"Doctor, Doctor: A Diagnostic Case Comparison of Misremembering, Misbehavior, Misunderstanding, and Mis- and Dys-Execution involving Two Doctoral Professionals

MCI Symposium, Miami, FL

Saturday 19 January, 2019

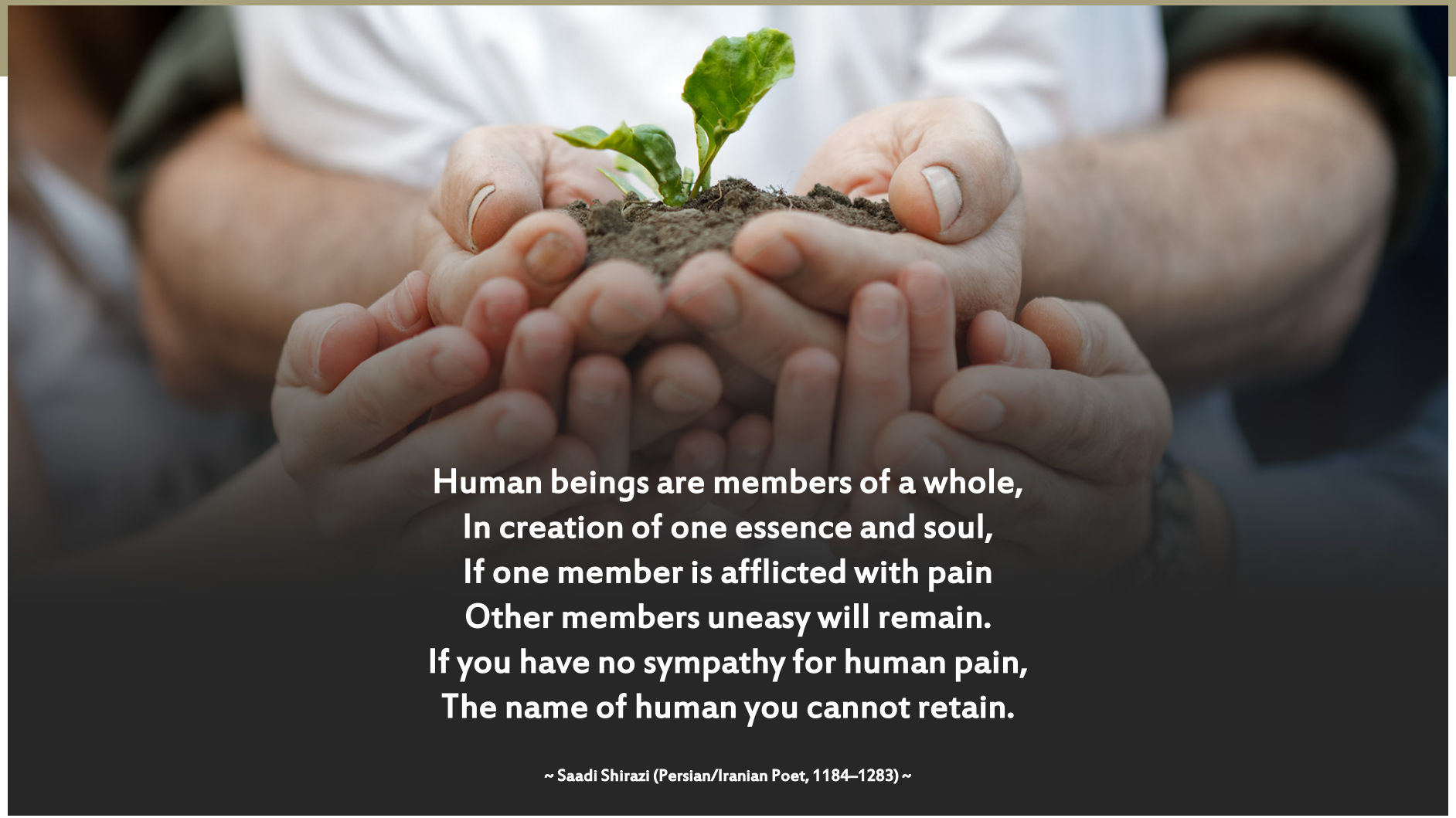
Alireza Atri, MD, PhD

Director, Banner Sun Health Research Institute
Banner Health, AZ

Lecturer in Neurology
Center for Brain/Mind Medicine
Department of Neurology
Brigham and Women's Hospital, and
Harvard Medical School

