YOUNG-ONSET DEMENTIA

VIC-SI LTCI LEARNING SERIES – APRIL 29, 2021

Alexandre Henri-Bhargava, MDCM, MScCH, FRCPC

Clinical Associate Professor of Medicine, UBC

Medical Director, Neil And Susan Manning Cognitive Health Initiative

DISCLOSURES

- Support for clinical trials related to dementia from corporate entities: Anavex, Shanghai Green Valley, Lilly, Boehringer Ingelheim, TauRx, Roche, AstraZeneca, IntelGenX,
- Consulting fees: Roche
- Support for clinical trials related to dementia from non-corporate entities: CCNA, CABHI

- *I will not be discussing any investigational products related to these trials*

MEET SHEILA

- 51yo F
- Born on Vancouver Island
- Married, lives with husband and 2 teenaged children
- Works 4 d / week as teacher's asst for special needs kids
- English first language; 13 years of education
- PMHx: MDD (in remission x 10 years on treatment), episodic migraine, hysterectomy for fibroids 2 years ago
- Rx: paroxetine 20mg OD, ibuprofen PRN, rizatriptan PRN
- Habits: vegetarian, 5 EtOH / wk, no tobacco, no cannabis, no illicit drugs
- Family Hx: Parents died of cancer in 70s, 2 healthy younger siblings

SHEILA'S STRESSES

- In supply role x 1 year, moving to different schools
- "Difficulty" at work, but not 1:1 with students
- Officially sanctioned by school district and asked to meet with MD
- Stress +++ - does not like supply teaching role, difficulty with work-life balance, husband and kids have "their own issues"
- Describes several months of anhedonia, feelings of worthlessness and guilt, insomnia, poor concentration, decreased energy, poor appetite
- Physical exam normal
- MoCA 27/30 (-3 memory); MIS – 9/10; PHQ-9 20

WHAT ARE YOUR NEXT STEPS FOR SHEILA?

SHEILA'S PROGRESS

- Diagnosed with major depressive episode
- Takes medical leave from work – now on longterm disability
- Undertakes CBT course – difficult to follow through on homework
- Paroxetine dose gradually increased to 40mg
- "With stress of work off my shoulders I feel much better"
- Increasingly difficulty with complex paperwork, using computer; forgetting to pick kids up on a few occasions; husband taking over doing taxes

QUESTIONS

- Should she be screened for dementia?
- What is the difference between screening and case finding?

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PERSPECTIVE

Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia

Zahinoor Ismail[1] | Sandra E. Black[2] | Richard Camicioli[3] | Howard Chertkow[4] | Nathan Herrmann[5] | Robert Laforce Jr.[6] | Manuel Montero-Odasso[7,8] | Kenneth Rockwood[9] | Pedro Rosa-Neto[10] | Dallas Seitz[11] | Saskia Sivananthan[12] | Eric E. Smith[11] | Jean-Paul Soucy[13] | Isabelle Vedel[14] | Serge Gauthier[15] | the CCCDTD5 participants

TABLE 3 Dementia case finding and detection

Is there a role for screening at-risk patients without clinical concerns? In what context is assessment for dementia appropriate?
1. Cognitive testing to screen asymptomatic adults for the presence of mild cognitive impairment or dementia, including asymptomatic persons with risk factors such as family history or vascular risk factors, is not recommended. 1C (95%)
2. Primary care health professionals should be vigilant for potential symptoms of cognitive disorders in older or at-risk individuals, including but not limited to: reported cognitive symptoms by the patient or an informant, otherwise unexplained decline in instrumental activities of living, missed appointments or difficulty remembering or following instructions or taking medications, decrease in self-care, victimized by financial scams, or new onset later-life behavioral changes including new depression or anxiety (1C). If there is a clinical concern for a cognitive disorder (which may not always be shared by the patient due to anosognosia) then validated assessments of cognition, activities of daily living, and neuropsychiatric symptoms are indicated (see subsequent sections for suggestions for valid tools). 1A (95%)

FURTHER STEPS – WHAT NEXT INVESTIGATIONS?

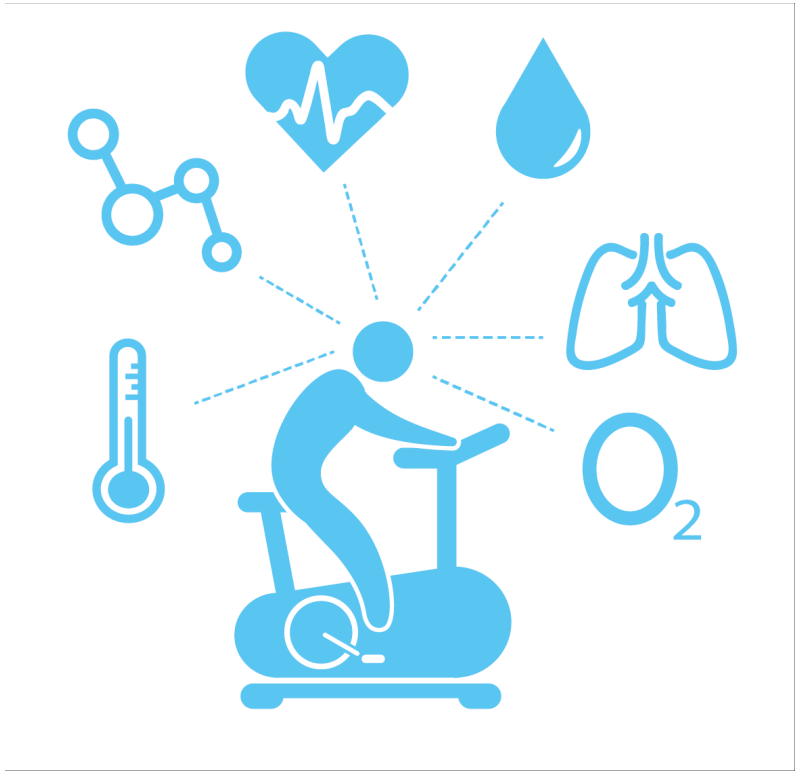
WHICH OF THESE TOOLS CAN BE USED TO OBTAIN IN-DEPTH INFORMATION TO DIAGNOSE MCI OR DEMENTIA

