Aging of the Human Nervous System: What do We Know?

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Disclosures for Richard W. Besdine, MD

- I have no financial relationship with a commercial entity producing health-care related products and/or services
- I have a deep and abiding passion for improving health and healthcare for older persons, and will do almost anything to achieve the goal
Learning Objectives

- Demonstrate knowledge of the changes of pure aging in the nervous system, including changes in the neurologic examination.
- Demonstrate understanding of the importance of the interactions of pure aging in the nervous system with common diseases, and how these interactions influence presentation and response to treatment of disease.
"I've never been old before so I don't know what to expect" (Ghandi, Yogi Berra?)

CNS changes of pure aging in key domains:
- Cognition/Memory
- Special senses
- Strength
- Balance
- Sensation

A few words about MCI and stroke
Age-related Structural Brain Changes

HEAD CT – Cross-sectional View

- Enlarged subdural space predisposes to SDH
- Narrower gyri
- Wider sulci
- Enlarged ventricles
Brain Weight by Age and Gender

~10% decline from age 20 to 85

Age at Autopsy

Men 1450 gm
Women 1310

Men 1310 gm
Women 1170

Brain weight decreases ~10% from 20-85; grey matter ↓ is linear, but white matter loss (vascular) steady until 40s, then more rapid ↓

+ No correlation between brain weight and cognitive loss until ~25-30%; then associated with degenerative diseases common in late life; e.g., AD, PD, VD

+ Peculiar finding that high education, though protective for AD, associated with more brain mass loss – unexplained
Pure Aging NS Changes

- Number of neurons declines, but losses are focal – greatest in hippocampus, STG, entorhinal cortex, NBM; fewer or no losses in brainstem, supraoptic & para-ventricular nuclei.
- $\text{O}_2^-$, OH radicals damage mitochondrial DNA and initiate cellular apoptosis.
- Non-neurotransmitter enzymes (glucose catabolism, OH quenchers) decline; they are protective against DNA damage, and decline results in more unrepaired errors.
Pure Aging NS Changes

- Dendritic density ↓, but new sprouting and synapses develop with intellectual stimulation in old experimental animals (and humans?)
- Lipofuscin ↑, especially hippocampus & frontal; vascular amyloid ↑; ↓ myelin in white matter
- Plaques & tangles accumulate, but far fewer than in AD, and not concentrated in AD loci
- CBF ↓ generally proportional to brain mass, but prefrontal & grey matter down more
- White matter shows gliosis, dendrite loss, small vessel sclerosis, demyelination → shrinkage
Age Changes in Neurologic Exam

Abnormalities in 20-50%, but not pure aging – doesn’t happen to everyone, for example:

- Frontal release - snout, palmar-mental, root, suck, grasp said to identify dementia, but found in 10-35% with normal cognition
- Ankle jerks more difficult to elicit, and absent in ~10%
- Vibration loss in toes common without pathology, but position sense unimpaired
Age Changes in Neurologic Exam

Pure aging – it happens to everyone

- arm swing, \( \uparrow \) tone - \( \Rightarrow \) Dopamine neurons
- \( \Rightarrow \) Gag reflex
- \( \Rightarrow \) Ability to prevent postural sway
- \( \Rightarrow \) Ability to prevent orthostatic hypotension
- \( \Rightarrow \) Baroreflex sensitivity
- \( \downarrow \) Hand- and foot-tapping speed
- Restricted upward gaze
Pure Aging CNS Changes: Cognition

- **Attention** - Mild decline in overall accuracy, begins in 60s, progresses slowly, but sustained attention very good in healthy older adults
  
  + Easier distractibility with age, especially if irrelevant information presented with relevant

- **Clinical point**: When giving crucial information, *stick to core data, repeat it, write it down*
Processing speed (reaction, retrieval, timed and perceptual tasks), free recall, multi-tasking all ↓

Encoding strategies help retrieval - mnemonics, mental hierarchies, clusters – all used less by elders; training gives long-lasting improvements

Distraction interferes with learning more in older persons than in young

**Clinical points**: Give instructions directly and simply, encourage encoding strategies, refer to reputable memory training
Human Memory

Sensory Memory (< 1 sec)

Short-term Memory (Working Memory) (< 1 min)

Long-term Memory (life-time)

Explicit Memory (conscious)

- Declarative Memory (facts, events)

Implicit Memory (unconscious)

