Mild Cognitive Impairment—An Added Value to Patient and Physician

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The recent commentary by Dr Ronald Pies concerning the changes in the diagnostic criteria for Alzheimer’s disease (AD) and Mild Cognitive Impairment (MCI), questioned the value of informing a patient early in the course of a dementing illness. Dr Pies suggests that because there are no available treatments for AD, it is a disservice to inform the patient of this diagnosis. His message is essentially, “ignorance is bliss.” He has confused treating the disease of AD when it manifests clinically with treating the pathological process of AD early in the course of the disease to slow progression.

I am a board member of the Brain Imaging Council of the Society of Nuclear Medicine and a psychiatrist. In this capacity I have helped to develop the procedure guidelines for the DaTscan—a diagnostic test to help differentiate Parkinsonian disorders. Currently, we are beginning to prepare similar guidelines for the amyloid neuroimaging markers. From this perspective, I can assure you that amyloid markers will offer more than a distant death knell. Rather, identification of those with early pathogenesis of AD will facilitate early mitigation and treatment of the disease process. While there are currently no treatments for AD, it is important to examine what we are treating. By the time AD is diagnosed by clinical symptoms, 8 to possibly 15 years of pathological damage has already occurred. Just as in Parkinson’s disease wherein over 80% of the substantia nigra neurons must be lost before symptoms manifest, the AD-related damage to the entorhinal cortex, hippocampus, and parietal cortex are much advanced by the time a drop in the Mini-Mental-Status Examination score occurs. Treatment at this point cannot undo the pathological damage. Therapeutic interventions, to be effective, must be introduced as early as possible in the pathological process.

Perfusion SPECT neuroimaging can identify MCI with an accuracy of as high as 99%. Amyloid markers can differentiate AD from controls with 85% to 95% sensitivity and 91% to 100% specificity in advanced cases. But these markers can also identify MCI with 80% sensitivity and 90% specificity; however, it must be noted that 10% of controls aged 50 years have a positive amyloid scan. This false positive rate increases by 10% each decade. Nonetheless, neuroimaging provides an endophenotype which can be quantified and detected long before the patient begins to show the cognitive dysfunction of AD or MCI. The implications are tremendous, not just in terms of early intervention, but also in terms of speeding clinical trials. Currently, we must wait years to see if a therapeutic intervention is making a difference in the cognitive function of patients with MCI. With neuroimaging, functional changes will be evident in a much shorter time and with higher accuracy, leading to more statistical power from smaller sample sizes.

The failure of semagacestat, among other medications, to show significant clinical benefit despite reducing amyloid burden represents a significant setback in the fight against AD. The lack of benefit with reduced amyloid burden challenged the underlying premise that amyloid is the primary etiological agent of AD. Nonetheless, there are 3 antibody therapies in clinical trials. In addition, recent findings have implicated norepinephrine in the pathological process of AD. Degeneration of the locus coerulesus neurons has been demonstrated in AD. Not surprisingly, norepinephrine reuptake inhibitors have shown some benefit in ameliorating the symptoms of early AD. Currently, phase II trials of atomoxetine in MCI are beginning under Dr Allan Levey at Emory University. Caution will need to be exercised given the mood dysregulating properties of atomoxetine. Alternatively, recent studies have shown that the DNA of Herpes-1 virus (the cold sore virus) is located in the pathological plaques in AD. Cultured brain cells with the genetic material of the Herpes-1 virus inserted into their DNA accumulate amyloid abnormally. Transgenic mice containing
the Herpes-1 virus genetic material develop the mouse equivalent of AD far more rapidly.18 As time goes on, research may confirm that infectious elements contribute to AD (and other neuropsychiatric illnesses), which will lead to exciting new treatments.18-20
In summary, this is a rapidly changing landscape. We are on the verge of important advances for patients with AD, both in terms of early diagnosis before the onset of symptoms and in terms of potentially effective treatments. This is a time to educate ourselves about these advances and bring them to our patients—to instill hope, not fear or despair.

References:


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