A. EEG analysis of cognitive ERPs
B. Standardized Mini-Mental State Exam
C. Toronto Cognitive Assessment
D. Zarit Burden Interview

In addition to neuropsychological testing (if available), we make the following recommendations with regard to the instruments available for more in-depth cognitive evaluation of MCI and dementia:

1. A number of well-validated instruments exist to help in the process of MCI or dementia diagnosis. However, diagnosis of MCI or dementia should not be solely based on an impaired result on cognitive screening tests. 1B (100%)
2. Cognitive screening tools exist specifically for the early identification of MCI (MoCA, TorCA[44]). Among them, the MoCA offers strong normative data (1C) while the TorCA has just been recently published (2B). (87%)
3. Consider the DCQ,[45] a new cognitive screening tool developed based on updated criteria for atypical syndromes (behavioral variant frontotemporal dementia, primary progressive aphasia, and Alzheimer's disease variants). It has been well validated in French and English and offers an option to commonly used screening tests (eg, MMSE, MoCA) which were not designed for screening atypical syndromes and are often not sufficient to capture subtle cognitive and social cognition changes associated with atypical dementia. 2B (84%)
4. Innovative new tools exist, similar to growth curves used in pediatrics, to allow longitudinal cognitive evaluation based on serial cognitive assessments.[32] 1C (80%)

WHICH OF THE FOLLOWING NON-COGNITIVE MARKERS CAN IDENTIFY PATIENTS WITH COGNITIVE IMPAIRMENT LIKELY TO PROGRESS TO DEMENTIA?

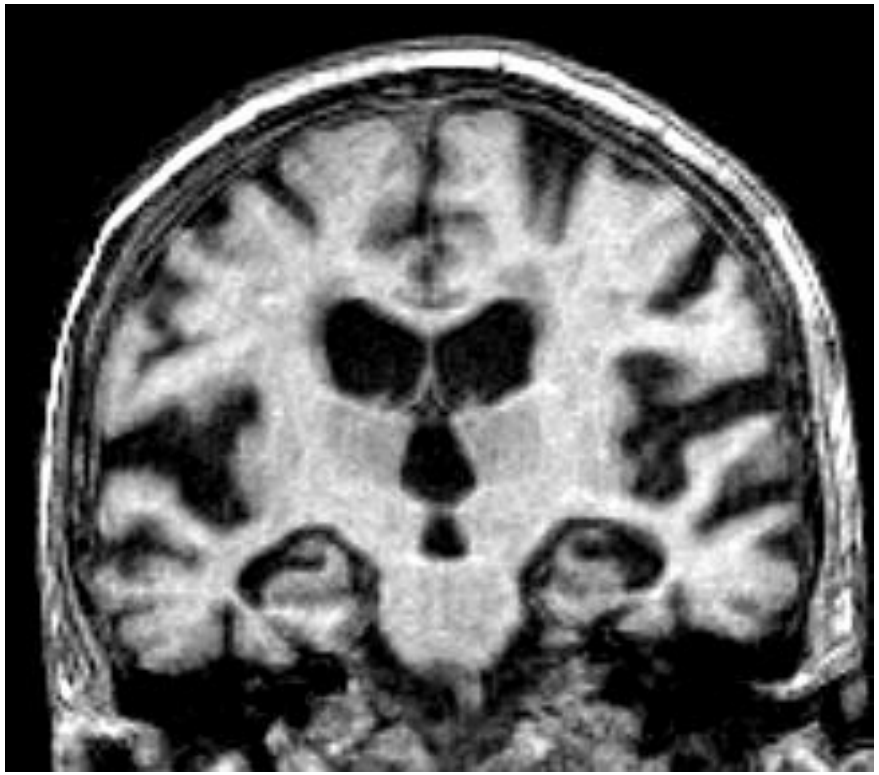


A. Body fat percentage with calipers
B. Dual-task gait impairment
C. Hand dynamometer grip strength
D. Composite frailty index

TABLE 5 Non-cognitive markers of dementia

1a. There is strong evidence that slower gait speed is associated with future dementia, in population studies. When gait speed (cut-off gait speed below 0.8m/s) is coupled with cognitive impairment (subjective or objective) the risk is higher. We recommend testing gait speed in clinics in those patients with cognitive complaints/impairments if time/resources are available. 1B (62%, 100%) Note: Protocols on how to assess gait speed with stopwatch are available. Testing takes, on average, 3 minutes to perform.[91]
1b. Dual-task gait impairment (lower speed or high cost) is associated with future incident dementia. In MCI samples, dual-task gait was shown to predict time to progression to dementia. Variability in the delivery of testing protocols is noted. We recommend that dual-task gait test may be used in specialized clinics (memory clinics) to help identify mild cognitive impairment (MCI) older adults at higher risk of progression to dementia if time/resources are available. 2B (60%, 100%) Note: Published protocols on how to assess Dual-Task Gait for dementia risk with just a stopwatch are available.
2. The presence of parkinsonism may increase by three times the odds of developing dementia. We recommend routinely assessing parkinsonism as a marker of risk of dementia in memory clinics. 1B (91%)

