

Meeting Report

A review of the “State of the Art” on Mild Cognitive Impairment:
The Fourth Annual Symposium

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Abstract

The fourth Annual Mild Cognitive Impairment (MCI) Symposium, held at the Eden Roc Hotel in Miami Beach Florida on February 24 and 25, 2006, brought together some 150 neuropsychologists, neurologists, and other specialists in the field to discuss the latest research on issues related to the diagnosis and progression of MCI across the broad range of cognitive and functional impairments that comprise its various subtypes. Four mini-symposia were convened on the topics of Cognitive Reserve and MCI, the Genetics and Proteomics of Cognitive Decline, Pathogenesis of Vascular/Metabolic Cognitive Impairment, and Systemic and Psychiatric Considerations in MCI. In addition, 2 keynote addresses were delivered; one on the Rotterdam Study and the other a review of clinical trials in MCI. Participants in the symposium also discussed whether the time has come to revise current diagnostic criteria for Alzheimer's disease.

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At the fourth Annual Mild Cognitive Impairment (MCI) Symposium, held at the Eden Roc Hotel in Miami Beach Florida on February 24 and 25, 2006, some 150 neuropsychologists, neurologists, and other specialists in the field came together to discuss the latest research on issues related to the diagnosis and progression of MCI across the broad range of cognitive and functional impairments that comprise its various subtypes. Four mini-symposia were convened on the topics of Cognitive Reserve and MCI, the Genetics and Proteomics of Cognitive Decline, Pathogenesis of Vascular/Metabolic Cognitive Impairment, and Systemic and Psychiatric Considerations in MCI. In addition, 2 keynote addresses were delivered; one on the Rotterdam Study and the other a review of clinical trials in MCI.

The presentations and discussions highlighted the evolution in thinking about MCI and related areas. Ranjan Duara, of the Wien Center for Alzheimer's Disease and Memory Disorders, Mt Sinai Medical Center, Miami Beach, FL, who is the Program Director of this series of symposia, emphasized the increasing acceptance of the term *MCI* as a generic

entity, encompassing a variety of etiologies and rates of change, including reversible forms of MCI. He outlined the clinical standardized thresholds that have been established for a diagnosis of MCI or Alzheimer's disease (AD) but at the same time encouraged consideration of the individual's cognitive reserve in making diagnoses. He also discussed the need for researchers studying MCI and AD to consider the slope of change over time rather than specific endpoints. Further, he emphasized the need to explore what current and future research tells us about the influence of cognitive reserve and genetic, environmental, and other factors on these slopes of cognitive change.

1. Vascular Risk Factors and Cognitive Reserve in the Evolution of Cognitive Decline and Dementia: Lessons from the Rotterdam Study:

In the first keynote address, Monique Breteler, from the Erasmus University Medical School in Rotterdam, the Netherlands, presented data collected from the Rotterdam Study. This longitudinal study of chronic diseases in an elderly population has followed up with all inhabitants older than 55 years from a defined district in Rotterdam, the Netherlands. Starting in 1990, clinical data were collected to

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assess cardiovascular disease, dysfunction of the locomotor system, endocrine disorders, ophthalmologic disease, and cognitive impairment.

The study has yielded important clues regarding the contribution of vascular factors to cognitive decline and dementia [1]. Not surprisingly, a previous stroke was associated with impaired cognition, as assessed by the Mini Mental State Exam (MMSE). Similar trends were also observed in patients with previous myocardial infarct or clinically overt vascular disease as well as in patients with noninvasive indicators of atherosclerosis.

Diabetes, atrial fibrillation, smoking, and high blood pressure also have been shown to increase the risk of both vascular dementia and AD, fueling the idea that vascular pathology is important, and raising the related question of whether factors that protect against vascular disease will also protect against dementia. Indeed, the Rotterdam study showed that mild to moderate intake of alcohol results in a decreased risk of dementia [2], with a larger effect on vascular dementia than on AD. This finding supports the idea that vascular pathology may be involved in AD, an idea that has been supported further by data showing that high levels of the inflammatory and coagulation factor fibrinogen are associated with an increased risk of dementia [3].

