Alzheimer's Criteria Angle for Earlier Diagnoses

Treatments to slow or halt Alzheimer's will be most effective before neuronal damage is done.

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

Updated diagnostic criteria for Alzheimer's disease will allow physicians to identify patients in the earliest possible stages of the disease, capitalizing on the treatments now available and enriching therapeutic research.

Unveiled at the meeting, the proposed criteria are the first updates to Alzheimer's diagnosis in 25 years, Dr. Ronald Peterson said in an interview.

"Our current criteria were established in 1984," said Dr. Peterson, director of the Mayo Clinic Alzheimer Disease Research Center, Rochester, Minn. "They functioned well for 25 years, but they were completely syndromic. The field has moved on. There has been an explosion of information, including neuroimaging and biomarkers, which allows us to recognize a milder state of clinical impairment and is informing us about the underlying pathology. These need to be included in our diagnostic workups."

The new criteria form the basis of a more flexible diagnostic tool—one that can be annually revisited and updated as new data demand, he said.

The National Institute on Aging and the Alzheimer's Association agreed last year to examine how to better incorporate new knowledge into the existing diagnostic criteria. The agencies created work groups to explore this idea in three stages of the disease process—preclinical, mild cognitive impairment, and Alzheimer's dementia.

Dr. Reisa Sperling, director of clinical research at the Memory Disorders Unit, Brigham and Women's Hospital, Boston, headed the preclinical group. "For me, this is the most exciting area, because it's the newest," she said in an interview. "We have never tried to set criteria to diagnose Alzheimer's before there is significant clinical impairment."

And yet, she said, this period may be the most crucial, for two reasons. First, because the earlier existing treatments are employed, the more effective they are. Second, because identifying a prodromal stage of Alzheimer's will, eventually, be key to developing new therapies.

Alzheimer's has never been viewed as a disease with an identifiable, but asymptomatic, prodromal state. "Our best chance at treating the disease and changing its course will be to treat before any symptoms appear, or when there are only very mild symptoms," Dr. Sperling said.

The preclinical group identified three diagnostic criteria for the earliest stage of Alzheimer's:

► Asymptomatic amyloidosis, defined by evidence of abnormal levels of amyloid in the spinal fluid or on a brain scan, but no cognitive or functional symptoms.

► Amyloidosis plus one other marker of disease, which could be brain atrophy on imaging, functional abnormalities on positron emission tomography (PET), or abnormal levels of phosphorylated tau in spinal fluid.

► Amyloidosis plus a biomarker and slight cognitive symptoms. "This may be the most important stage, because there is good evidence that people experience cognitive changes years before they progress to mild cognitive impairment," Dr. Sperling said. "Right now, we can't differentiate normal aging from the very beginning of Alzheimer's. But the combination of these biomarkers and memory trouble will allow us to predict who is on the Alzheimer's trajectory."

Research may especially benefit from this identification, because drugs to slow or halt disease progression will be most effective in patients with the least neuronal damage, she added.

COURTESY ALZHEIMER'S ASSOCIATION/LUCY PEMONI

The criteria may help diagnose AD before there is significant impairment, Dr. Reisa Sperling said.

Dr. Peterson is a member of the work group that examined diagnostic criteria for mild cognitive impairment (MCI). That group also identified three criteria:

► The already-established clinical syndrome of MCI in which patients are aware of their memory problem and have a measurable deficit, but other cognitive and functional skills are preserved.

► In addition to MCI, there is some evidence of change in brain topography—either hippocampal atrophy or hypometabolic brain regions.

► In addition to MCI and topographical brain changes, a confirmed measure of amyloid abnormality, including reduced amyloid-beta$_{42}$ in cerebrospinal fluid (indicating its accumulation in the brain) or positive amyloid brain imaging.

"This represents the progression in a perfect world," Dr. Peterson said. "But the devil is in the details. What if you have the clinical syndrome but your biomarkers go in the opposite direction, or you have an incomplete set? That is where research is going to fill in the gaps in our knowledge."

Dr. John Morris, director of the Alzheimer's Disease Research Center at Washington University, St. Louis, is a member of the dementia working group. Because diagnostic algorithms for dementia were already in place—albeit 25 years old—his group made modifications to the existing criteria.

"With the addition of biomarkers to support the clinical suspicion of dementia, we have been able to strengthen those criteria substantially, giving physicians the ability to be much more confident in their diagnoses," Dr. Morris said.

Previously, the only way to obtain a definitive Alzheimer's disease diagnosis was through brain autopsy; the presence of amyloid plaques and neurofibrillary tangles has been the key diagnostic feature. "With these strengthened criteria, we can now diagnose it in a living person."

Documented and measurable memory deficits in the presence of at least one biomarker now correlates to the diagnosis of "probable Alzheimer's." In addition to memory deficits, the presence of several biomarkers—structural brain changes, functional brain changes, positive amyloid imaging, spinal fluid abnormalities, or genetic markers—can strengthen the diagnosis of probable disease.

The presence of a genetic marker in this mix, especially the apolipoprotein E e4 allele, equates to a definitive diagnosis.

The work groups are now seeking feedback on the criteria. Comments can be submitted to the Alzheimer's Association Web site (www.alz.org/research/diagnostic_criteria), which is hosting the criteria.

"By the time symptoms appear, there has already been substantial neuronal loss in critical brain areas, and it's been impossible to arrest the disease once this damage has occurred," Dr. Morris said. "It makes great sense to intervene earlier—even before MCI—to see if we can treat with the hope of preventing disease progression."

The project was funded by the National Institute on Aging and the Alzheimer's Association. None of the physicians reported any potential financial conflicts. ■

MY TAKE

The Criteria Mark Our Progress

The proposal to update Alzheimer's disease diagnostic criteria will incorporate the progress made these last 20 years in our understanding of the disease. We already have a number of promising approaches to the disease that include both drug and non-drug interventions and much has been done to understand the basic biology and pathology of disease progression. Even though we have no cure and currently cannot prevent Alzheimer's disease, I prefer my patients to run toward a diagnosis rather than away from it, so I expect that these criteria will help.

With each advance in medicine, more sensitive and specific tests (i.e. biomarkers) are validated and used to diagnose and treat a wide assortment of conditions. This is now the case with Alzheimer's disease. It is the inclusion of these biomarkers in the updated diagnostic criteria that will help us arrive at a diagnosis sooner and to allow us to study a variety of drug and non-drug interventions in an attempt to modify disease progression.

Clinicians use a variety of tools to assess the patient. We use laboratory tests including blood, urine and cerebrospinal fluid, imaging studies, pathologic findings, and interpretation of the history and physical to arrive at our conclusions. The more sensitive and specific the test, the more sure we are that the diagnosis is correct. Alzheimer's disease is coming of age and if new tests move us forward, then we need to incorporate these tools into our plan of care.

Our understanding of amyloid and its toxic role in Alzheimer's disease has led to its inclusion as one of the biomarker criteria. The sophistication of our imaging studies has placed positron emission tomography (PET), targeted radiolabeling, and other imaging modalities into the equation as well. The genetic work that has been done including apolipoprotein E and tau now let us use this information as well in formulating a diagnosis.

As we wait for additional treatments to become available, the new criteria should not be burdensome to the clinician. Those interested in earlier interventions will need to understand these criteria and their application in establishing a diagnosis. We will need to judge if these biomarkers lead us down the right path to be worth the effort in case finding. If the criteria provide us with a more efficient route to therapy, the better we are at addressing the patient and family needs sooner rather than later.

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