WHICH OF THE FOLLOWING IS TRUE REGARDING THE ROLE OF STRUCTURAL IMAGING IN THE INVESTIGATION OF DEMENTIA

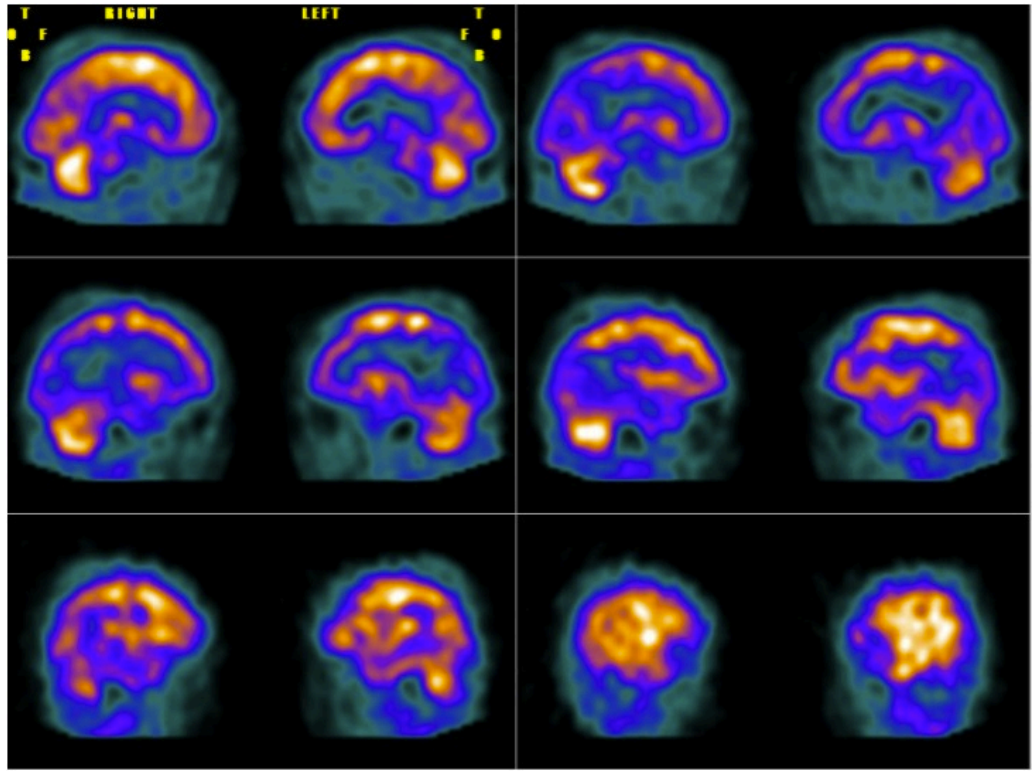


A. Imaging is rarely indicated except in atypical cases
B. MRI scanning is indicated in many cases of possible dementia
C. CT scanning is indicated in many cases, but not MRI
D. CT or MRI may help to rule out non-dementia diagnoses

Structural Imaging

1. Even in older subjects, anatomical neuroimaging is recommended in most situations, using the following list of indications: onset of cognitive signs/symptoms within the past 2 years, regardless of the rate of progression; unexpected and unexplained decline in cognition and/or functional status in a patient already known to have dementia; recent and significant head trauma; unexplained neurological manifestations (new onset severe headache, seizures, Babinski sign, etc.), at onset or during evolution (this also includes gait disturbances); history of cancer, in particular if "at risk" for brain metastases; subject at risk for intracranial bleeding; symptoms compatible with normal pressure hydrocephalus; significant vascular risk factors. 1C (76%; 93%)
2. Magnetic resonance imaging (MRI) is recommended over computed tomography (CT), especially given its higher sensitivity to vascular lesions as well as for some subtypes of dementia and rarer conditions (2C). (87%) If available, and in the absence of contraindications, 3T MRI should be favoured over 1.5 T. (2C) (91%) If MRI is performed, we recommend the use of the following sequences: 3D T1 volumetric sequence (including coronal reformations for the purpose of hippocampal volume assessment), fluid-attenuated inversion recovery (FLAIR), T2 (or if available susceptibility-weighted imaging [SWI]) and diffusion-weighted imaging (DWI). 1C (98%) We recommend against the routine clinical use of advanced MR sequences such as rs-FMRI, MR spectroscopy, diffusion tensor imaging (DTI), and arterial spin labelling (ASL). However, these sequences are promising research tools that can be incorporated in a research setting or if access to advanced expertise is present. 2C (98%)
3. If CT is performed, we recommend a non-contrast CT and coronal reformations are encouraged to better assess hippocampal atrophy. 1C (100%)
4. We recommend the use of semi-quantitative scales for routine interpretation of both MRI and CT scans including: the medial temporal lobe atrophy (MTA) scale for medial temporal involvement, Fazekas scale[88] for white matter changes, and global cortical atrophy (GCA) to qualify global atrophy. 1C (96%)
5. We recommend against the routine clinical use of quantification software pending larger studies demonstrating the added diagnostic value of these tools. Of note, this is a rapidly evolving field and such recommendation could change in the future. 2C (93%)

