Toward New Clinical Criteria for Alzheimers Disease and Mild Cognitive Impairment

One development from this summer’s International Conference on Alzheimers Disease is progress toward new criteria for Alzheimers and MCI.

By Ronald Devere, MD

There were no major breakthroughs in Alzheimers therapy announced at the International Conference on Alzheimers disease and related disorders in Honolulu, Hawaii this past July, but there was some very clinically pertinent information presented at the meeting.

A major highlight of the meeting was the convening of a number of workshops to establish new clinical criteria for the diagnosis of Alzheimers disease (AD) and establish guidelines for mild cognitive impairment (MCI) and preclinical (asymptomatic) MCI and Alzheimers disease. These workshops have been desperately needed, given that the last time this was studied was in 1984. The 1984 criteria have been defined as the NINDS-ADRDA and have been used in Alzheimers and dementia research ever since. These old criteria have had some reliability in the diagnosis of probable AD with a sensitivity of 80 percent and specificity of 70 percent. We as clinicians are very aware that these 25-years-old criteria have many shortcomings, which include:

1. New detailed information of other dementias that occur in the same aged population, like Lewy Body and Frontal Dementia, were not well defined and recognized 25 years ago.
2. MRI, PET imaging, and cerebral spinal fluid studies were not included in any diagnostic criteria.
3. Lack of genetic information.
4. The old criteria implied that memory impairment was always the primary cognitive deficit.
5. MCI and its implication was not recognized.

Moving Forward: AD Diagnosis

The goal of the new workshops was to include where possible the above information and be sure updated guidelines are flexible enough for general health practitioners, who may not have some of these new specialized tests, and those researchers who have access to specialized testing.

The basic diagnosis for Dementia is not changed: It still is defined as a gradual cognitive and behavioural disturbance that represents a decline from prior levels and involves two or more areas of cognitive function (memory, executive, speech/language, personality, and visual perception) documented by a standard office mental status exam and/or neuropsychological testing and impairs activities of daily living. Additional criteria especially for Alzheimers disease included:

a.) amnestic presentation, which is the most common, and
b.) non-amnestic presentation, which can include language, visual perception, or executive dysfunction presentation.

The workshop proposed a number of new categories for Dementia of the Alzheimer type:

A. Pathologically proven AD
1. Meets clinical and cognitive criteria during life
2. Proven AD by pathological exam

B. Clinical AD
1. Probable AD. Meets clinical and cognitive criteria for AD without evidence of any other diagnosis (no significant cardiovascular disease). Diagnosis of probable AD can be enhanced by one or more of these features that increase certainty:
   a. Progressive cognitive decline information by informants and cognitive testing (e.g., MMSE and Neuropsychological testing) OR
   b. Positive Biomarkers to include: 1. Low CSF AB42, increased Tau or P-tau; 2. Positive amyloid PET imaging; 3. Decreased FDG uptake in temporal-parietal region by PET scan;
   4. Selective atrophy on MRI of Hippocampus, basal and lateral temporal lobe and medial parietal isocortex or Mutation carrier (has autosomal dominant mutation for Presenelin 1, Presenelin 2 or APP).
2. Possible AD. Meets clinical and cognitive criteria for AD but no evidence for progressive decline or Biomarkers are negative or non specific or meets clinical and cognitive criteria for AD but has concurrent cardiovascular disease (greater than one lacunar infarct or a simple large infarct, or extensive white matter disease) or features of dementia with Lewy bodies, but not definite clinical Lewy body dementia.
3. Not AD. Does not meet clinical criteria for AD or has sufficient evidence for an alternative diagnosis such as HIV, Huntingtons, etc.

MCI Diagnosis
A workshop also met to discuss new criteria for MCI due to AD and proposed the following:
1. There should be changes in cognition compared to the individual’s prior level, documented by patient, known informant, or from a skilled clinician observing the patient.
2. Evidence of lower performance in one or more cognitive domain greater than expected for age and education. The changes can occur in one or a number of cognitive domains, including memory, executive function, personality, language or visual perception skill. Episodic memory impairment (inability to learn and retain new information is seen most commonly in MCI patients who progress to AD).
3. ADLs may be mildly impaired but are often normal. These include paying bills, preparing a meal, shopping, which all require minimal aid or assistance.
   Note: Cognitive assessment, especially episodic memory who progress to AD. The best tests for this are word list learning with multiple trials. This also is useful to assess paying attention. These tests are part of a battery of tests performed by a neuropsychologist and include the Rey Auditory Verbal Learning test, California Verbal Learning test, Wechsler Memory Test 1 & 111. Other areas of cognition such as executive function, language, visual perception, etc. are best identified by Trail making (executive function), Boston naming test (fluency), figure copying, and digit span forward (attention). If above tests are not available, the clinician can ask the patient to learn a street address, and recall after five minutes. One can also ask the patient to name three objects and place them in different locations, then ask the patient to recall the names and locations after five to 10 minutes. (These tests may be normal in early MCI.)
   Close follow-up and progressive decline in cognition strongly suggests MCI due to AD. Full workup is still needed to rule out vascular causes, trauma and medical conditions.
   Carefully look for history of prominent visual hallucinations and symptoms of REM Sleep Behaviour Disorder, seen more commonly in Lewy body disease. Extensive vascular risk factors and cardiovascular disease suggest vascular cognitive impairment.
   Prominent behavior or language disturbance may suggest Frontal dementia. Shorter duration cognitive decline may suggest Prion disease, tumor, metabolic, or HIV disease, etc.

