td>Strength</td>
<td>Localization</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>fluency in 5 languages</td>
<td>left temporal cortex</td>
</tr>
<tr>
<td>personality/social skills</td>
<td>right-&gt;left orbitofrontal cortex and connections</td>
</tr>
</tbody>
</table>

**Music: a language in itself**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluency in 5 languages</td>
<td>left temporal cortex</td>
</tr>
<tr>
<td>personality/social skills</td>
<td>right-left orbitofrontal cortex and connections</td>
</tr>
<tr>
<td>names of old actors</td>
<td>long-term storage, neocortex</td>
</tr>
</tbody>
</table>

| Pitch discrimination      | left hemisphere (by PET)                                                    |
| Harmony                   | right hemisphere/ ? bilateral                                               |
| Timbre ("color")         | right hemisphere (especially R superior and middle frontal gyr)             |
| Rhythm/meter (timing)     | R>L hemisphere                                                               |
| Pitch interval            | left hemisphere                                                              |
| Performance tasks         | left hemisphere                                                              |
| musical ability           | multifocal, R and L hemispheres                                             |
### On basis of history alone

**Weaknesses**

<table>
<thead>
<tr>
<th></th>
<th>Subcortical</th>
<th>Cortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confabulation</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Navigation</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Sequencing</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Loss of memory order</td>
<td>++</td>
<td>++++</td>
</tr>
</tbody>
</table>

**Strengths**

<table>
<thead>
<tr>
<th></th>
<th>Subcortical</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluency</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Personality</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>Old actors</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Musical ability</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

### On basis of history alone

- Insidiously progressive
- Very long duration
- Urinary symptoms likely central and long-standing (despite the urological hints that initially looked LMN)
- Triad evolution not suggestive of NPH
- Mixed subcortical/cortical dementia (islands of highly preserved cognitive function in a sea of patchy cognitive dysfunction)

= primary neurodegenerative process

### Past Medical History

- No history of hypertension, strokes, diabetes or cardiac disease.
- Medications:
  - Aricept, Celexa, Wellbutrin, Ritalin
  - Levbid, Premarin
  - Multivitamin, vitamins C, E and D, gingko biloba, L-phosphatidyl serine, acetyl L-carnitine
Social History
- Married with 2 daughters in their late 30s and 4 grandchildren.
- No significant history of alcohol or tobacco use.

Family History
- Ethnic background is Ashkenazi Jewish.
- Mother had Alzheimer’s dementia (diagnosed by autopsy) that began in her 80s. She also had urinary incontinence and a gait abnormality late in life.
- Father had CHF and prostate cancer, died at age 79.
- Sister developed mild dementia in lates 70s.
- Daughters and grandchildren all healthy.

Physical Examination
- Vital Signs: Pulse = 84; BP = 134/84
- General: Pleasant, cooperative, well-dressed healthy-appearing woman appearing stated age. Noted to be short-statured and mildly obese.
- Mental Status
  - MMSE 24/30 (off day by one and did not know what floor she was on, 0/3 recall even with category clues)
  - Frequent confabulatory responses, but language function was relatively normal.
  - Able to perform Luria hand sequence, but slow bilaterally.
  - Marked deficits in spatial tasks.
Physical Examination

- Cranial nerves: II-XII normal except for mild breakdown of smooth pursuit and mild decreased hearing, left worse than right. Had a mild voice tremor.
- Motor: Mild atrophy in distal lower extremities and mild spastic quadripareis. Finger tapping normal bilaterally. Strength 5/5 throughout except for 4/5 in the interosseous, iliopsoas and extensor hallucis longus muscles bilaterally.

Physical Examination

- Reflexes: Mild increased jaw jerk, 3+ throughout except for absent ankle jerk on the right and 1+ on the left. Plantar responses extensor bilaterally.
- Coordination: Accurate finger-to-nose bilaterally. Able to do heel-to-shin, right better than left. Normal rapid alternating movements, though hand clapping better on the right.
- She had a high-frequency resting tremor of the hands, left greater than right.

Physical Examination

- Gait: Very cautious getting onto and off exam table. Mildly wide-based, and slightly spastic gait. Difficulty turning, needed to hold on to objects. Was unable to tandem walk. Romberg was mildly positive.
- Sensory: Slightly decreased temperature and pin-prick sense in distal lower extremities up to the shin. Slightly diminished vibration in the toes, left worse than her right. Proprioception preserved at the toes.