WHICH OF THE FOLLOWING IS TRUE REGARDING THE ROLE OF FUNCTIONAL IMAGING IN THE INVESTIGATION OF DEMENTIA



A. Functional imaging is always indicated if structural imaging is
B. MSP-funded options include FDG-PET and brain SPECT
C. SPECT is more sensitive than FDG-PET for distinguishing normal vs dementia
D. No modality is >90% specific in diagnosing dementia

Functional and Ligand-Based Imaging

3a. For a patient with a diagnosis of a cognitive impairment who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a cognitive disorders specialist but whose underlying pathological process is still unclear, preventing adequate clinical management, an [^{18}F]-FDG PET scan is an effective and accurate tool for differential diagnosis purposes. 1A (88%)

3b. If such a patient cannot be practically referred for a FDG-PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes. 1B(86%)

SHEILA – IN DEPTH ASSESSMENT

- Disability insurers request neuropsychological assessment
  - "In summary, Sheila exhibited impairments in aspects of learning, visual and verbal recall, and executive functioning that were greater than expected for age, occupation, and estimated pre-morbid intelligence level. She demonstrated mild depressive symptomatology, which in our opinion cannot exclusively account for her deficits. A diagnosis of mild neurocognitive disorder, and possibly major neurocognitive disorder, NOS is entertained. Specialist medical evaluation is recommended."
- Referred to Specialist Memory Clinic at RJH
  - Scores abnormally on the Toronto Cognitive Assessment (TorCA)
  - Has abnormally increased dual-task cost when performing 10m gait speed
  - MRI – essentially normal
  - SPECT scan – normal brain perfusion pattern
  - Dx: MDD in partial remission; probable major neurocognitive disorder, NOS; r/o major neurocognitive disorder due to AD

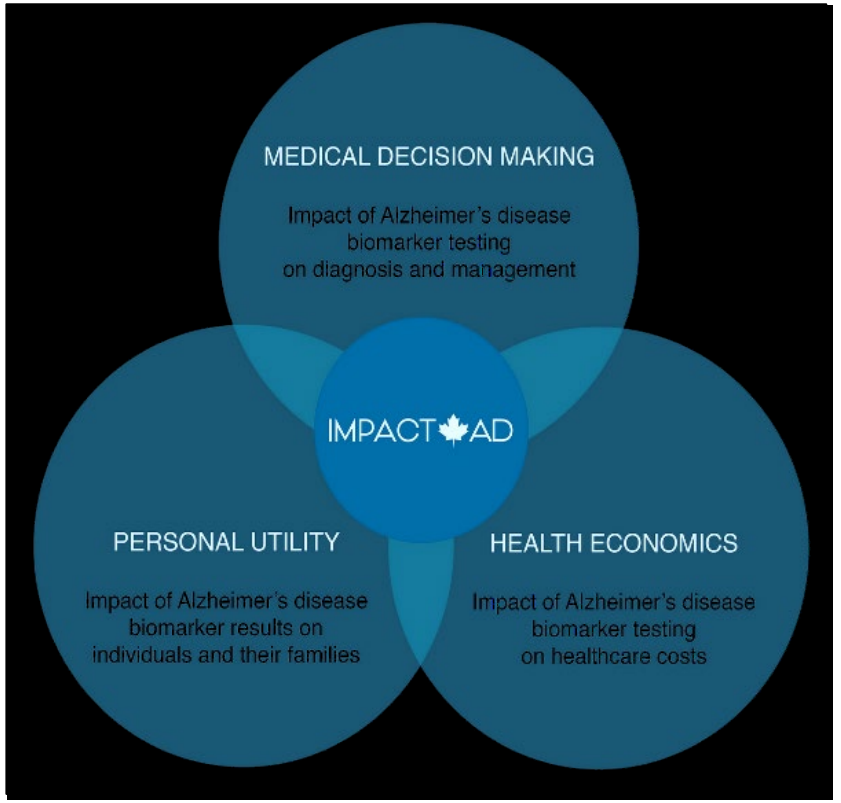
ARE THERE ANY OTHER TESTS AVAILABLE?

Fluid Biomarkers

6. Cerebrospinal fluid (CSF) analysis is not recommended routinely, but it can be considered in dementia patients with diagnostic uncertainty and onset at an early age (<65) to rule out Alzheimer's disease (AD) pathophysiology. 1C (78%; 100%)
7. CSF analysis can also be considered in dementia patients with diagnostic uncertainty and predominance of language, visuospatial, dysexecutive, or behavioral features to rule out AD pathophysiology. 1C (78%; 100%)

IMPACT AD – DR. M. DEMARCO, SPH

- Multi-site observational, longitudinal cohort study
- Participants: dementia specialist or patients of a consenting specialist
- Purpose: the goal is the understand how access to Aβ and tau CSF testing impacts clinical decision making of dementia specialists and
  how patients and/or care providers are impacted by the results
- Clinicians complete 3 questionnaires to assess impact of results
- Patients and/or care providers are contacted for follow up interview at approximately 1 and 6 months from follow up visit (where results are given)



Neurodegenerative Biomarker Profile, CSF

Results

Analyte, Ratio, Profile	Result	Reference value
Aβ42, CSF	**229 ng/L**	≥ 1200 ng/L
Total tau, CSF	**720 ng/L**	≤ 450 ng/L
Total tau/Aβ42 ratio, CSF	**3.145**	≤ 0.28
Aβ40, CSF	9940 ng/L	Not applicable
Aβ42/40 ratio, CSF	0.023	Not available
ATN Profile	**A+T*N+**	A-T*N-

Interpretation

The biomarker profile is consistent with an Alzheimer's pathologic change.