Disclosure/conflict of interest – Last 3 years

- I am not/have not been part of any speakers bureau
- Institutional Research Grants or clinical trials:
  - American College of Radiology, AbbVie, Avid, Biogen, Lilly, Lundbeck, Norvartis, vTV
- Scientific/Medical/Data Monitoring Advisory Board, Consultation, lectures/CME programs, or Work Groups/Committes:
  - Alzheimer's Association, Allergan, Axovant, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education (HMS CE), Lundbeck, Medical Learning Group, Merck, Roche/Genentech, Sunovion, Suven
- Book/Authorship:
  - Oxford University Press (OUP)


Human beings are members of a whole,
In creation of one essence and soul,
If one member is afflicted with pain
Other members uneasy will remain.
If you have no sympathy for human pain,
The name of human you cannot retain.
~ Saadi Shirazi (Persian/Iranian Poet, 1184–1283) ~

- Case 1: 74 yo RHWM retired Pharm D with 3-4 year of cognitive and behavioral changes
- Case 2: 51 yo RHWM with PhD in Cognitive Sciences employed executive at a large corporation with 2 years of cognitive and behavioral changes
- Concerns from spouses regarding cognitive and behavioral changes in common to both men that prompted the clinical visit involved:
  - Memory: forgetful of recent events, timelines and conversations; misremembering; repetitive
  - Executive Function: less organized; less mentally efficient; mild difficulties with complex planning, task initiation, follow through and timely completion, and overall judgment
  - Behavior: “something is off”; lower mood; less motivated; more irritable; less “sensitive”; more impulsive;

3-Step Diagnostic Approach

- Step 1: Is there something wrong?
  - What level or delineation in the spectrum of CU-SCD-MCI-Dementia
- Step 2: What is wrong?
  - What are the characteristic of what is wrong – define the clinical syndrome
  - Define the Cognitive-Behavioral Syndrome (e.g. single domain aMCI; multidomain amnestic, dysexecutive, and behavioral dementia in the mild stages)
- Step 3: What is causing it?
  - Etiological diagnosis
  - What is/are cause(s)/etiology – the underlying driver(s) and contributing diseases (e.g. AD, DLB) and disorders (e.g. OSA, alcohol, polypharmacy)

Case 1: 74 yo RHWM retired PharmD 3-4

- HPI: ~3 yrs of subtle but in retrospect clear changes in memory, executive function and behavior
- Pt: “a couple of years” not remembering as well otherwise “good”
- Spouse:
  - Was meticulous planner; quit job as director of hospital pharmacy “out of the blue” 7 years prior to presentation; same ~3 yrs ago with part-time job in local pharmacy
  - Progressively more forgetful and repetitive and doing less around the house but ”all day on the computer” – ordering things and forgetting he ordered them; “things we don’t need”
  - Office and desk is a mess – was so clean and neat – can’t find things in his office, missed bills
  - Gets so focused on somethings and forgets other things (letting the dog out) but then makes poor decisions or doesn’t care (“opens the door for the dog to go out in the rain knowing he’s going to come covered with mud”)
  - Been told he’s just aging but there’s a family history of Alzheimer’s

Case 1: 74 yo RHWM retired PharmD 3-4

- Structured multidomain review of cognition, daily function, behavior/neuropsychiatric symptoms, sensorimotor function
- Scale for below: 0 = wnl, Tr = subtle/very mild, 1+ = mild, 2+ = moderate , 3+ = severe)
- Cognition:
  - Memory: 2+
    - Repetitive, Missed some bills
  - Attention: 1+
  - Executive Function: 1-2+
  - Language: Tr-1+
    - Seems to not understand as well, + word finding pauses/difficulties
  - Behavior: 1-2+
    - Judgment, “cares less”, sensitivity (less empathy), “watching porn on internet”

Case 1: 74 yo RHWM retired PharmD 3-4

- Daily Function: independent with subtle decline
  - FAQ 6/30 (bill paying, taxes, shopping, current events, remembering appts)
- Behavior/Neuropsychiatric Symptoms:
  - NPIQ severity = 9 (irritability, depression/dysphoria, disinhibition, lability, appetite/eating)
  - NPIQ distress = 11
- Sensorimotor: slower, ?shuffling feet more walking the dog

Case 1: 74 yo RHWM retired PharmD 3-4

- Risk Factors for Cognitive-Behavioral Impairment/Dementia: + FHx “Alzheimer’s” (father died age 81; older sister age 84), cerebrovascular/cardiac
- Safety: okay
- PMH: HTN, dyslipidemia
- Meds: EC ASA, pravastatin, amlodipine
- Supplements: Omega-3 Fatty Acis
- Developmental Hx: no issues; very good student
- SHx: married x50 yrs, retired PharmD; adult son lives with them
- Health Related Behavior: EtOH – one scotch (measured by wife) per evening, gaining wt (sweets), walks dog daily, no formal exercise
- Caregiver: Zarit like scale moderate to high burden

