Detect · Diagnose

Lilly ConnectAD™

Welcome to ConnectAD™, a clinical case series created by the Eli Lilly and Company Neuroscience medical education team. This series is intended to connect healthcare professionals to resources that help them detect, diagnose, and manage Alzheimer's disease.

Disclaimer

The content for this clinical case was developed in collaboration between a group of global clinicians who care for patients with Alzheimer's disease and Eli Lilly and Company.

A variety of cognitive and diagnostic tests can reasonably be used in the detection and diagnosis of Alzheimer's disease. Inclusion of specific cognitive and/or diagnostic tests in this case reflects the diversity of clinical preferences, and the use of particular diagnostic tools does not imply endorsement or recommendation by Lilly.

Learning Objectives

Through completing this course, you will have a deeper understanding of:

1. The clinical presentation of Alzheimer's disease

2. How to integrate clinical and biomarker assessments to make an accurate diagnosis of Alzheimer's disease in the earliest stages

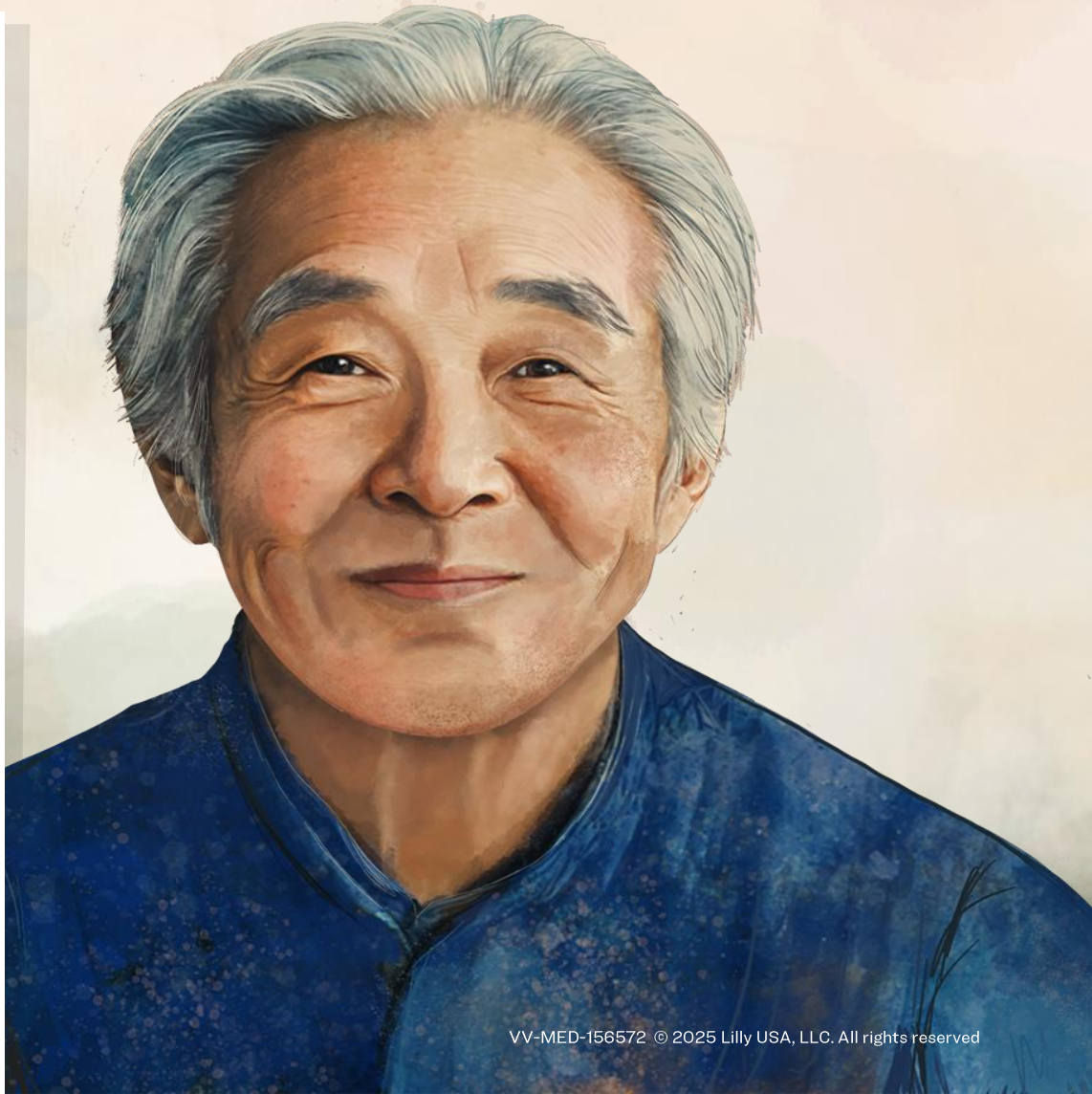
Lilly ConnectAD™

Connect *with Jian*

Detect · Diagnose

Our Patient Jian

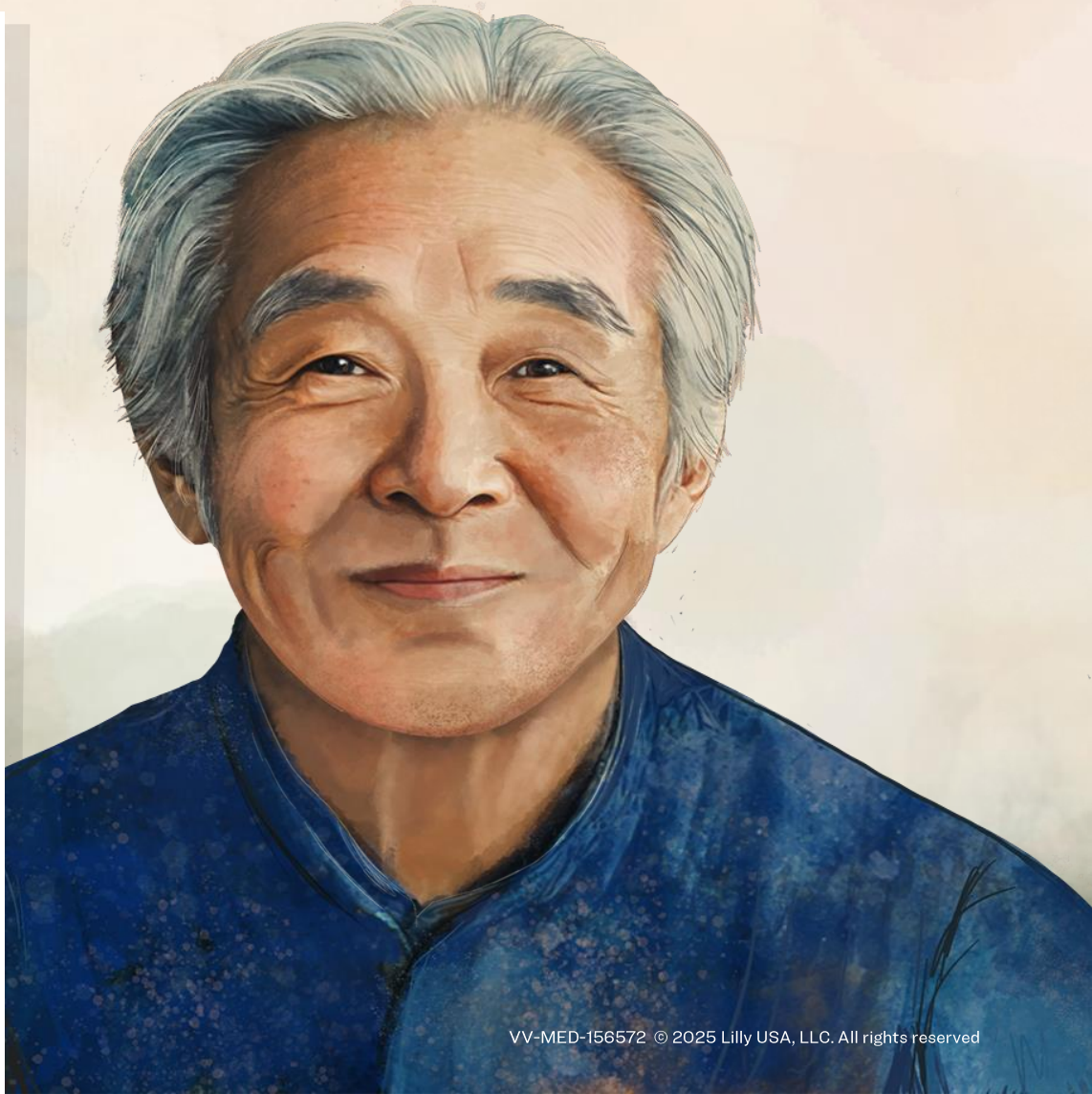
- 69 years old
- Male
- Asian
- Divorced, no children
- College degree
- Small business owner (retired)
- Family history:
  - Cardiovascular disease
  - Obesity



Clinical Information and History

Jian reports several cognitive symptoms, which have noticeably progressed over the last 2 years. These include:

- Difficulty remembering recent events and conversations
- Trouble following complex instructions
- Issues finding words
- Getting lost while driving (stopped driving as a result)



Clinical Information and History

General health

- Hypertension
- Obesity
- Type 2 diabetes
- Prior myocardial infarction (received a stent)

Current medication

- Angiotensin-converting enzyme (ACE) inhibitor
- Beta-blocker
- Antiplatelet agent
- No anticoagulant due to fall within the last 6 months

Note: CHA_2DS_2-VASc is a scale for stroke risk in the setting of atrial fibrillation.[1]

1 .Lip GY, et al. *Chest*. 2010;137(2):263-272.