Discussion
Additional Data

- Confirms systemically healthy
- Hereditary hints:
  - Similar disorder in mother
    - autosomal dominant vs. mitochondrial
    - but autopsy confirmed AD
  - Ashkenazi background

Mental Status Exam

- Luria hand sequence: complex motor programming
- Confirmed preservation of language and impairments of confabulation and spatial ability
- recalled 0/3 even with category clues

Memory

- Immediate (working).........left angular gyrus
  ... in conscious awareness without active memorization
  ...digits forward
- Short-term (recent).........hippocampus
  ...register and recall after minutes/hours
- Long-term (remote).........cortex
  ...names of grandparents, teachers

Encoding vs Retrieval

0/3 in 20 minutes:

- if a clue +/- recognition test works, then encoding was intact in hippocampus and the problem is retrieval memory from the median temporal lobe
  - Retrieval ➔ Subcortical
- since category clues do not help, then encoding did not occur in the hippocampus
  - Encoding ➔ Cortical
**Neurologic Exam**

- Mild breakdown of smooth pursuit
- Moderate pyramidal, symmetrical
- Mild left and possibly midline cerebellar extrapyramidal (resting L>R high frequency tremor, difficulty turning)
- Mild peripheral neuropathy, symmetrical
- Multi-system, largely symmetrical

**Serologies**

- Normal CBC, Chemistry, LFTs, Ck; ESR = 30
- Normal TSH, B12, Folate, MMA, vitamin E and alpha-tocopherol levels
- Total cholesterol = 285; LDL=162; HDL=96; TG=136
- Negative ANA; normal SPEP/UPEP; negative anti-Hu, anti-Ri and anti-Yo antibodies
- Nonreactive RPR; negative Lyme and HTLV-I and II
- Normal ammonia, lactate, pyruvate, urine arylsulfatase, very long chain fatty acids
- Negative Athena Mitochondrial DNA profile

**CSF Studies**

- 0 wbc, 0 rbc
- Protein = 28, glucose = 59
- IgG index = 0.4; no oligoclonal bands
- Negative cytology

**Neuropsychological Testing**

- Mild attentional problems and perseverative stimulus-bound behavior, but performed well on attention/concentration tasks (digits backward, “WORLD” backwards)
- Strength in language function (12/15 and 15/15 with cues on the BNT, good comprehension, repetition, and reading)
- Good executive function (completed Trails in 45 secs, 46 points on the Stroop test, named 22 “D” words and 17 animals in one minute)
Neuropsychological Testing
- Moderate impairment of verbal memory (on CVLT scored 5/5/6/6 after four trials, recalled 3 after a brief delay and 2 after a longer delay 2, recalled 4 with cues with 7 intrusions and had 9 correct with 13 false positives on delay)
- Moderate impairment of visuospatial function (able to identify the correct Rey-O figure out of a choice of four, core of 9 on design fluency testing)

Electrodiagnostic Testing
- EMG/NCS - No evidence of myopathy. Mild progressive length-dependent sensory-motor axonal polyneuropathy (compared to 3 years prior).
- EEGs (2 and 3 years prior) - normal.
- VEPs - delayed (130-132 msec) responses bilaterally; BAEPs - normal.

Skin and Muscle Biopsies
- Skin: No evidence of granular osmiophilic deposits or other abnormalities detected.
- Quadriceps muscle: Neurogenic rearrangement with large type 1 and type 2 muscle fiber groups without grouped atrophy and occasional small angulated fibers consistent with neurogenic atrophy. No evidence of mitochondrial abnormalities.

Imaging
**RADIOGRAPHIC FEATURES**

- Progressive volume loss
- Extensive leukaraiosis
- White matter cavitation
- Absence of enhancement
- Absence of reduced diffusion
- Elevated choline, low NAA, lactate

**RADIOGRAPHIC DIFFERENTIAL**

- CNS malignancy
- Ischemic leukaraiosis
- Primary demyelinating disease
- Chronic infection/inflammation
- CNS vasculitis
- Toxic encephalopathy
- Metabolic leukodystrophy
- Inborn error of metabolism
RADIOGRAPHIC DIFFERENTIAL

CNS malignancy
Ischemic leukoaraiosis
Primary demyelinating disease
Chronic infection/inflammation
CNS vasculitis
Toxic encephalopathy
Metabolic leukodystrophy
Inborn error of metabolism
Discussion