Case 1: 74 yo RHWM retired PharmD 3-4

- Exam:
  - Trophic skin changes w/ hair loss in legs to mid shins
  - Neuro:
    - Tr-1+ hypomimia,
    - Tr-1+ overall bradykinesia,
    - 1+ saccadic breakdown of smooth horizontal pursuits
    - 1+ postural and action tremor R>L fingers especially at target
    - 1+ diminished cold and vibration sense at toes bilat
    - 1+ diminished arm swing on R

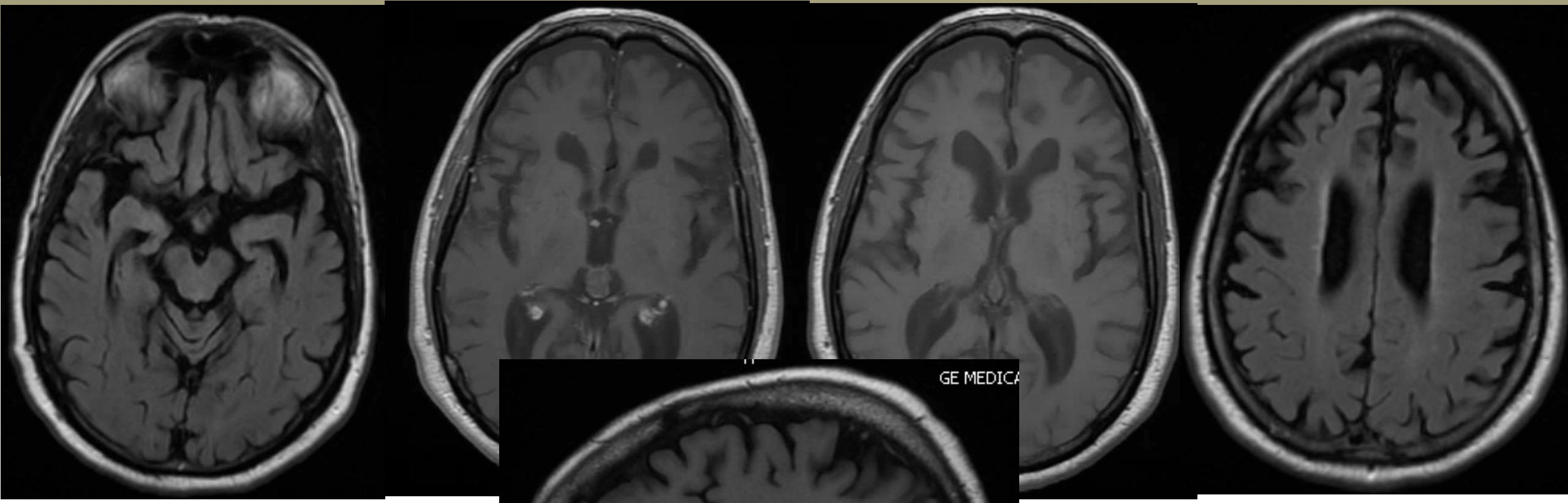
Case 1: 74 yo RHWM retired PharmD 3-4

- Neurobehavioral Status Exam:
- Appropriate, attentive to examiner
- MoCA = 23/30 (-1 trails, -1 Letter fluency, -5, recall)
- MoCA MIS (Memory Index Score 0-15) = 7/15 (two with cue, one with multiple choice)
- Letter Fluency (F) in 60 sec 9
- Animal Fluency in 60 sec 11
- Clock Draw Test = 4/5
- Naming (from ACE-R): 12/12.

  Occasional word-finding difficulties and paraphasias.
- Calculations and word problems: 15% tip of $120 dinner check = "10 would be 12, and 5 would be 6 so ... $16".