Biomarker results require interpretation in the context of other medical information.

SHEILA – FINAL DIAGNOSIS

- Major neurocognitive disorder due to Alzheimer disease (aka clinically probable Alzheimer disease)
- What's next for Sheila?.... stay tuned

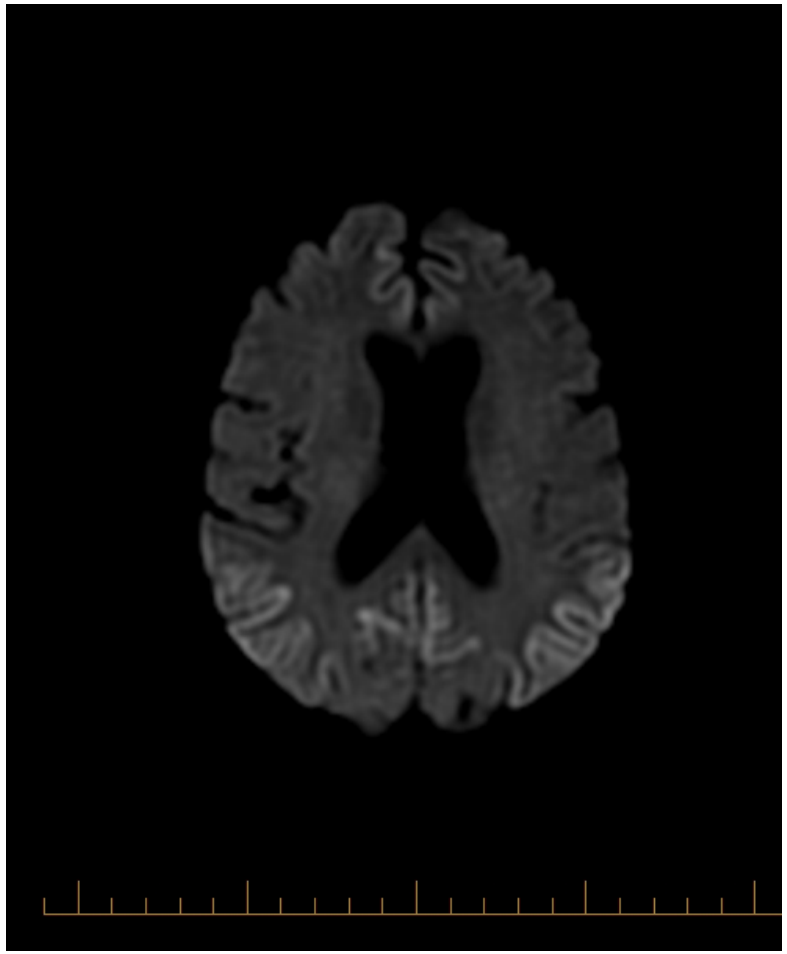
DETOUR

- Let's look at a few other cases presenting issues regarding diagnosis…

WILLIAM

- 53yo single man
- Lineworker in remo
- Previously healthy, o
- Smoker, drinks 14-2
- Complains of troubl balance
- MoCA 24/30
- MRI reported as no

Assay	Result	
EP-QuIC	Positive	Sens 96% Spec 99%
14-3-3	29 000 AU/mL	Sens 84% Spec 90%
hTau	1436 pg/mL	Sens 92% Spec 88%



CHARMAINE

- 55yo single mother of teenaged son
- High-functioning academic
- No past medical history, Rx
- Healthy lifestyle
- "Couldn't function" during sabbatical
- ? Depression – ruled out by extensive psychological evaluation
- MoCA 18/30; imaging normal
- Developed facial twitches – seizures?

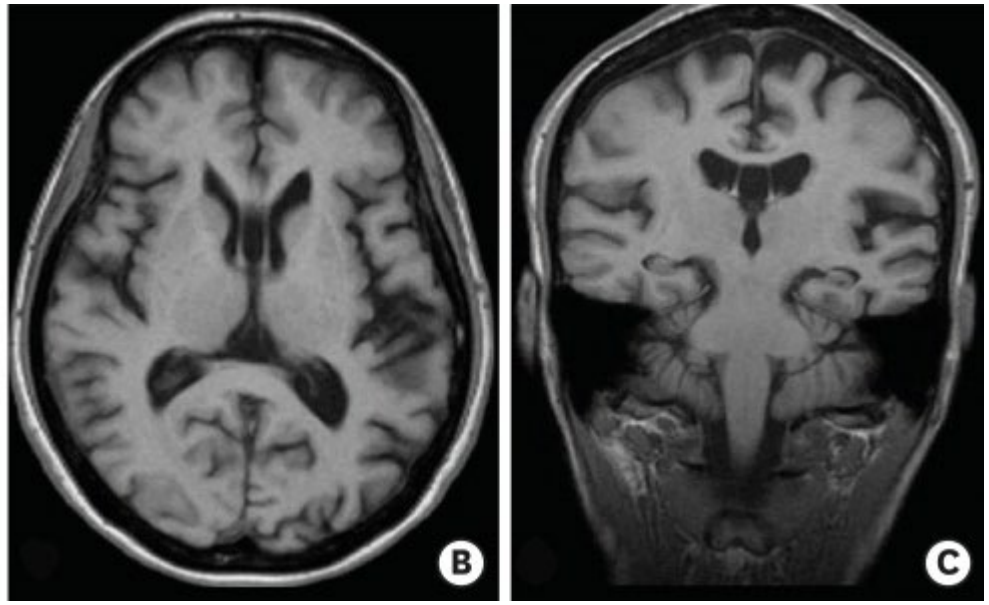
- PET scan done to r/o malignancy
  - **Hypermetabolism** of basal ganglia and insular cortices
- CSF showed 30WBC, mildly elevated protein
- CSF and serum positive for LGi1 Ab
- Dx – LGi1-mediated autoimmune encephalitis
- Rx – IV methylprednisolone, IVIg, Rituximab