Initial Clinical Assessment

General neurological exam: Normal

Mental status

- Alert, insightful, frustrated during testing
- Impaired instrumental activities of daily living (driving)

Cognition

- MoCA: 22/30 (normal ≥26)
  - Delayed recall: 1/5
  - Clock drawing: 1/3
  - Mini trails: 0/1
  - Cube copy: 0/1
- ACE-III: 72/100 (normal ≥82)
  - Deficits in memory, attention, and visuospatial processing

ACE-III=Addenbrooke's Cognitive Examination-III; MoCA=Montreal Cognitive Assessment.

Additional Findings

Blood work within normal limits, including:

- Complete blood count (CBC)
- Electrolytes
- Glucose
- Creatinine
- Thyroid stimulating hormone (TSH)
- Vitamin B12

Brain MRI:

- Mild diffuse cortical atrophy, with superimposed moderate hippocampal atrophy
- Single non-lobar microhemorrhage
- Mild white matter disease

Amyloid PET:

- The scan is positive and demonstrates moderate-to-frequent Aβ deposition

Aβ=Amyloid Beta; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography.

Given the Patient Information Presented, What is the Diagnosis?

1. Mild dementia mixed pathology (AD and vascular)
2. MCI due to AD
3. Mild dementia due to AD
4. Vascular cognitive impairment
5. Other

Jian

AD=Alzheimer's Disease; MCI=Mild Cognitive Impairment.

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Jian

AD=Alzheimer's Disease; MCI=Mild Cognitive Impairment.

JUSTIFICATION FOR DIAGNOSIS

Why is Jian Diagnosed with Mixed Dementia Due to AD and Vascular Etiologies?

Jian is presenting with clinical symptoms consistent with early symptomatic AD. However, they are not exclusive to AD, namely the significant deficits outside the memory domain.

His MRI results are consistent with underlying vascular pathology, likely representing a contributor to cognitive impairment, thus warranting a diagnosis of vascular cognitive impairment. However, MRI alone does not rule out a contribution from AD pathology.[1]

Presence of Aβ fibrils and plaques in the brain, as confirmed via amyloid PET, represents biomarker confirmation of pathology of AD.[1] Taken together, clinical and biomarker data are consistent with a diagnosis of mixed AD and vascular pathology, at the mild dementia stage.

Aβ=Amyloid Beta; AD=Alzheimer's Disease; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography.

1. Frantellizzi V, et al. *J Alzheimers Dis.* 2020;73(4):1279-1294.

Key Learnings in Jian's Case (1 of 5)

Mixed dementia refers to more than one possible cause in an individual patient. In practice, it is frequently applied to cases displaying clinical and/or neuropathological evidence of both AD and cerebrovascular disease.[1,2]

1. AD and vascular dementia is the most common combination seen in mixed dementia.[2]
2. Vascular contributions to clinical symptoms can be inferred by:
   - Involvement of cognitive domains other than memory[1,2]
   - Identification of cerebrovascular lesions (infarcts, microhemorrhages, white matter disease) on MRI[3,4]
3. A definitive diagnosis of mixed dementia warrants AD neuropathologic confirmation using appropriate biomarkers[1,5]:
   - CSF Aβ and tau
   - Aβ or tau PET neuroimaging

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography.

1. Fierini F. *J Neurol Sci*. 2020;410:116662. 2. Custodio N, et al. *Dement Neuropsychol*. 2017;11(4):364-370. 3. Frantellizzi V, et al. *J Alzheimers Dis*. 2020;73(4):1279-1294. 4. Chui HC, Ramirez-Gomez L. *Alzheimers Res Ther*. 2015;7(1):21. 5. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14(4):535-562.

Key Learnings in Jian's Case (2 of 5)

It is common for patients to have brain changes associated with multiple causes of dementia,[1,2] and Jian presented with multiple risk factors that are related to vascular dementia.

Vascular dementia:

- Accounts for ~15% of dementia cases[1,2]
- Has more variability in clinically observed cognitive changes compared to other disorders[1,2]; specifically in memory, language, and praxis[1]
  - Disruption of frontostriatal circuits contributes to impairments in attention, information processing, and executive function[1]
  - Community studies have shown some symptoms are more common in vascular dementia compared to AD (eg, depression and apathy)[1]
- Diagnosis requires the presence of significant cerebrovascular disease on brain imaging[1]
- Common risk factors include:
  - Advancing age[1,3]
  - Hypertension[1-3] and hyperlipidemia[1,2]
  - Atherosclerosis[2,3]
  - Diabetes[1-3]
  - Smoking[1-3]
  - Stroke[1,3]

AD=Alzheimer's Disease.