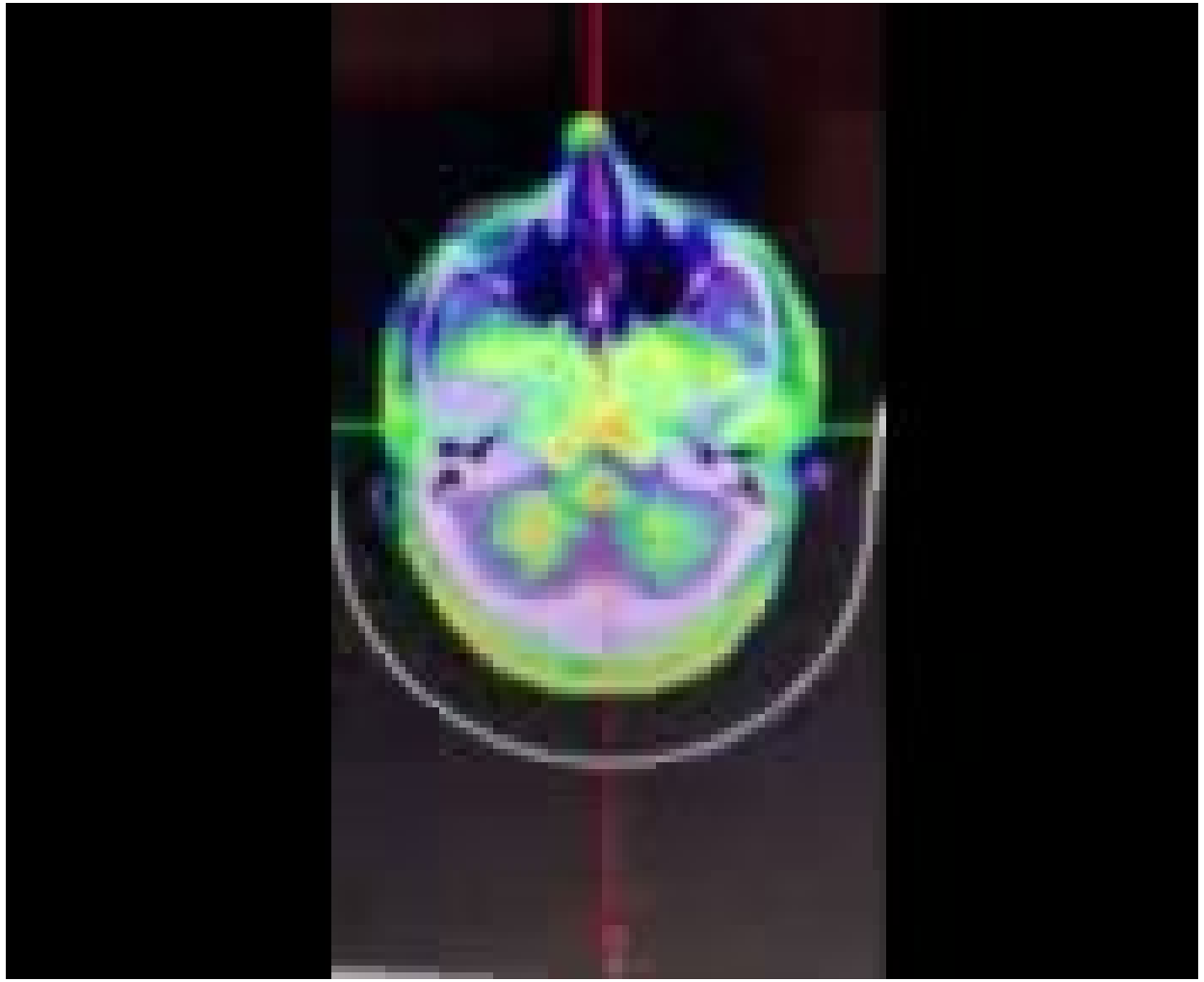
Case 1: 74 yo RHWM retired PharmD 3-4

- Something wrong?
- What is the Syndrome?
- What next?
  - Neuropsychological Evaluation:
    - Estimate of Pre-morbid IQ: superior
    - Moderate impaired performance in frontal/executive domains characterized by mildly impaired multitasking/set-shifting and working memory, difficulties with organization/planning, perseveration, and monitoring/error checking, and moderately to severely impaired inhibition and verbal fluency (with difficulties persisting over time). Impairments or low performance (relative to expected level) in non-verbal abstract reasoning, naming, oral production, and processing speed.
    - Attention: intact
    - Language: Auditory comprehension mildly impaired
    - Memory:
      - Verbal - mild encoding difficulties, flat learning, mildly impaired retrieval, and relatively intact recognition, small degree of storage loss
      - Visual – Moderately impaired encoding, moderately impaired recall (though with 100% retention) and intact recognition
      - Overall, memory difficulties were consistent with frontal/executive impairment impacting encoding and retrieval, rather than frank memory loss (some in verbal but not in visual domain)
  - Cognitive Assessment Panel: okay
  - Structural brain imaging: MRI



