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

By 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 Maria*

Detect · Diagnose

Our Patient Maria

- 72 years old
- Female
- Hispanic
- Married, 4 children, 3 grandchildren
- College degree
- Accountant (retired)
- Family history:
  - Cardiovascular disease
  - Type 2 diabetes
  - Alzheimer’s disease (mother)

Clinical Information and History

Maria has experienced onset of the following symptoms, which have gradually progressed over the last 2 years:

- Difficulty remembering dates and events
- Problems finding words

Clinical history

- Type 2 diabetes
- Hypertension

General health

- Heart rate: 72 bpm
- Blood pressure: 138/70 mmHg

Current medication (class)

- Angiotensin-converting enzyme (ACE) inhibitor
- Biguanide

bpm=Beats Per Minute.

Initial Clinical Assessment

General neurological exam: Normal

Mental status

- Alert, insightful, good effort on testing
- Independent in all activities of daily living

Cognition

- MoCA: 25/30 (normal ≥26)
  - Word recall: 1/5
  - Figure copy: Incorrect
  - Clock drawing: 3/3

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
- Mild microangiopathy
- Small old lacune in left external capsule

CSF assay:

- Aβ42/Aβ40: Low
- P-tau: High
- T-tau: High

Aβ=Amyloid Beta; CSF=Cerebrospinal Fluid; MRI=Magnetic Resonance Imaging; P-tau=Phosphorylated Tau; T-tau=Total Tau.

Given the Patient Information Presented, What is the Diagnosis?

1. Generalized anxiety
2. MCI due to AD
3. Preclinical AD
4. Vascular cognitive impairment
5. Other

Maria

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

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Maria

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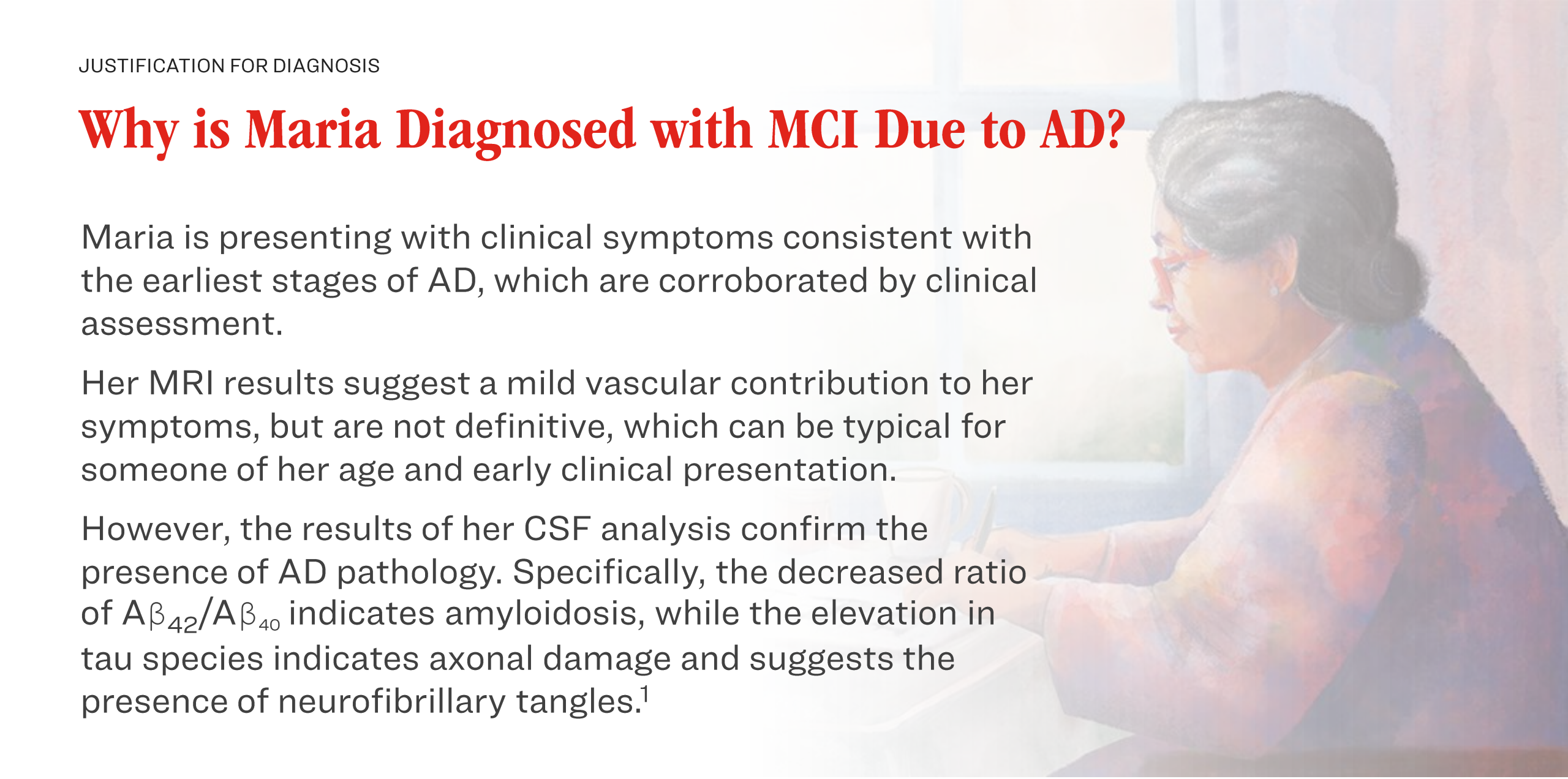
JUSTIFICATION FOR DIAGNOSIS