1. O'Brien J, Thomas A. *Lancet*. 2015;386(10004):1698-1706. 2. Wong EC, Chui HC. *Continuum (Minneap Minn)*. 2022;28(3):750-780. 3. Smith EE. *Clin Sci (Lond)*. 2017;131(11):1059-1068.

Key Learnings in Jian's Case (3 of 5)

Vascular dementia and AD have many overlapping symptoms and neuropathologies, but with some clear differences.[1]

	Vascular dementia[1]	AD[2]
Clinical features	• Impairments in attention, information processing and executive function • Commonly reported depression and apathy	• Difficulty remembering recent conversations, names, or events • Impaired communication, disorientation, confusion, poor judgment, behavioral changes; difficulty speaking, swallowing, and walking later in the disease
Pathological features	• Presence of cerebrovascular disease (eg, infarcts, extensive white matter lesions, lacunes)	• Accumulation of Aβ neuritic plaques and intraneuronal neurofibrillary tangles[2,3]

Aβ=Amyloid Beta; AD=Alzheimer's Disease.

1. O'Brien J, Thomas A. *Lancet*. 2015;386(10004):1698-1706. 2. Alzheimer's Association. *Alzheimer's Dement*. 2022;18:700-789. 3. DeTure MA, Dickson DW. *Mol Neurodegener*. 2019;14(1):32.

Key Learnings in Jian's Case (4 of 5)

MRI can be a useful assessment to[1]:

- Rule out non-AD conditions that can cause cognitive decline
- Provide information suggestive of AD; for example, observed hippocampal atrophy

However, the scan does not provide information on amyloid and tau biomarkers and cannot be used to diagnose AD in isolation.[2]

Structural neuroimaging (MRI) can detect atrophy, which correlates with cognitive status and is a marker of neurodegeneration[1]

Advantages include:

- Noninvasive and widely available[3]
- No ionizing irradiation[4,5]
- Excellent soft tissue contrast and high spatial resolution[4,5]

Disadvantages include:

- Some patients find the scanner claustrophobic[5,6]
- Patients with magnetic metal implants should not receive MRI exams[5]
- Atrophy patterns seen are not specific to AD[6]

AD=Alzheimer's Disease; MRI=Magnetic Resonance Imaging.

1. Park M, Moon WJ. *Korean J Radiol.* 2016;17(6):827-845. 2. Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;3(8):371-386. 3. McEvoy LK, Brewer JB. *Expert Rev Neurother.* 2010;10(11):1675-1688. 4. Pysz MA, et al. *Clin Radiol.* 2010;65(7):500-516. 5. https://www.fda.gov/radiation-emitting-products/mri-magnetic-resonance-imaging/benefits-and-risks. (Accessed January 2024). 6. Johnson KA, et al. *Cold Spring Harb Perspect Med.* 2012;2:a006213.

Key Learnings in Jian's Case (5 of 5)

Jian's case is challenging, but assessment of pathologic biomarkers helps to confirm or reject a diagnosis of AD. In this case, an amyloid PET scan was used to assess the level of amyloid plaque present in the brain.

Benefits and limitations of using amyloid PET imaging to detect a pathologic biomarker of AD

- Amyloid PET is a diagnostic imaging procedure in which a radioactive agent binds to Aβ in the brain[a] allowing clinicians to estimate Aβ neuritic plaque density[1-3]

Advantages include:

- Aβ plaques are one of the earliest known neuropathological hallmarks of AD[4]
- Amyloid PET imaging indicates presence or absence of pathological insoluble plaques[1-3]

Limitations include[4]:

- Weak correlation between Aβ deposits and clinical severity
- Aβ accumulation stabilizes in late-stage AD

[a]Florbetapir F 18 binds to Aβ aggregates; florbetaben F 18 and flutemetamol F 18 bind to Aβ plaques.[1-3]
Aβ=Amyloid Beta; AD=Alzheimer's Disease; PET=Positron Emission Tomography.

1. Amyvid (florbetapir F 18) [US Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2019. 2. Vizamyl (flutemetamol F 18) [US Prescribing Information]. 3. Neuraceq (florbetaben F 18) [US Prescribing Information]. Warwick, UK: Life Molecular Imaging Ltd., 2021. 4. van Oostveen WM, de Lange ECM. *Int J Mol Sci.* 2021;22(4):2110.

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Thank you for Connecting *with Jian*

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