Case 1 Brain MRI

Case 1 Amyloid PET



Case 1: 74 yo RHWM retired PharmD 3-4

- Etiological Dx: bvFTLD* with amnestic and dysexecutive presentation
- Improvement with low dose donepezil, more organized, more motivated and engaging and attentive to wife's feedback, more aware – MoCA had dropped to 20 increased after donepezil to 25
- Over years, more emergent behaviors, repetitive and compulsive behaviors, asking neighbor for sex and from his wife, apathy and "staying in bed all day", resistive
- Added escitalopram
- Increasing ADL dependence, stopped driving, couldn't be left home alone

Case 2: 51 yo RHWM employed executive

- HPI: ~1-2 yrs of subtle changes in behavior (interactions at work), and executive function, +/- changes in memory depending on who you ask
- Pt: Dynamics at work; admits to being less mentally efficient – “but that’s just aging --- that’s what I’ve been told”
- Spouse:
  - Issues at work …
  - A few times conflict regarding conversation, their plans and timing life events – jolting to her
  - More anxious; “stressed a lot”; staying up late trying to do work; sleeping less
  - D/w primary clinician and was re-assured; wife told not to worry about him so much;

Case 2: 51 yo RHWM employed executive

- Structured multidomain review of cognition, daily function, behavior/neuropsychiatric symptoms, sensorimotor function
- Scale for below: 0 = wnl, Tr = subtle/very mild, 1+ = mild, 2+ = moderate , 3+ = severe)
- Cognition:
  - Memory: 1+
    - Repetitive, misremembering
  - Attention: 2+ (“always been that way to some degree”)
  - Executive Function: 1-2+
  - Language: 0-Tr (wife 0, pt Tr) (+ word finding pauses/difficulties when tired)
  - Behavior: 1-2+
    - Judgment and interaction issues with team at work, considered to be more aloof and less sensitive and dismissive, anxious, mildly less motivated

Case 2: 51 yo RHWM employed executive

- Daily Function: independent with subtle decline
  - FAQ 2/30 (taxes, travel)
- Behavior/Neuropsychiatric Symptoms:
  - NPIQ severity = 7 (irritability, anxiety depression/dysphoria, disinhibition, lability, night-time behaviors)
  - NPIQ distress = 9
- Sensorimotor: none

Case 2: 51 yo RHWM employed executive

- Risk Factors for Cognitive-Behavioral Impairment/Dementia: none (parents alive and well)
- Safety: okay
- PMH: no significant
- Meds: none
- Supplements: multivitamin
- Developmental Hx: no issues; could be inattentive “or absent-minded in a professorial way”, BS/PhD from elite universities
- SHx: married x27 yrs, working as high level executive, adult children
- Health Related Behavior: rare EtOH, good exercise in past less now
- Caregiver: Zarit like scale moderate burden

Case 2: 51 yo RHWM employed executive

- Exam:
  - Trophic skin changes w/ hair loss in legs to lower shins
  - Neuro:
    - 1+ saccadic breakdown of smooth horizontal pursuits
    - 1+ diminished cold and vibration sense at toes bilat
    - Tr to 1+ diminished arm swing on L