Why is Maria Diagnosed with MCI Due to AD?



Maria is presenting with clinical symptoms consistent with the earliest stages of AD, which are corroborated by clinical assessment.

Her MRI results suggest a mild vascular contribution to her symptoms, but are not definitive, which can be typical for someone of her age and early clinical presentation.

However, the results of her CSF analysis confirm the presence of AD pathology. Specifically, the decreased ratio of $A\beta_{42}/A\beta_{40}$ indicates amyloidosis, while the elevation in tau species indicates axonal damage and suggests the presence of neurofibrillary tangles.[1]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MCI=Mild Cognitive Impairment; MRI=Magnetic Resonance Imaging.

1. Hansson O, et al. *Alzheimers Res Ther*. 2019;11(1):34.

Key Learnings in Maria's Case (1 of 3)

MCI due to AD is vastly underdiagnosed,[1] and can be difficult to distinguish from other causes of cognitive impairment.[2] AD biomarkers can provide the confirmatory information needed for diagnosis.[3]

1. Despite variations in labeling, there is broad agreement on the stages and continuum of events in the progression of AD.[4]

2. Evidence of AD pathology is present many years before cognitive symptoms appear. This period is referred to as the preclinical period.[4]

3. As the disease progresses, patients will experience increasing cognitive impairment, which may impact ability to perform activities of daily living. These sequential stages of disease are referred to as mild cognitive impairment, or dementia (characterized as mild, moderate, or severe) due to AD.[4]

AD=Alzheimer's Disease.

1. Liu Y,et al. *J Prev Alzheimers Dis.* 2024;11(1):7-12. 2. Albert MS, et al. *Alzheimers Dement.* 2011;7(3):270-279. 3. Jack CR Jr., et al. *Alzheimers Dement.* 2024;20(8):5143-5169. 4. Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;3(8):371-386.

Key Learnings in Maria's Case (2 of 3)

The CSF biomarker assay can be used to confirm the presence of pathology consistent with AD.[1]

CSF assays:

1. Quantitatively measure the levels of Aβ and tau protein within the fluid of the lumbar sac.[2]
2. Reflect the rates of Aβ and tau protein production and clearance.[2]

Advantages include:

- Less expensive than PET by 10- to 15-fold[3]
- Simultaneous information on Aβ and tau biomarkers[4]

Limitations include:

- CSF is obtained via lumbar puncture; this is invasive and can be uncomfortable for patients[5]
- Limited availability outside of specialized clinics[6]
- Do not detect regional Aβ or tau deposition[2,3]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MCI=Mild Cognitive Impairment; PET=Positron Emission Tomography.

1. Jack CR Jr., et al. *Alzheimers Dement.* 2024;20(8):5143-5169. 2. Jack CR Jr, et al. *Alzheimers Dement.* 2018;14:535-562. 3. Hansson O, et al. *Alzheimers Res Ther.* 2019;11(1):34. 4. Dubois B, et al. *Lancet Neurol.* 2021;20(6):484-496. 5. Lee JC, et al. *Exp Mol Med.* 2019;51(5):1-10. 6. Zetterberg H, et al. *Alzheimers Dement (Amst).* 2019;784-786.

Key Learnings in Maria's Case (3 of 3)

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.

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Thank you for Connecting *with Maria*

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