- Procedural Memory (skills, tasks)

Episodic Memory (events, experiences)

Semantic Memory (facts, concepts)
Sensory memory - earliest stage (visual, auditory, tactile) - unstable, rapid decay; **no age-related change**

Primary (short-term) memory - rehearsal transfers sensory to short term memory - **no loss with age**

Long term (secondary) - hours, days, years
  - Semantic memory – facts, meanings - no Δ
  - Procedural – biking, music, knots - no Δ
  - Episodic – events, time, place - ↓
Pure Aging CNS Changes: Language

- Vocabulary and store of information increase into 60s and 70s, and beyond if continued input and use - use it or lose it?

- Syntactic skills - combine words in meaningful sequence - no decline with age, and again, increase with use

- Errors or failures in naming occur with increasing frequency, beginning in mid-life; encoding strategies very helpful
When to be Concerned About Memory

- Phenomena in adults at any age
  - Transience (normal forgetting)
  - Absent-mindedness (where are my car keys?)
  - Blocking
  - Worrying about memory
  - Misattribution, Suggestibility
  - Why am I in front of the open refrigerator?
When to be Concerned about Memory

- Phenomena of aging
  - Slow retrieval
  - Temporary loss of names
  - Decline in aspects of long-term memory

- Sometimes we need to be concerned
  - Never retrieving names, words; work failures
  - Losing the car, major financial mistakes
  - Forgetting entire conversations or events
  - Not recognizing that there is a memory problem
  - Repetition not just for emphasis
Criteria for Diagnosis of Dementia

Global cognitive impairment with clear sensorium

- Development of multiple cognitive deficits, with memory impairment, & one or more of the following:
  - Aphasia - speech
  - Apraxia – purposeful movement
  - Agnosia – recognition (not naming)
  - Disturbance in executive functioning (run your life)

- Cognitive deficits are a significant decline from baseline and cause significant functional impairment

- Deficits are not caused by delirium (R/O by work up)
Mild Cognitive Impairment (MCI)

- MCI is a disease state, NOT pure aging
- Subjective & objective memory trouble (1.5 SD below the mean healthy level)
- Usually only memory affected, ADL intact
- Does not meet criteria for dementia
- For many, a pre-AD transition state; conversion to AD 5-20% per year, 60% after 5 years

Mild Cognitive Impairment (MCI)

- Mild cognitive impairments predict dementia in non-demented elders.
- Memory loss alone rarely (6%) progresses to dementia over two years.
- Memory loss plus other cognitive impairments does predict conversion to AD:
  - 48% at two years
  - 77% at 4 years vs. 24% of memory only.
Special Senses - Vision

- Decline in accommodation (presbyopia), low-contrast acuity, glare tolerance, adaptation, color discrimination, attentional visual field – eye and central processing
  - Consequences – reading, balance, car crashes
- Common diseases superimposed (macular degeneration, glaucoma, cataracts, diabetes mellitus)
Special Senses - Hearing

- Neural, conductive and sensory hearing loss (presbycusis); primarily high tones (consonants)
- Impairment defined as auditory threshold >25 db – found in >50% >age 80
- But clinically important hearing loss is not pure aging, since nearly half are not affected - HHIE
  + Consequences are difficulty in localizing sound and understanding speech, and hypersensitivity to loud noise
- Common diseases are superimposed
Special Senses – Taste, Smell

- Number of taste buds constant with age, but salt detection declines; bitter exaggerated; sweet, sour no change; volume, quality of saliva decrease
  - Impact may be less interest in food
  - Compounded by common diseases (periodontal) and medications

- Smell - olfactory bulb atrophy, ↓central processing
  - Decreased perception; less interest in food
  - Compounded by disease (AD and PD have major diminution and alteration of smell)
Motor System - Strength

- Major confounders are disuse and disease
- Muscle mass, strength decline, but modifiable by training – at best ~15% decline in both by 80; slow twitch aerobic type 1 preserved – size ↑
- Sarcopenia (50%↓) common, NOT pure aging
- Spinal reflex amplitude shrinks; tendons stiffen, easier rupture in old athletes and patients taking quinolone antibiotics
- Striatum and substantia nigra show neuronal loss, especially dopaminergic D1 – set stage for PD
- Cerebellum shrinks, especially anterior vermis
  + Balance, gait, tone, movement affected
Balance – A Complex Function