Case 2: 51 yo RHWM employed executive

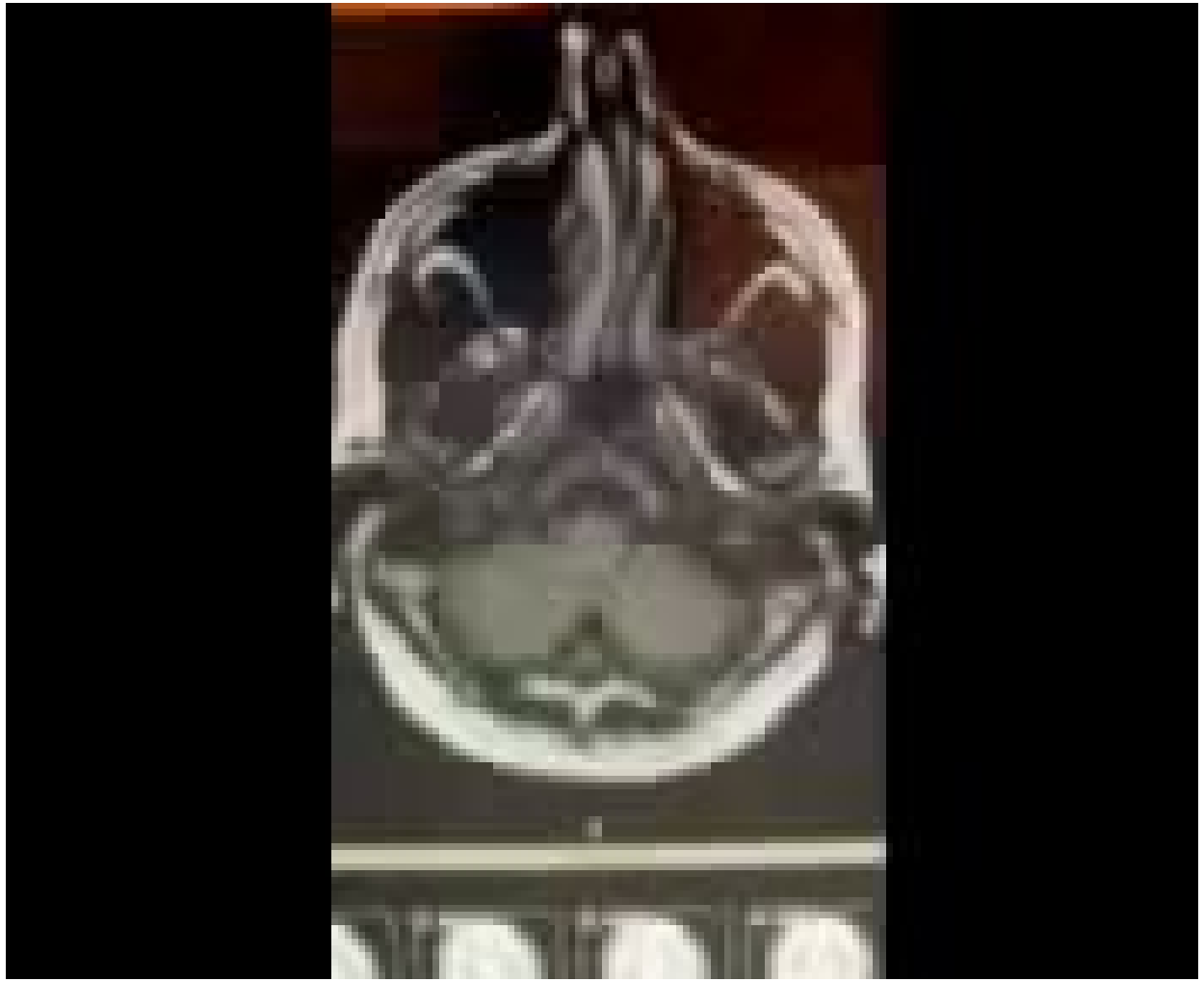
- Neurobehavioral Status Exam:
- Appropriate, attentive to examiner
- MoCA = 26/30 (- 1 cube copy, -3, recall)
- MoCA MIS (Memory Index Score 0-15) = 4/15 (1 cue, 1 multiple choice)
- Letter Fluency (F) in 60 sec 25
- Animal Fluency in 60 sec 15
- Naming (from ACE-R): 12/12.

  Very occasional word-finding difficulties and paraphasias.

Case 2: 51 yo RHWM employed executive

- Something wrong?
- What is the Syndrome?
- What next?
  - Neuropsychological Evaluation:
    - Pre-morbid estimate of IQ: very superior
    - Storage loss (verbal and visual), variable executive functions, some score low or borderline
  - Cognitive Assessment Panel: okay
  - Structural brain imaging: MRI