JOHN

- 51yo organic farmer and teacher, father of 4
- History of IBS but otherwise healthy
- 18yrs education, bilingual English/French
- No Rx, low FODMAP diet, no habits
- 85yo mother recently diagnosed with MCI
- 2 years of progressive hesitancy of speech, word-finding difficulties
- Memory, executive function intact
- Recent visit to ER for laceration – ER physician reported to motor vehicles

JOHN

- Physical exam normal
- MoCA 25/30 (could not repeat sentences, 4 "F" words)
- Many word-finding hesitations in speech
- Trouble repeating sentences, single words better
- Memory and executive function relatively intact
- MRI reported as normal (shown right)
- SPECT: mildly reduced perfusion to left hemisphere, nonspecific pattern

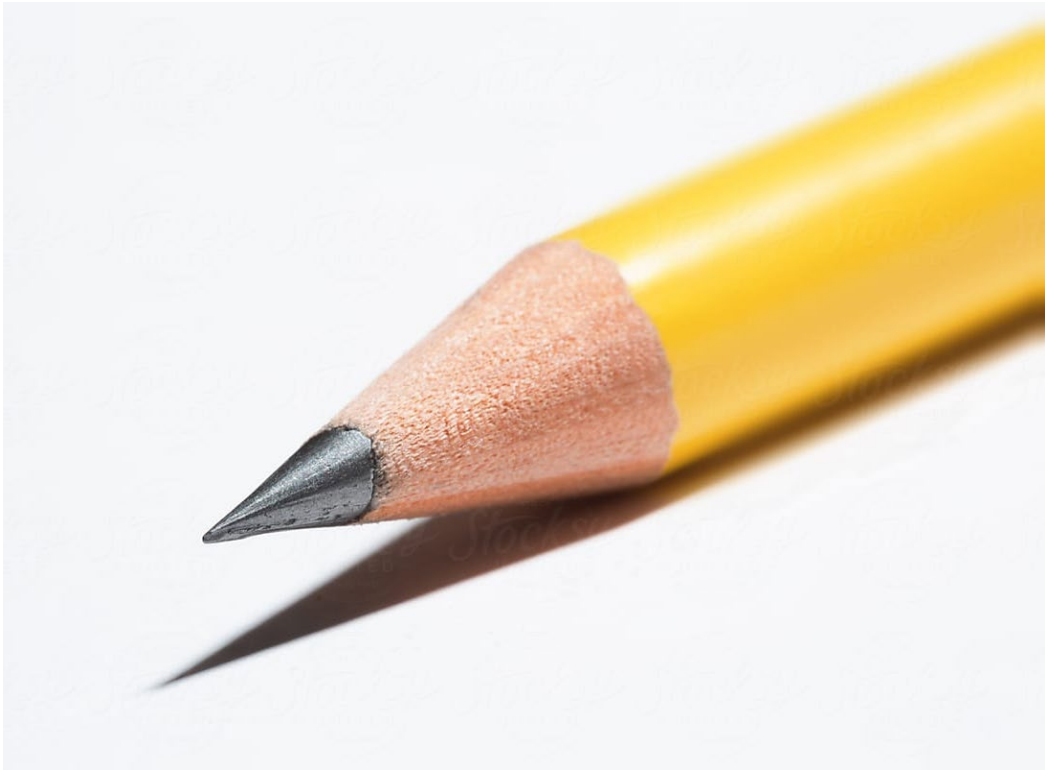


JOHN

- Speech-language pathology assessment:
  - Nonfluent spontaneous speech
  - Anomic pauses
  - Impaired repetition
  - Normal comperehension, reading
  - Difficulty with writing
  - Reduced fluency task
  - Impaired calculation

- Dx: single-domain, non-amnestic mild cognitive impairment (language)
- Primary progressive aphasia, logopenic subtype (aka logopenic progressive aphasia)
- Language variant of Alzheimer disease

DIAGNOSIS OF YOUNG-ONSET DEMENTIA: WHAT'S THE POINT?