- Strength, cerebellar integrity, hearing and vision all play a role in balance

- Vestibular-cochlear function in addition to hearing (vestibular portion of 8th N) – otoconia (granules of the otolith) degenerate
  + Many diseases, 8th N sensitive to drugs

- Proprioception – muscle spindle and mechano-receptor functions decline with age alone
  + Many diseases of peripheral nerves, central processing
Somatic Sensation

- Sensory nerves lose myelin selectively, predisposing to neuropathy – vibration ↓
- Pain perception changes with age
  - Decreased pain fMRI responses in anterior insula, primary somato-sensory cortex (S1), supplementary motor area; less grey matter - reduced processing capacity
  - Endogenous pain inhibition reduced
  - Heat sensitivity ↓, pressure sensitivity ↑
- Painful disorders often less or not painful in elders
Asymptomatic Brain MRI Findings

- 2000 persons (mean age 63 [46-97]), population-based Rotterdam Study of healthy volunteers
- High-res brain MRI (1.5 T); trained reviewers recorded abnormalities – previously not detected, potential clinical relevance; unrelated to exam cause
- Infarct, 7.2%; aneurysm, 1.8%; benign tumors, 1.6%
- Prevalence of asymptomatic infarcts, meningiomas, volume of white-matter lesions increased with age
- Incidental but important brain MRI findings, including sub-clinical vascular pathology, are common
- Information on their course over time is needed

Linguistic Ability Predicts Cognition and AD

- The Nun Study: Longitudinal follow up of 678 sisters, 75-107 to identify predictors of cognitive vigor or loss; annual physical and cognitive eval, brain autopsy

- Idea density, grammatical complexity from youthful writings – low values predicted low cognition in late life, AD at autopsy; no high density had AD

- In 61 subjects with AD by neuropathology, stroke (lacunes in basal ganglia, thalamus, deep white) had more and more severe dementia; fewer AD lesions→dementia if strategic lacunes, but little dementia if lacunes without AD pathology

Snowden et al. JAMA. 1996;275:528-532
Snowden et al. JAMA. 1997;277:813-17
Sister Matthia at Age 104, 3 Months Before Death
Relation of AD Lesions to Dementia

- Most AD research has studied young-old victims, in whom plaques and tangles $\propto$ dementia severity
- Longitudinal study of elders 69-103 correlated neuropathology (classic AD findings, cerebral atrophy, vascular) with clinical cognition
- Association of AD path with dementia severity attenuated with age – OR 9 at 75, only 2.5 at 95
- Association of atrophy with dementia severity persisted – OR 5 at 75, 6 at 95
- Implications exciting – neuro-protection in very old, rate of accumulation matters?

Savva G et al. NEJM 2009;360:2302-2309
Prevalence of Moderate or Severe AD Lesions by Age & Dementia
Benefits last longer than cholinesterase inhibition, fewer side effects, lower cost
The fatality rate within 1 month of an acute stroke is 20% to 30% across all age groups.

Mortality is highest among older people.

Survival in part depends on the location and severity of the stroke.

The most important predictor is the severity of neurologic signs.
Incidence Of Stroke In Men by Age

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<tr>
<th>Age</th>
<th>Incidence per 1000</th>
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<tr>
<td>55-64</td>
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<tr>
<td>65-74</td>
<td>4.5</td>
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<tr>
<td>75-84</td>
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Stroke Risk Factors

- Hypertension
  - Most prevalent, and powerful risk factor
  - Greatest attributable risk
  - Treatment substantially reduces risk
- Atrial fibrillation - greatest relative risk
- Diabetes mellitus
- Cigarette smoking
- Elevated blood lipids
- Excessive alcohol use
### CHAD2 Stroke Risk Calculator in AF

<table>
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<th>Condition</th>
<th>Points</th>
<th>Score</th>
<th>Risk (annual rate)</th>
</tr>
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<tbody>
<tr>
<td>Congestive heart failure</td>
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<td>0</td>
<td>1.9</td>
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<tr>
<td>HTN (systolic &gt;160 mmHg)</td>
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<td>1</td>
<td>2.8</td>
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<tr>
<td>Age over 75 years</td>
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<td>2</td>
<td>4.0</td>
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<tr>
<td>Diabetes</td>
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<td>3</td>
<td>5.9</td>
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<tr>
<td>Prior cerebral ischemia</td>
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