

The logo features the word "Lilly" in a red cursive script font, followed by "ConnectAD" in a red sans-serif font with a trademark symbol (TM). The background is a soft, textured watercolor wash in shades of pink, peach, and light green, with faint botanical illustrations of leaves and stems. The entire graphic is enclosed in a thin red border.

Lilly ConnectAD™

Detect · Diagnose

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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



The clinical case presented here is entirely fictional and is not based on any real patient.
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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



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

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 $A\beta$ deposition

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

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

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 A β 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.

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 A β and tau
 - A β or tau PET neuroimaging

A β =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 praxis¹
 - Disruption of frontostriatal circuits contributes to impairments in attention, information processing, and executive function¹
 - 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 imaging¹
- Common risk factors include:
 - Advancing age^{1,3}
 - Hypertension¹⁻³ and hyperlipidemia^{1,2}
 - Atherosclerosis^{2,3}
 - Diabetes¹⁻³
 - Smoking¹⁻³
 - 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 (Minneapolis, 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 dementia¹	AD²
Clinical features	<ul style="list-style-type: none">• Impairments in attention, information processing and executive function• Commonly reported depression and apathy	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Presence of cerebrovascular disease (eg, infarcts, extensive white matter lesions, lacunes)	<ul style="list-style-type: none">• Accumulation of Aβ neuritic plaques and intraneuronal neurofibrillary tangles^{2,3}

A β =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 to¹:

- 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 neurodegeneration¹

Advantages include:

- Noninvasive and widely available³
- 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 exams⁵
- Atrophy patterns seen are not specific to AD⁶

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 A β in the brain, allowing clinicians to estimate A β neuritic plaque density¹⁻³

Advantages include:

- A β plaques are one of the earliest known neuropathological hallmarks of AD⁴
- Amyloid PET imaging demonstrates a positive or negative finding for A β plaques¹⁻³

Limitations include⁴:

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

A β =Amyloid Beta; AD=Alzheimer's Disease; PET=Positron Emission Tomography.

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/202008s046lbl.pdf (Accessed September 18, 2025).

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203137s024lbl.pdf (Accessed September 18, 2025).

3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204677s024s034lbl.pdf (Accessed September 18, 2025). 4. van Oostveen WM, de Lange ECM. *Int J Mol Sci.*

2021;22(4):2110.

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