The Rotterdam Study added a longitudinal magnetic resonance imaging (MRI) scanning component to the study in 1995, so as to capture some of the preclinical antecedents to dementia that are identifiable on MRI. Markers of cerebrovascular and degenerative disease on MRI scans have found a number of structural brain changes that are associated with lower cognitive function and a greater risk of dementia. These include periventricular white matter lesions, generalized brain atrophy and hippocampal atrophy, and silent brain infarcts [4]. Based on these studies, they concluded that hippocampal volume can be used as a proxy marker for AD. The use of continuous data points in these longitudinal studies has improved the power of the analyses by including all the cognitive scores and MRI variables and avoiding the need to enter only fixed endpoints, such as MCI or dementia.

The investigators also showed that high levels of homocysteine, which is linked to vascular disease, stroke, and the risk of dementia, were associated with increases in silent brain infarcts, white matter lesions, and hippocampal atrophy. Diabetes, which increases the risk of stroke, was shown in a related study [5] to be associated with brain atrophy but not vascular pathology and with lower performance on memory but not executive function tests. Plasma A β levels were associated with lacunar infarcts and white matter lesions only in those who carried the *APOE* ϵ 4 allele but not in noncarriers of this allele [6]. Those subjects who had infarcts over the course of the study also showed cognitive decline, suggesting that dementia may be caused by vascular events in these patients. Further findings in demented individuals, using transcranial Doppler imaging, suggest

that hypoperfusion is associated with cognitive decline and that this measure may indicate changes in the brain even before cognitive impairment is detectable [7].

Breteler emphasized that vascular disease does play an important role in cognitive decline and dementia. Moreover, she said that clinical dementia shows only the tip of the iceberg in cerebrovascular and neurodegenerative brain changes and that these changes actually occur far earlier than clinical signs and symptoms. She also noted that there is no clear distinction between vascular dementia and AD or between normal and MCI. These observations argue for a shift in thinking toward a multidimensional continuous concept rather than a dichotomous concept of the disease; and more focus on presymptomatic markers of the disease.

2. Cognitive Reserve and MCI

In the first mini-symposium, 6 investigators presented data from different population studies that have explored the idea that cognitive reserve explains the discrepancy between the severity of brain pathology and the clinical syndrome in people with MCI and dementia. According to Yaakov Stern of the Columbia University College of Physicians and Surgeons in New York, reserve could result from either “hardware” differences in the brain itself, eg, increased numbers of synapses, or from an increased ability of the brain to cope with physiological insults, eg, as a result of neural plasticity or neural compensation. The latter is referred to as cognitive reserve. Intelligence (IQ), educational level, occupational attainment, and leisure activity have all been associated with reduced risk of incident dementia and of cognitive decline in normal aging and thus have been used as proxy measures of cognitive reserve. Although the onset of the clinical syndrome appears to be postponed in people with high cognitive reserve, once the symptoms are manifest, the rate of progression and cognitive decline tends to be more rapid, reflecting the true severity of the underlying pathology, which appears to “catch up” over time.

Stern favors a functional imaging approach, rather than proxies, to assess cognitive reserve. He presented unpublished data from a functional MRI (fMRI) study that identified a network of cerebral functional connectivity that appears to represent the neural basis of cognitive reserve. This network is expressed in both young and old subjects, whereas other networks he has characterized are expressed exclusively in older subjects. Measurement of an individual's expression of these networks could yield indices of their cognitive reserve, said Stern. Because the clinical diagnosis of MCI may be accompanied by varying levels of pathology, measuring cognitive reserve would provide a more accurate assessment of a patient's true status. In addition, this fMRI-defined network could provide an objective measure of cognitive reserve in the evaluation of the effectiveness of nonpharmacologic treatments, such as enhancement

of leisure or educational activities, for degenerative and vascular disorders of the brain.

Lawrence Whalley, of the University of Aberdeen, Scotland, followed Stern with a description of longitudinal studies he has conducted with subjects who originally participated in the Scottish Mental Surveys of 1932 and 1947. These surveys collected IQ scores on 160,000 Scottish children at age 11. From 1998 through 2001, Whalley and colleagues traced 1,290 surviving participants from the earlier surveys and recruited them for participation in a follow-up study to assess the influence of childhood intelligence and factors such as education, lifestyle, and occupation on cognitive, psychological, locomotor, cardiac, and other functions. Later, an imaging component was added to the study.

Whalley's studies found that the aging brain is shaped by the younger mind, and that cognitive reserve comprises the major pervasive influence of childhood intelligence combined with the cumulative effects over the life-course of a complicated set of influences, including lifestyle and genetic factors. Among the genetic factors he studied, *APOEε4* had a negative influence on late-life cognitive function, and 2 specific polymorphisms, in *Nicastrin* and *KLOTHO* genes, positively influenced both childhood IQ and retention of cognitive ability with age.