Case 2 MRI



Case 2 FDG-PET

Case 2 CSF Profile

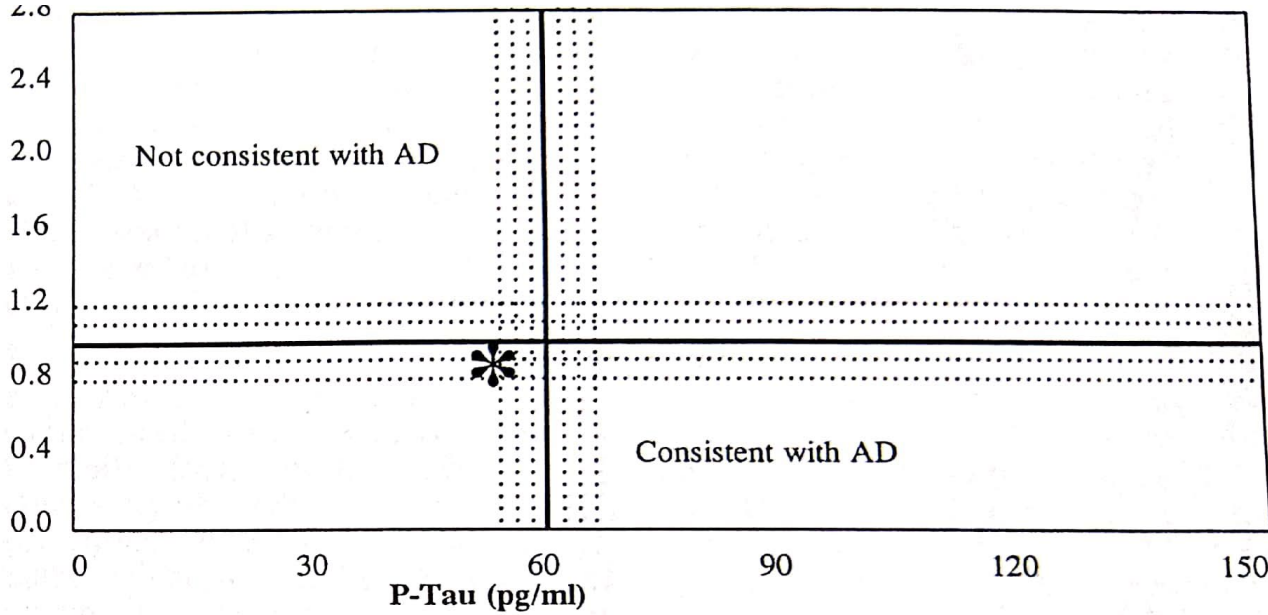
between diagnostic categories. A borderline result can occur in individuals with and without AD and therefore does not strongly support the inclusion or exclusion of AD in the diagnosis. Please see the Comments section for additional information.

Technical Results

Aß42	461.65 pg/ml
T-Tau	257.25 pg/ml
P-Tau	53.75 pg/ml
ATI	0.85

Patient data is plotted on the graph below to illustrate the relative position of this individual's result compared to recognized reference points for diagnostic cutoff values (AT Index of 1.0 and P-tau concentration of 61 pg/ml). Clinical studies indicate that ranges for all three biomarkers overlap to some extent (zones of 0.8 to 1.2 AT index and 54 - 68 pg/ml P-tau shown on the graph) between the AD and non-AD populations as reflected in the sensitivity and specificity figures.

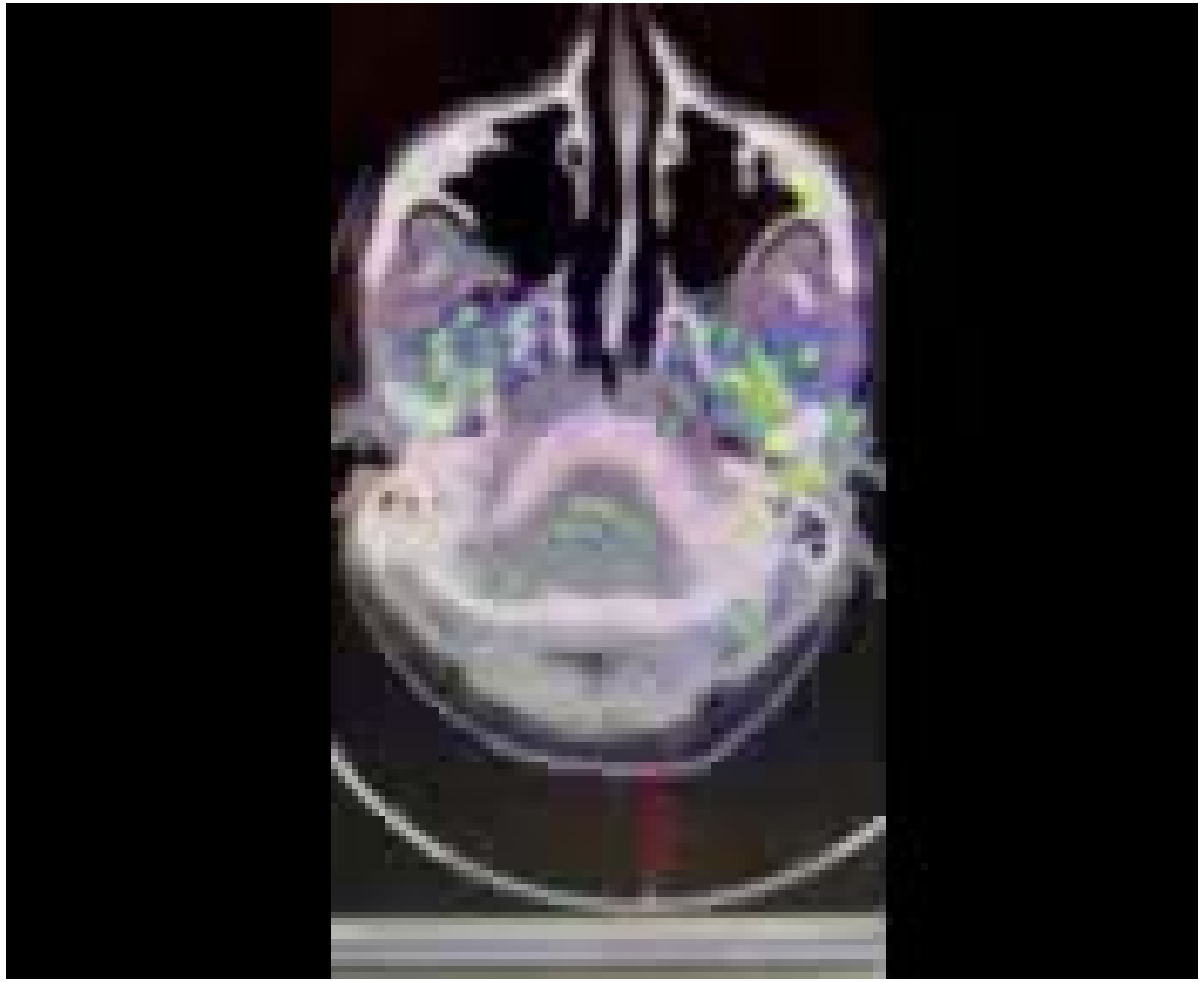
- Not in cleanly in AD quadrant
- Low Abeta 42
- Tau not elevated
- p-tau not high but “close”?