- Broader differential to consider in younger patients
  - Refer for specialist assessment
- Typical dementias are still the most common to present in younger patients
  - May present with atypical prodrome (e.g., burnout, depression)
  - May present with atypical features
- Imaging (MRI +/- functional) almost always indicated
- CSF analysis increasingly useful

SOME STATISTICS

- Dementia before age of 60 accounts for 2-8% of all cases
  - 10% of AD are genetic (vs. 1% total); >40% FTD are genetic
- Causes:
  - 35% Alzheimer disease (10% of these are genetic vs 1% in entire AD population)
  - 15% Frontotemporal dementia (>40% genetic)
  - 15% Vascular dementia (rare genetic causes include CADASIL)
  - 10% Alcohol-related disorders
  - 5% dementia with Lewy bodies
  - 20% Rare illnesses (HIV, Huntington, CJD, mitochondrial diseases, autoimmune, etc.)

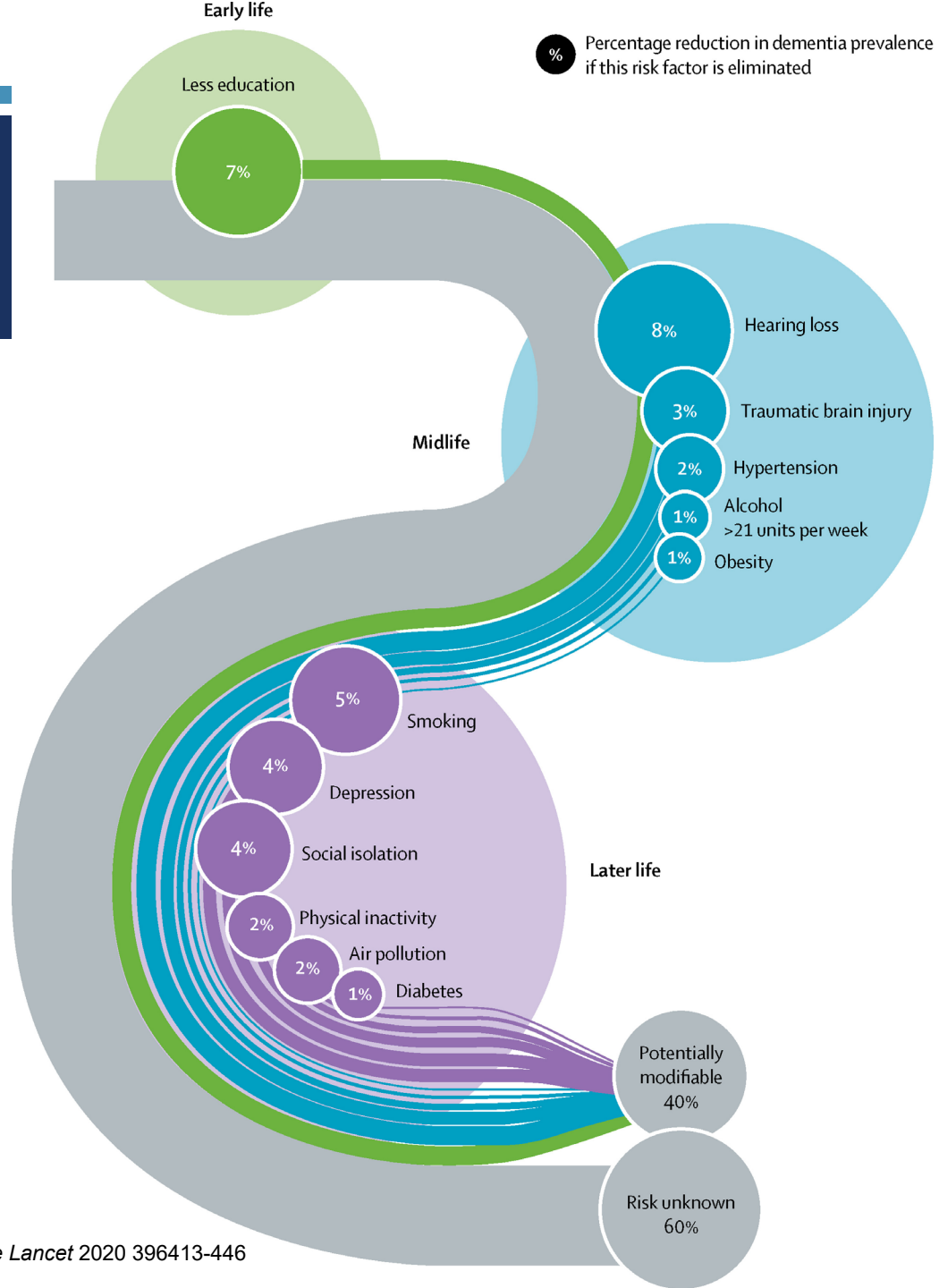
BACK TO SHEILA – AFTER THE DIAGNOSIS

Which of the following medications are indicated for treating Sheila's condition at this stage?

A. Donepezil
B. Memantine
C. Refer for clinical trials
D. A + B
E. A + C

SHEILA – LIFESTYLE

- Which of the following modifiable risk factors have **NOT** been associated with risk of developing dementia?
  - A. Air pollution
  - B. Midlife hearing loss
  - C. Physical inactivity
  - D. Vitamin D deficiency
  - E. Excess alcohol consumption



Livingston *et al. The Lancet* 2020 396413-446

HOW ELSE CAN YOU SUPPORT SHEILA AT THIS STAGE OF THE DIAGNOSIS?

SHEILA – MULTIDISCIPLINARY PLAN

- Rx cholinesterase inhibitor
  - Consult with pharmacist
  - Follow-up on side effects / efficacy
- Counsel on lifestyle factors, follow-up with RN
  - Exercise and activity plan
- Refer to Alzheimer Society of BC FirstLink program
- Refer to social work
  - Power of attorney, healthcare rep, will
  - Vocational assistance
  - Family support
- Liaise with employer / insurance
- Counsel on driving cessation
- Offer to follow over time

HELPFUL RESOURCES:

Here are some excellent resources for drivers considering their options.