In the imaging study, Whalley set out to determine whether MRI findings were related to vascular risk factors, cognitive status, or cognitive decline. These studies, done in subjects without dementia, showed that cognitive function in elderly individuals is influenced by white matter lesions and, independently, by hypertension [8]. In trying to fit the data to active or passive models of cerebral reserve, Whalley showed that the active model, which takes into account lifestyle factors, is a better fit. This model shows that after adjustment for childhood IQ, cognition at age 79 is positively influenced by education and occupation minus the effects of brain atrophy and white matter lesions [9].

Holly Tuokko, from the University of Victoria in British Columbia, Canada, presented data from the Canadian Study of Health and Aging (CSHA), which suggests that ascertainment bias, rather than cognitive reserve, is responsible for the low incidence of dementia in individuals with high levels of intelligence, education, and occupational attainment [10]. The problem, according to Tuokko, is that the criteria for identifying AD and MCI is frequently based on a threshold approach, eg, a MMSE less than 24, or a normative approach, eg, 1 standard deviation below the norm. Both of these approaches are affected by ascertainment bias, said Tuokko.

Tuokko and colleagues looked at data from subjects tested at baseline (CSHA-1) and again 5 years later (CSHA-2). In accordance with the cognitive reserve hypothesis of Yaacov Stern, those who were high functioning in terms of educational level at CSHA-1 were less likely to progress to dementia at CSHA-2 than those who had low educational

levels. However, when performance at CSHA-1 on 5 memory measures was examined, high-functioning individuals who proceeded to dementia had lower scores on memory tests at CSHA-1, suggesting that the low incidence of dementia in high-functioning individuals was at least in part a function of the criteria used to define dementia, rather than underlying brain differences or cognitive reserve.

Tuokko concluded that, currently, clinicians' ability to detect impairment in high-functioning people is compromised and may jeopardize access to treatment in this group. Her solution to this problem is to adopt measures that will detect intraindividual, rather than interindividual decline.

Daniel Mungas, from the University of California at Davis, addressed the use of structural MRI to define cognitive reserve. His data were collected from a community-based, multicultural sample that represented a broad range of cognitive function and educational levels. Using memory score as a proxy for cognitive function, Mungas defined cognitive reserve as the residual cognitive test score that is not explained by brain volume. He showed, using a cross-sectional analysis, that an inverse relationship exists between memory score and normalized brain volume. Using longitudinal analysis, he further showed that reserve, as defined above, was inversely related to the likelihood of cognitive decline and incident dementia. In other words, these results show that a combination of structural neuroimaging and measures of cognitive function can be used to estimate cognitive reserve, and that these measures have an important relationship to clinical status and prognosis.

Cheryl Grady, from the Rotman Research Institute at the University of Toronto used functional neuroimaging to study cognitive reserve. Her studies show that older people recruit different brain areas than do younger people while doing a variety of tasks. She showed that these patterns of brain activity are related to levels of education and cognitive reserve, modified by the age of the subjects. In comparing AD patients with normal controls, she found that patients show increased activity in the prefrontal areas of the brain and that greater activity in this area correlated with better performance on cognitive tasks [11]. She concluded that recruitment of the dorsolateral prefrontal cortex may be a general manifestation of compensation or reserve.

David Bennett, from the Rush University Medical Center in Chicago, Illinois, presented data from the Rush Memory and Aging Project [12], a longitudinal study of 1,100 residents of retirement communities in the Chicago area. All subjects provide data on their medical histories and engagement in cognitive activities and social networks and get annual medical and cognitive assessments. In addition, they provide blood and DNA samples and agree to donate brain, spinal cord, muscle, and nerve tissue when they die. The study was designed to explore how genetic and experiential factors affect the nervous system to cause MCI, AD, and other age-related conditions.

At baseline, only patients without known dementia were

recruited; however, a small number (6.3%) were found to have mild dementia at their baseline evaluation. At the time of this presentation, 130 autopsies had been done. Interestingly, about 40% of those without any cognitive impairment (no MCI and no dementia) met the National Institute on Aging (NIA)/Reagan criteria for a pathologic diagnosis of AD [13].