Ancillary Data

- Lab studies: essentially unremarkable
- CSF: non-inflammatory
- NCS: axonal sensorimotor neuropathy
- VEP: bilateral delay
- Imaging:
  - white matter process, progressive
  - proclivity to anterior temporal lobes, asymmetrical
  - white matter cavitation
  - cortical grey relatively preserved
  - ventricles fairly normal initially, then increased
  - spinal cord atrophy
In summary our patient

- Insidiously progressive
- 15 years urinary, 8-10 years gait, 5 years dementia
- Cognitive function: mixed subcortical and cortical
- axonal neuropathy
- symmetrical pyramidal and asymmetrical cerebellar and extrapyramidal signs
- Imaging confirming diffuse white matter involvement
- Ancillary studies adding two new pieces of data
  - spinal cord atrophy by MRI
  - optic nerve involvement by VEP

Adult Polyglucosan Body Disease

1980 Robitaille, DiMauro et al
- 4 patients
  - progressive UMN and LMN signs and neurogenic bladder
  - 2 with dementia
- Pathology:
  - prominent structures that resembled LaFora Bodies in central and peripheral neural processes and astrocytes but not perikarya
  - Chemical analysis = glucose polymers
  - Identical to corpora amylacea, seen in much smaller numbers in subpial and subependymal regions with normal aging
  - Identical to glucose deposits seen in some cases of Type IV glycogenosis
  - Invisible on H & E; PAS positive

Adult Polyglucosan Body Disease

- No mention of ethnicity or family history in the first report
- 25 reported cases by 2001
- Rare disorder of glycogen-branching enzyme deficiency

Glucose diffuses into cells
Converted to G-6-P so it cannot leave

To avoid a hyperosmolar gradient and then cell swelling, the G-6-P is converted to glycogen, which is osmotically not active
• The glycogen is linear until after at least 11 glucose molecules, a branching enzyme (amylo(1,4 --<1,6)-transglycosylase) creates a new branch point

• Most reported cases have autosomal recessive mutation in the gene encoding glycogen branching enzyme

• Most common mutation is a tyrosine to serine substitution at codon 329, a mutation of increased frequency in Ashkenazi Jewish population

• 2000 Ziemssen et al
  – 2 novel missense mutations in a non-Ashkenazi Jewish patient with APBD

• With accumulation of cases, clinical picture of APBD is a relatively distinctive quartet:
  – early urinary incontinence
  – then gait disorder
  – then peripheral neuropathy
  – finally dementia (subcortical/cortical)

Differential Diagnosis : White Matter Metabolic Disease

• Adult Metachromatic Leukodystrophy
  – dementia 20’s to 30’s, rarely later
  – corticobulbar, corticospinal, cerebellar
  – Delayed VEP; often demyelinating neuropathy
  – But urine arylsulfatase normal (?skin fibroblasts, ? Leucocytes)

Differential Diagnosis : White Matter Metabolic Disease

• Adult Krabbe’s Disease (Globoid Cell Leucodystrophy)
  – late onset to age 40’s
  – spastic paraplegia
  – cerebellar signs; dystonia
  – visual loss; painful neuropathy; rarely seizures
  – tested by dramatically decreased activity of galactosidase in leucocytes or skin fibroblasts
Differential Diagnosis: White Matter Metabolic Disease

- Adrenomyeloneuropathy
  - X-linked but 20% female carriers affected
  - Spastic paraparesis
  - 10-20% dementia/behavioral symptoms
  - But her VLCFA were normal
  - (NB: male cases could look like our patient with dementia, incontinence, UMN signs)

Differential Diagnosis: White Matter Metabolic Disease

- Adult Orthochromatic Leukodystrophy
  - Mixed inheritance, some autosomal dominant
  - Dementia, corticospinal, cerebellar, autonomic
  - More rapid course

- Adult Pelizaeus-Merzbacher
  - X-linked, but female carriers occasionally
  - Gait difficulty, personality changes

Differential Diagnosis: White Matter Disease

- CADASIL
  - TIA/stroke-like, stepwise progression
  - Granular osmiophilic material not seen on our pt

In keeping with the diagnosis

- Clinical picture
  - Time course
  - Distinctive quartet of symptoms

- Widespread white matter involvement by imaging, VEP and NCS

- Spinal cord atrophy by imaging

- Ashkenazi heritage
Problems with the diagnosis

- very rare

- significance of mother’s disease
  - urinary/gait/dementia
  - but most Ashkenazi cases autosomal recessive
  - ? Ashkenazi inheritance significant, not mother’s illness

- skin biopsy “negative”
  - but ? good sample of apocrine glands

Interactive Question #5

In my opinion, the diagnosis most likely is:

1. Adult Polyglucosan Body Disease
2. Another white matter hereditary disease
3. A white matter non-hereditary disease
4. A different diagnosis entirely
5. None of the above!

