A Diagnosis of Exclusion: Keys to Consider on the Diagnostic Accuracy of Alzheimer’s Disease

New research suggests that the diagnosis of Alzheimer’s Disease is not as simple as previously thought.

By Ronald Devere, MD, FAAN

The public fear of Alzheimer’s Disease (AD) has reached epidemic proportions in the US and worldwide. The terms “memory loss” and “dementia” invariably evoke the diagnosis of AD and immediately strike fear. After all, as the CEO and scientific directors of the National Alzheimer’s Association regularly state: “Alzheimer’s Disease is progressive—there is no treatment and invariably leads to death.”

But perhaps the outlook on AD isn’t as bad as most of us fear. Since I began practicing cognitive neurology and opened my Alzheimer’s Disease and Memory Disorders Center in Houston in 1993, my motto when it comes to dementia and memory loss has always been that the glass is half full, not half empty. I always have and continue to focus on the true positive facts.

THE FACTS

1. Recent studies have shown that the incidence of AD is decreasing in four well-developed countries: the US, Germany, Netherlands (Rotterdam), and Scandinavia (Stockholm). This is partially attributed to increases in college education, more aggressive treatment of hypertension, diabetes, high cholesterol, and reduced cigarette smoking. Nevertheless, many papers and seminars about AD often begin with the observation that there are over five million AD cases in the US and the incidence continues to rise every year.

2. One of the most common causes of cognitive decline that can lead to mild cognitive impairment/dementia is untreated sleep disorders, including obstructive sleep apnea (OBS), periodic leg movements in sleep (PLMS), and rapid eye movement behavioral disorder (REMBD). Untreated or insufficient treatment of OBS has been shown to cause hypoxia during sleep, hypertension and multiple strokes. Untreated PLMS and REMBD can impair cerebral sleep and lead to cognitive decline, including memory loss and worsen MCI/Dementia. Some studies have reported improvement in AD from moderate to mild stages when the OSA disorder was treated. This has also been shown in MCI.

By giving patients and the public at large a more accurate understanding of cognitive disease, perhaps we can imbue a more hopeful outlook on the future of AD diagnosis and treatment.

3. Multiple small white matter strokes (moderate to severe) as seen on CT/MRI scans of the brain are no longer considered a non-specific finding or due to aging. Diffusion tensor imaging has shown damage to the myelin and some cases the axons that connect many different parts of the brain and clearly cause cognitive decline. Aggressive treatment in those
patients who frequently have underlying hypertension, diabetes, high cholesterol, and cigarette smoking, along with exercise and cognitive therapy, can delay/improve impaired cognition.\textsuperscript{5}

4. Aggressive search for and treatment of alcohol and drug abuse, overuse of prescribed medications, low vitamin B\textsubscript{12}, folate, thyroid, and vitamin D, can help improve/delay cognitive decline in many patients.\textsuperscript{6-8}

5. Autoimmune memory loss/dementia can mimic (not uncommonly) Alzheimer’s disease. In the majority of cases, this is an acute/subacute disorder with behavior problems, seizures, and delirium. Many, however, present like a slowly progressive cognitive decline and could be misdiagnosed as AD unless this diagnosis is included in the differential diagnosis of dementia. To make a diagnosis, physicians must take serum and spinal fluid and look for autoimmune antibodies and other inflammatory markers. This condition is very treatable and responds to Intravenous steroids and other autoimmune therapies.\textsuperscript{14}

**ACCURACY OF DIAGNOSIS IN QUESTION**

A recent paper in *JAMA Neurology*\textsuperscript{9} has shaken the accuracy of the diagnosis of AD in clinical and research practice in a way that many neurologists may not be aware of. This paper came to fruition based on two recently published papers that suggested that greater than one third of APOE4 non carriers with clinical diagnosis of mild to moderate AD showed low levels of Beta amyloid on amyloid PET studies, and that 20 to 30 percent of all individuals with clinical diagnosis of AD may not meet clinical Neuropathological diagnosis for AD.\textsuperscript{9,11}

The study authors decided to try to answer the following questions:

- Are the findings of low amyloid uptake on the amyloid PET scans due to low PET scan affinity for diffuse A-beta plaques?
- Is this due to actual low A-beta plaque accumulation in the cerebral cortex?
- Are these cases misdiagnosed as AD and have a different neurological cognitive disorder?

The study sample comprised of research participants of 34 past and present National Institute of Health-sponsored AD coordinating centers. These cases also consented to brain autopsy. Of the 2,288 total cases with autopsy consent, 1,834 died within 24 months of last neurological clinical assessment. Of this group, only 230 cases had a MMSE score between 16 and 26. When checking for those cases with APOE4 typing, the final total was of 200 cases (100 APOE4 carriers and 100 non APOE4 carriers). In the APOE4 carriers, the age of AD onset was 78 years old; 59 percent were males, with last clinical assessment being at 85.2 years of age and death at age 86 years of age. In the non-APOE4 carriers, the age of onset was 76 years old, with 51 percent being female and the age of last clinical evaluation 83.3 years old and death at 84 years old.