Biomarkers Strongly Support that MCI is Likely Due to AD
a. MRI evidence of medial temporal lobe (hippocami) atrophy or
b. FDG PET scan showing decreased temporal parietal glucose metabolism. Note: even if above tests are normal or equivocal, AD is still moderately likely to develop.

c. Increased cerebral spinal fluid tau, phosphorylated tau and low AB42. Note: A recently published paper in *Archives of Neurology* suggests that a positive spinal fluid study is 100 percent specific for AD in an MCI patient.

d. Positive genetic tests: Presenelin 1 (PS1), Presenelin 2 (PS2) and Amyloid Precursor Protein (APP)

**Pre-Clinical AD Diagnosis**

A Workshop also met to discuss criteria for Pre-Clinical AD. Criteria are still being developed using all biomarkers including amyloid imaging, cerebral spinal fluid for Tau and AB42, Neuropsychological testing, FDG PET scanning, genetics, and clinical evaluation.

**Other Conference Highlights:**

**Important Clinical Papers and Conclusions**

**Physical Exercise and Dementia Risk.** Zaldy Tan et. al, of Brigham and Womens Hospital estimated the levels of 24-hour physical activity of 1,200 elderly from the Framingham study during their 20th exam cycle, which originally began in 1986, and followed them for the development of dementia. They used five levels of physical activity. Over two decades of follow-up (mean 10 years), 242 subjects developed dementia (193 AD). The subjects with moderate to heavy physical activity had a 40 percent lower risk of developing dementia. Those in the lowest level physical activity group were 45 percent more likely to develop dementia than the higher levels of physical activity. These associations were more evident in men.

This study suggests that at least moderate physical activity is helpful to reduce dementia risk even into the eighth decade of life. This study is the first to follow people for greater than six years and include many older people in the eighties. This study continues to support the recommendation of moderate physical activity and exercise to all ages, especially the elderly, to help decrease the risk of dementia.

**The Role of Vitamin D and Cognitive Decline.** This subject matter has been mixed in past studies in Europe and the US. David Llewellyn, et. al, at the University of Exeter in England studied 3,325 adults aged 65 years and older. Vitamin D levels were measured in blood and urine and compared with a measure of cognitive function that included memory, orientation, and ability to maintain attention. The study classified participants as being cognitively impaired if their score was in the lowest 10 percent of adults.

Cognitive impairment was 42 percent higher in those deficient in vitamin D and 394 percent higher in people severely deficient. Cognitive impairment increased as vitamin D levels went down. The big question is whether vitamin D supplementation has any therapeutic benefit to treat cognitive decline and dementia. This dilemma is similar with Homocystine, of which increased levels raised risk of cognitive impairment and AD. Treating increased Homocystine levels has not shown to decrease cognitive impairment or improve dementia.

**The Role of the (fat) Gene FTO.** Caroline Graff, et. al, at the Karolinska institute in Sweden explored the role of the FTO Gene in AD and dementia risk in the elderly and FTO interaction with APOE. This FTO Gene has been correlated with obesity in humans and shown to affect BMI, Leptin levels, and Diabetes risk. They followed 1,003 people 75 years and older without dementia for nine years to see who developed dementia. People in the study who carried the Autosomal Dominent gene variant in the FTO Gene had a 58 percent increased risk of developing AD compared with those not having this genetic variant after adjusting for age, education, and APOE genotype.

If FTO and APOE4 are present together, the dementia risk is 100 percent after adjusting for diabetes, BMI, cardiovascular disease and physical activity. The increased risk of dementia with FTO presence was independent of traits usually associ-
NIH Consensus Report of Currently Available Data on Prevention of AD and Cognitive Decline
(Not Part Of International Meeting)

A 15 member non-advocate panel representing fields of Preventive Medicine, Geriatrics, Internal Medicine, Neurology, Neurosurgery, Psychiatry, Mental Health, Human Nutrition, Pharmacology, Genetic Medicine, Nursing, Health Economics, Health Service Research, Family Caregiving and a public representative plus another 20 experts from pertinent fields reviewed the literature on prevention of AD and cognitive decline. The consensus report was independent of NIH or the Federal Government. Here’s what they concluded:

Nutritional and Dietary Factors
The evidence does not support a clear role for most nutritional and dietary factors studied. The most consistent evidence is available for longer chain Omega 3 fatty acids (fish consumption) that have been shown to be associated with reduced cognitive decline in longitudinal studies. There is no consistent association between vitamins B, E, C, Folate, and Beta Carotene or diets low in saturated fat and high vegetable intake.