- **ICBC Driver Medical and Re-exams:**
  www.icbc.com/driver-licensing/re-exam
- **Public Transit (BC Transit):**
  call 250-383-6161
  www.bctransit.com

  Discounted monthly pass ($45/month) for passengers over 60 years of age
- **BC Bus Pass for Low Income Seniors:**
  www.buspass.gov.bc.ca
- **For Information on handyDart, handyPass:**
  call 250-727-7811
  www.bctransit.com

  For people with disabilities who are not able to use regular bus service. Custom transit with door-to-door service and online or telephone booking.
- **Parking Permits:**
  call 250-595-0044
  www.drcvictoria.com

  For persons with disabilities that limit mobility. Application completed by physician; processing fee of $25 at the Victoria Disability Resource Centre.

For more information about transportation resources in your community:

Call 211 (it's FREE)

- **Driving Miss Daisy:**
  Fee based assistance and accompaniment services.
  Victoria and Saanich:
  250-588-4638
  Westshore: 250-813-0440
  www.drivingmissdaisy.ca
- **TaxiSaver (BCTransit):**
  call 250-995-5618

  Subsidized vouchers sold by BC Transit to registered handyDART passengers. Travel booked directly with participating taxi companies.
- **Volunteer Drivers**
  For medical appointments and other activities as drivers are available:
  - Capital City (Victoria): 250-388-7844
  - Oak Bay Volunteer Services: 250-595-1034
  - Saanich Volunteer Services: 250-595-8008
  - Westshore Better at Home: 778-677-3540
  - Sooke Community Assistance: 250-389-4661
  - James Bay Community Project: 250-388-7844
  - Metchosin Seniors Information Resource Centre: 250-478-5150

When is it time to hang up the keys?

Creating a road map for your transportation options in Greater Victoria

island health

TABLE 7 Psychosocial interventions

Individual Level
1. We recommend exercise (group or individual physical exercise) for people living with dementia.[98-101] We cannot recommend any specific exercise duration or intensity at this time. 1B (93%)
2. Group cognitive stimulation therapy is an intervention for people with dementia which offers a range of enjoyable activities providing general stimulation for thinking, concentration, and memory usually in a social setting, such as a small group. We recommend considering group cognitive stimulation therapy for people living with mild to moderate dementia.[101-104] 2B (96%)
3. Psychoeducational interventions for caregivers aim at the development of problem-focused coping strategies while psychosocial interventions address the development of emotion-focused coping strategies. These can include education, counseling, information regarding services, enhancing carer skills to provide care, problem solving, and strategy development. We recommend considering psychosocial and psychoeducational interventions for caregivers of people living with dementia.[105-110] 2C (96%)
Community Level
4. Dementia friendly organizations/communities are defined as the practice and organization of care/communities that is aware of the impact dementia has on a person's ability to engage with services and manage their health. It promotes the inclusion of people living with dementia and their caregiver in decisions and discussions with the aim of improving outcomes for the persons living with dementia and their caregivers. We recommend considering the development of dementia friendly organizations/communities for people living with dementia.[111-114] 2C (91%)
5. Case management is defined as the introduction, modification, or removal of strategies to improve the coordination and continuity of delivery of services which includes the social aspects of care. We recommend considering the use of case management for people living with dementia.[115-118] 2B 93%

SHEILA'S PROGRESSION

- Devastated but initially accepting of diagnosis
- Decides with husband to disclose to children
- Covered by LTD after much back-and-forth with insurer
- Tolerates medication with mild diarrhoea
- Looks into clinical trials – decides against this
- Husband works with friends to combat stigma
- Plan is made for gradual retirement from driving

UNIQUE CHALLENGES IN THE YOUNG-ONSET POPULATION

- Alzheimer Society of Canada / NISE Gap Project
  - Stigma (early retreat from the world)
  - Work responsibility
  - Financial struggles
- Relationship struggles including changing sexual relationships
- Lack of specialized support groups / services
- "Sandwich generation" (children, parents)
- More rapid progression?

QUESTIONS RELATED TO WORK

- Should patients be counselled to stop working after diagnosis?
- When is the right time to stop working?
- What alternatives exist to working?
  - How to replace life meaning derived from employment?
- How do you guide a patient through the disability process?

Photo credit: Rob Porter, Rocktographers

STIGMA AND ISOLATION

WHAT STRATEGIES MIGHT YOU EMPLOY WITH YOUR PATIENT TO COMBAT THESE?

SHEILA'S PROGRESSION

- Three years later:
  - Sheila has very poor short-term memory
  - Has lost insight
  - Insists on wanting to find a job, going for a drive
    - Frequent conflict
  - Far-away siblings feel she is not helping elderly parents enough

SHEILA'S PROGRESSION

- Four years later
  - Severe delusions of infidelity
  - Children "walk on eggshells" at home
  - Symptoms fluctuate diurnally and over time
  - Forgets / refuses to bathe, change clothes
  - Becoming physically frail
  - Resists attempts at home supports

SHEILA'S PROGRESSION

- When is the right time to consider LTC placement?
- What might some issues be affecting this decision?

QUESTIONS?

Thank you for your attention!

alexhb@uvic.ca