Interactive Question #5

In my opinion, the diagnosis most likely is:

A. Adult Polyglucosan Body Disease
B. Another white matter hereditary disease
C. A white matter non-hereditary disease
D. A different diagnosis entirely
E. None of the above!
Slow progressive decline in short-term memory and cognitive function with episodes of confusion and confabulation.

Slow progression of mild spastic quadraparesis and sensory neuropathy with increased spontaneous retropulsion and instability.

Initially maintained her personality and social skills, as well as her ability to speak five languages and play the piano.

Patient Course

Started to have some dysphagia and became mildly dysarthric and an aspiration risk.

Began to suffer from orthostatic hypotension and have fecal incontinence.

Gait became more wide-based and ataxic, required two-person assistance.

MRI showed significant interval progression of diffuse white matter disease and cerebral volume loss.

Patient Course

Tried ketogenic diet and memantine, without noticeable improvement.

Tried “mitochondrial cocktail” (l-glutamine, coenzyme Q10, and l-carnitine) without noticeable improvement.

Fatigue remained a significant issue (failed trials of amantadine and modafinil).

Patient Course

Memory worsened to point where had trouble remembering the names of her children.

Language decreased significantly, tending to give one-word answers, though retained some ability to converse in Yiddish, Spanish, French, and English, and could still sing songs in French.

Maintained ability to play piano.
Patient Course

- Eventually became nonverbal and wheel-chair bound.
- MRI showed even more significant interval progression of white matter disease with more extensive cavitation and cerebral volume loss.
- She passed away peacefully at home at the age of 75, approximately 7 years following diagnosis.

Pathology

**Brain – Macroscopic Features**

- Severe global atrophy with fixed wt = 1010g, with relative preservation of the gyral architecture.
  - atrophy of the mid-brain and pons

- Severe involvement of the subcortical and deep white matter.
- Hydrocephalus ex vacuo
- Thinning of the corpus collosum
Loss of pyramidal cells in CA1 > CA2 Numerous PB in CA4 / Hilus of Dentate Gyrus

- Marked Accumulation of PAS+ polyglucan bodies (PB)
  - ranging from 2-20µ (mean 7±3 µ)
- Accumulation in white matter >>> grey matter (layer 5)
- Subcortical and deep white matter affected
- Variable leukoaraiosis / tissue loss
- Astroglialosis with increased lysosomal activity
- Variable microglial infiltrates
PB accumulate in both neuronal and astrocytic processes

Brain – Macroscopic
- Multifocal leukomalacia in the mid-brain

Occipital Cortex
- Mild neuronal loss
- Subcortical loss of tissue / demyelination
- Variable astrocytosis
  - white matter >> grey matter
- Abundant PB in astrocytic processes
- Rare perivascular macrophage infiltrates

Heterogeneous PB accumulation in SN

GFAP and CD68 staining: GFAP positive staining in astrocytes, CD68 positive staining in macrophages.
Increased extracellular pigment in substantia nigra adjacent to Medial Ventral Group Medial lemniscus

Brain – Macroscopic
- Multifocal demyelination in the pons
Increased astrocytic lysosomal activity and macrophage infiltrates

Leukomalacia -- dentate nucleus
marked astrogliosis demarcating the cavitary loss of myelin

SPINAL CORD -- CORTICOPSINAL TRACT DEMYELINATION

SPINAL CORD -- ANT. HORN
Ultrastructural Features – Fifth Cranial Nerve
Overall reduction of myelinated axons

Intra-axonal polyglucosan bodies

Polyglucosan bodies – admixture of filamentous/amorphous components

Differential Diagnosis
- Vascular (Binswanger’s Disease, Vasculitis, CADASIL)
- Mitochondrial Encephalopathy (MELAS)
- Demyelinating (ADEM, MS)
- Infectious (HTLV-I)
- Hereditary Spastic Paraparesis
- Inherited Metabolic/Storage Diseases:
  - Peroxisomal (X-linked ALD)
  - Lysosomal (MLD, Krabbe’s or Globoid Cell Leukodystrophy)
  - Glycogen Storage Diseases (Adult Polyglucosan Body Disease)

Diagnosis
- White blood cells sent for glycogen branching enzyme (GBE) activity (Dr. Salvatore Di Mauro’s laboratory, Columbia University):
  - GBE activity level = 20 nmoles/min/mg protein (normal 350-400)
- Genetic analysis: Compound heterozygosity for Tyr329Ser mutation in GBE gene.