In their analysis, the authors found that 37 percent of the APOE4 non-carriers (mild to moderate AD) had minimal A-beta plaque score. In the APOE4 carrier group, only 13 percent had a low score. Neurochemical assay for soluble and non-soluble A-beta peptides in 22 of 50 brain donors with minimal A-beta plaque score and mild to moderate AD were revealed to have the same outcome. In addition, 45 percent of these cases had extensive neuro-fibular degeneration (Braak stages III-VI). Several of these cases have been reported in the literature and named Tangle only or Tangle Predominant Dementia.\textsuperscript{10}

The NIAAA guidelines for neuropathological evaluation in 2014 recommended that this constellation of features not be reported as AD and that other tauopathies be excluded. They also went as far as to say that this same pathological features with minimal A-beta plaque and minimal to normal cognitive impairment be called primary age related tauopathy. Dugger, et al.\textsuperscript{12} found that 37 percent of individuals who were clinically normal at death met NIA-Reagan criteria for intermediate probability of AD with Braak stages III or higher. Also of note is that in two large phase 3 clinical trials of bapineuzumab for mild to moderate AD the authors stated that 36 percent of APOE4 non-carriers and six percent of APOE4 carriers did not meet the PET cutoff for amyloid positivity.\textsuperscript{13} These important clinical and neuropathological findings suggest the following:

1. Moderate to severe tauopathy may not be related to Dementia but may imply healthy aging.
2. Slower plaque deposition and slower clinical progression in these cases could possibly eventually lead to AD.
3. Soluble or fibrillary A-beta modifying treatments are unlikely to benefit these patients if successful in helping remove A-beta material. A new treatment strategy will be necessary.
4. Patients with low A-beta amyloid levels were older, less cognitively impaired, and had slower cognitive decline and misdiagnosed as AD. Further studies will clarify this diagnosis.

It is important to note that, of the 50 cases with sparse A-beta plaques, five had a normal brain and 33 had a non-AD pathological diagnosis which included vascular disease,\textsuperscript{8} Lewy Body Dementia,\textsuperscript{6} Hippocampal Sclerosis,\textsuperscript{5} Frontal Temporal Dementia,\textsuperscript{4} and Tangle only Dementia.\textsuperscript{3} Some of these diagnoses were also evident in the amyloid
positive individuals and were likely comorbid even though non-AD causes of dementia were clinically excluded.

**A DIAGNOSIS OF EXCLUSION**

So what does all of this information mean for clinical neurologists? Here are several points worth considering:

- **The diagnosis of AD is becoming more a diagnosis of exclusion.** Therefore, a very thorough workup should be considered in all cognitively impaired patients. Using the diagnosis of Mild Cognitive Impairment or dementia of unknown cause is better than saying possible or probable AD when the cause is unclear, especially if the workup is incomplete. Neuropathological and more advanced radiological and spinal fluid studies suggest that significant questions remain about the diagnosis of AD. Rushing patients into clinical trials without a thorough workup and low A-beta amyloid levels could seriously impair trials of different future medications and current medications employed to remove amyloid in the brain. This information is also a positive note for many of our patients who are worried about having AD, since diagnosis of AD is not a slam-dunk diagnosis at this time.

- **Discuss all the possible causes of cognitive decline with your patients and caregivers.** Inform them that the diagnosis of AD is not always easy and can often be incorrect. This will help reduce worry, fear, and some stress when they hear this.

- **Incorporating PET scanning in your practice is worthwhile.** FDG PET, which measures radiolabeled sugar uptake in different brain areas, is the only PET scan covered by Medicare. Private medical insurance does not even cover FDG PET and call it “experimental.” Currently, amyloid or tau PET scanning is not paid for by any insurance (including Medicare) and is cost prohibitive for most people. Remember that positive FDG PET, which is decreased sugar uptake in the bi-parietal temporal regions, correlates with AD in 85 percent of cases. A strongly positive Amyloid PET scan in the presence of a negative or non-specific FDG PET scan in the correct clinical setting is strongly suggestive of AD.

- **Consider spinal fluid evaluation for inflammatory, infectious, neoplastic, or autoimmune causes for cognitive decline.** It has also been shown to strongly help in the diagnosis of AD, which is characterized by low AB42 and high Tau and especially high Phosphorylated Tau. This pattern is equally diagnostic to a very positive Amyloid PET SCAN. The spinal fluid for ABeta42 and Tau may not be covered by Medicare or private insurance but is much less expensive than FDG or amyloid PET scans. Further clinical research on Amyloid and Tau PET scans with neuropathology from patient donors will continue to improve the accuracy and detection of AD and other degenerative dementias.

- **Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine); glutamate inhibitor (memantine) can be costly and have potential side effects.** They are not indicated in MCI of unknown cause (with possible exception of Donepezil) or some Dementias (not indicated in; Frontal Temporal, cortical basal degeneration, PSP and other Tauopathies), hence a definitive diagnosis of the Dementia is essential.

- **Based on this study and others, there is a strong suggestion that APOE4 testing be considered in our AD suspected cases because low A-beta amyloid brain scores were much less likely to occur in APOE4 positive patients (13 percent in APOE4+, 37 percent in APOE-).**

**A CAUSE FOR HOPE**

The diagnosis of AD is no longer a slam-dunk in our cognitively impaired patients. Now more than ever, it should strongly be considered a diagnosis of exclusion and a thorough evaluation should be conducted, as outlined in this article. When it comes to discussing these matters with patients, we should offer more possible treatment choices and help reduce fear of cognitive impairment, as may help improve the clinical and research study population of definite AD. By giving patients and the public at large a more accurate understanding of cognitive disease, perhaps we can imbue a more hopeful outlook on the future of AD diagnosis and treatment.

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