Comments

This analysis detected levels of $A\beta_{(1-42)}$ peptide, total tau and/or phospho-tau protein in cerebrospinal fluid which are within a borderline zone between diagnostic categories. A borderline result can occur in individuals with and without AD and therefore does not strongly support ruling in or ruling out AD.[1-11] The technical results section provides details of the numbers and the graphical representation indicates the

Case 2 Amyloid PET

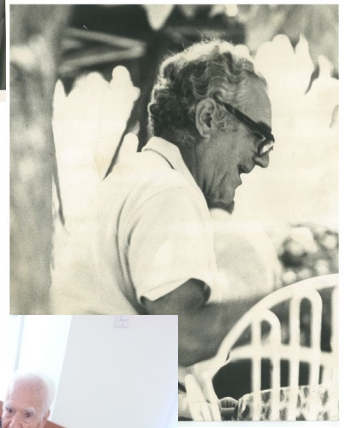


Case 2: 51 yo RHWM employed executive

- Etiological Dx: Early-onset AD in MCI stage (amnestic, dysexecutive, mild neuropsychiatric sx's)
- ApoE-e4 homozygous (e3/e4)
- Escitalopram while we went through diagnostic process, then low dose donepezil 5 mg daily after more clear sx's to them (MoCA down to 22; 0/5 recall, MIS 2/15) -- Improvement with low dose donepezil with MoCA back up to 25 (3 years out), compensating with memory aides and organization in daily life, driving – repeat neuropscyh eval shows progression overall in memory, executive functions, and hints of language
- Temporary disability, then one year, then retired.
- Exercising a lot, stress "free" life,
- FAQ higher 9-12 range
- Enrolled in anti-amyloid passive antibody Phase 3 efficacy clinical trial

"Doctor, Doctor: A Diagnostic Case Comparison of Misremembering, Misbehavior, Misunderstanding, and Mis- and Dys-Execution involving Two Doctoral Professionals

- Misremembering – for different reasons
- Misbehavior and Misunderstanding – Case 1 more frontal-based; Case 2 more memory systems based and reactive → more perceived (misunderstood) by others as misbehavior
- Dysexecutive function: Both cases, in Case 2 in a very high functioning and demanding environment thus “superhigh level complex ADLs” affected early
- Mis-execution and undercentainty regarding “normal or age-related” (ascribing observation), dichotomizing continuous traits and measurements: clinician heal thyself …



No man is an island, entire of itself... Any man's death diminishes me, because I am involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee

~

Collective global problems require collective global commitment, investments, and efforts → <u>our problems requires our solutions</u>

"The journey of a thousand miles begins with one step."

-Lao Tzu

THANK YOU!

To prevent sometimes

To help often

To console always

"Where there is no hope, there can be no endeavor."

-Samuel Johnson