Adult Polyglucosan Body Disease
- Rare, adult-onset, autosomal recessive, glycogen storage disease that involves the central and peripheral nervous system.
- Caused by a deficiency GBE activity resulting in reduced ability to store glucose residues in glycogen and accumulation of abnormally branched glycogen leading to formation of polyglucosan bodies (PB) in the central and peripheral nervous system.
Adult Polyglucosan Body Disease

- GBE is essentially the same enzyme that caused the wrinkling of the peas that Gregor Mendel famously studied.
- GBE activity is also diminished in Glycogen Storage Disease Type IV (Anderson disease), a deadly disorder that occurs in infants or young children and in which PBs found in many organ systems.

APBD: Clinical Course

- Clinically heterogeneous, but most develop a tetrad of urinary incontinence (frequency and urgency), gait disorder (paraparesis or quadraparesis), sensory > motor polyneuropathy, and cognitive impairment.
- Most cases begin with urinary or gait symptoms, followed several years later by a neuropathy, and lastly cognitive impairment in which memory is almost always affected.
- Rarely considered ante-mortem.

APBD: Clinical Course

- Urinary dysfunction typically characterized by urgency and frequency, ultimately leading to incontinence.
- Gait disorder usually begins as spasticity, eventually leading to paraparesis and even paraplegia. In most cases upper extremities less or not involved.
- May have sensory complaints, such as numbness and tingling, and electrophysiologic studies consistently show a sensory greater than motor axonal neuropathy.

APBD: Clinical Course

- Presentation of dementia variable and only few reports of formal neuropsychological evaluation.
- Most commonly reported problem was loss of short-term memory. Difficulty with executive and visual function, apathy, and apraxia have been described.
**APBD: Clinical Course**
- Review of 47 fully documented cases by Medline search:
  - 62% were female
  - Age of onset = 54 (+/- 9) yrs
  - Disease duration = 10 (+/- 7) yrs (many still alive)
  - 21% had family history
  - 76% had urinary dysfunction
  - 85% had UMN signs
  - 79% had evidence of peripheral neuropathy
  - 64% had cognitive dysfunction or dementia
  - Small number of patients reported to have associated parkinsonism, cerebellar symptoms, ALS, frontal dementia.


**APBD: Imaging**
- MRI abnormalities can be variable, but often suggestive of a leukodystrophy or leukencephalopathy.
- May see moderate cerebral atrophy, multifocal white matter rarefaction, small cavitary lesions in cerebral white matter and basal ganglia, and cervical cord atrophy.

**APBD: Pathology**
- In most autopsy cases, PBs found in central and peripheral axons, as well as in the apocrine sweat glands and astrocytic processes.
- Spinal cord atrophy noted in majority of autopsy cases and about half noted optic nerve atrophy.
- PBs have also been found in visceral organs such as the heart, liver, smooth muscle, lung and kidney.
- Only one report documented PBs in a skin biopsy (in dermal nerve bundles).
- Skeletal muscle may show evidence of denervation atrophy.

**APBD: Genetics**
- Familial patients suggest AR inheritance.
- Milder form of GSD-IV linked to a Tyr329Ser mutation in GBE on chromosome 3p16, which led to linking 7 cases (5 families) of APBD in Ashkenazi Jews to the same mutation.
- Most Tyr329Ser mutations found in Ashkenazi Jews are homozygous.
- At least 8 other mutations in the GBE gene causing APBD have been identified.
APBD: Summary

- Consider in patients presenting with combination of urinary incontinence, gait abnormalities, and neuropathy, as well as later cognitive impairment.
- Clinical progression may be over many years.
- May have family history.
- MRI suggestive of leukoencephalopathy.
- EMG/NCS shows sensory > motor axonal length-dependent neuropathy.

If suspect diagnosis, measure GBE activity in blood leukocytes, or if family history, check for mutation in GBE on chromosome 3pq16.
- Consider sural nerve biopsy looking for PBs.
- Prevalence may be much higher than reported in the literature, and as neurologists become more aware of this fascinating disorder many more cases may be uncovered.

Acknowledgements

- UCSF Memory & Aging Center
  - Michael D. Geschwind, MD, PhD
  - Bruce L. Miller, MD
- UCSF Parkinson’s Disease Clinic & Research Center
  - Michael J. Aminoff, MD, DSc

Thank You