Medical factors
A number of cardiovascular risk factors have been consistently associated with increased risk of cognitive decline. These are: increased blood pressure (most consistent with risk of severe cognitive decline), diabetes (increased risk of modest cognitive decline), and metabolic syndrome (increased risk of modest cognitive decline). There is, however, lack of good studies as relates to sleep apnea, obesity, and brain trauma.

Psychological and emotional health
Depression and depressive symptoms have been consistently found to be associated with MCI and cognitive decline.

Medication
No consistent studies exist for an association with statins, antihypertensives, anti-inflammatory or Alzheimer medications.

Social and cognitive engagement
Findings are inconsistent regarding living alone, but a robust association exists between loss of spouse and cognitive decline. Inconsistent evidence suggests that increased involvement in cognitive activity in later life is associated with slower cognitive decline and lower risk of MCI.

Physical activity
Preliminary evidence suggests a beneficial association of physical activity and range of leisure activity (club membership, religious services, painting, gardening) and preservation of cognitive function.

Tobacco and alcohol
Current smoking and cognitive decline shows an association. Past smoking and alcohol use are inconsistently associated.

Genetic factors
Cognitive decline in the elderly, especially on memory tasks and perceptual speed and other cognitive domain changes, are very inconsistent.

Overall Conclusion of this Panel
1. Firm conclusions cannot be drawn about the association of modifiable risk factors for cognitive decline or AD.
2. There is an absence of highly reliable consensus-based diagnostic criteria for cognitive decline, MCI and AD, and available criteria have not been uniformly applied.
3. There is insufficient evidence to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline, MCI or AD.
4. However, ongoing additional studies including those with antihypertensive medications, omega 3 fatty acids, physical activity, and cognitive engagement (the strongest associations) may provide new insight into the prevention or delay of cognitive decline and AD.
5. Large-scale, population based studies and randomized control studies are critically needed to investigate strategies to maintain cognitive function in individuals at risk for decline, to identify factors that may delay the onset of AD among individuals at risk, and to identify factors that may slow the progression of AD among individuals already diagnosed with the disease.
ated with the FTO gene, such as obesity and diabetes, suggesting the mechanism by which FTO increases risk of dementia is likely different than how it increases obesity. Further studies are clearly needed.

Alzheimers Association Trial Match Program. One of the most positive developments coming out of the international meeting was the announcement of the Alzheimer’s Association trial match program. This a web-based and national 800-line-based service which contains a comprehensive constantly updated database of institutional review board-approved AD, MCI and other dementia trials across the USA. Specialists at the AD association national helpline, available 24 hours a day, assist in the process of matching individuals to clinical trials for which they are eligible, based on study inclusion/exclusion criteria, diagnosis, treatment history and locations. They will describe all studies for which each person is eligible but will not recommend any specific trial. They will connect individuals with trial sites based on their unique profile. The caregivers and patients will be encouraged to discuss these trials with the treating neurologist.

We as neurologists can refer our patients to this trial match program instead of having to look up sites of ongoing research ourselves. The website is www.alz.org/trialmatch, or call toll-free: 1-800-272-3900.

The TOMM 40 Gene in Alzheimer’s Disease. The TOMM 40 Gene has been recognized as a risk factor for AD and recently, like APOE4, to influence age of onset of AD. Mark Sager, et. al at the University of Wisconsin medical school reported they had studied 726 middle-age people with a family history of AD who were genotyped for TOMM 40 and APOE. Of these, 129 had low risk version of TOMM 40 gene and 229 had high risk version. The group with high-risk gene performed significantly worse on standard tests of learning and memory than the low risk group. This was independent of the APOE type.

TOMM 40 genotyping appears to help find early evidence of AD—20 years before symptoms. Sterling Johnson, et. al from the same medical school found that healthy middle aged adults (mean 57 years) who have APOE 3/3 genotype and high risk version of the TOMM 40 Gene had significantly less gray matter volume in two brain regions affected by early AD then those with low risk version, again suggesting a connection between brain loss in asymptomatic AD and high risk version of the TOMM 40 Gene. All this new information does not help us clinically as yet, but will add to all the new information obtained in the preclinical diagnosis of AD and its future treatment.

Intranasal Insulin in the treatment of MCI and AD. Susanne Craft, et. al from the VA hospital in Puget Sound Health Care Centre at University of Washington in Seattle, studied 109 patients with MCI, or AD or controls. They studied the use of 20 or 40 units of intranasal insulin versus placebo. They found in the 20-unit group (10 units BID) that delayed recall testing significantly improved compared to those receiving placebo.

The dementia rating scale severity decreased in those AD patients receiving insulin. This improvement in delayed memory recall persisted for two months after the insulin treatment ended. Fifteen of the insulin-treated participants had cerebral spinal fluid studies for Tau and AB42. The fluid showed a reduced Tau /AB42 ratio correlating with the memory improvement. This positive outcome will be followed by a large multicenter trial.

Ronald Devere, MD is Director of the Taste & Smell Disorders Clinic and Alzheimer Disease & Memory Disorders Center in Austin, Texas.

1. The international Alzheimer’s Association meeting in Honolulu Hawaii, July 2010. The web site: www.alz.org/icad/.

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