Bennett et al [14] have also used data from the study to explore the effect of cognitive stimulating activities on cognitive function and brain pathology. In a cross-sectional study, they showed that engagement in cognitive activities across the lifespan was associated with better cognitive performance. Bennett suggested that engagement in these activities may be associated with neurobiological indices, such as neurons and synapses, that could represent cognitive reserve and modify the relation of AD pathology to cognition. They are currently exploring these and other factors that may modify the relation of AD pathology to cognition [15].

In the discussion after these 6 presentations, Walter Kukull of the University of Washington questioned whether the label “cognitive reserve” is an effective explanation for a clinical condition or simply a descriptive surrogate for biological characteristics that can be quantitatively assessed, such as brain volume or the number of neurons or synapses. If cognitive reserve can be modified, might it be useful to tie such modifications to predictable and measurable effects on plasticity in the brain?

Brent Small of the University of South Florida agreed that there are measurement and analytic challenges to studying cognitive reserve and cognitive impairment, but noted how much interest in the concept of cognitive reserve has grown in recent years. The big question, he said, is whether cognitive reserve is an appropriate intervention target. He cited a study [16] that suggested a link between cardiovascular fitness and improvements in the plasticity of the aging human brain. Yaakov Stern commented that many investigators are convinced that intervention research is important; however, he noted that studies will be expensive and difficult to randomize. Lawrence Whalley added that there has already been a huge and successful effort to promote heart-healthy interventions, such as public health strategies, to lower blood pressure and blood lipids, detect diabetes, and encourage people to quit smoking and get more exercise, and that interventions that have been so effective in lowering morbidity and mortality from heart disease in the middle aged may next prove effective in preventing cognitive decline in old people. “Maybe things that are already in place to reduce heart disease will next reduce dementia, and we could be out of business in 20 years!” he said.

3. Genetics and Proteomics of Cognitive Decline

Richard Mayeux, from the Columbia University College of Physicians and Surgeons, opened the second

mini-symposium on the genetics and proteomics of cognitive decline. He described a memory classification system and the brain regions associated with specific subtypes of memory function. He went on to describe studies in which people have assessed different types of memory in normal aging. These studies have found that declarative memory tends to decline with age, even in healthy adults. Moreover, twin studies show that there are substantial genetic influences over memory.

Some investigators have tried to tie memory loss in normal adults with various AD candidate genes. For example, one study showed that having the *APOE*ε4 allele is associated with impaired ability to recall names and faces. Others investigators have shown that α2 macroglobulin and ACE (angiotensin converting enzyme) appear to have an effect on delayed recall and recognition. However, interaction studies show that the effects of age are far more important than these candidate genes. Mayeux emphasized that these single gene studies are controversial and have not been replicated. Few family studies using linkage analysis have been conducted in people with memory impairments. One study, in families with alcoholism, identified 2 regions on chromosomes 11 and 14 that seemed to be associated with cognitive performance, although the generalizability of this study is questionable because families were recruited because they have alcoholism. Nonetheless, Mayeux said that linkage studies such as this may be the best way to unravel the genetic underpinnings of normal memory.

Mayeux went on to describe a study he has conducted in more than 500 families, each with at least 2 affected members affected with AD in the Dominican Republic and Puerto Rico [17]. The investigators concluded that about half of the variation in memory performance was genetically based, with lower heritability estimates for other cognitive functions such as abstract reasoning, attention, language, and visual-spatial ability. Mayeux emphasized that in genetic studies it may be more important to evaluate the interaction of genes with certain endophenotypes, rather than with the entire clinical syndrome. Endophenotypes are specific clinical features, such as memory performance, within a more complex clinical entity such as AD. Mayeux concluded that memory performance may be useful in identifying genes related to AD and MCI and that investigation of the relationship between the known AD-related genes and cognitive phenotypes has already led to a better understanding of the pathogenesis of AD and MCI. These discoveries may point to new therapies in the future, he said. Nevertheless, an analysis of the influence of *APOE*ε4 suggested that *APOE*ε4 plays a limited role in memory performance, at least in the cohort studied by Mayeux and his colleagues.

Peter St. George Hyslop from the University of Toronto followed Mayeux by probing further into the complex genetics of AD. Genetic factors are responsible for about 40% of the variance in risk for AD, with mutations in four genes

(*APP*, *PS1*, *PS2*, and *APOE ϵ 4*) accounting for about half of the genetic component. All of these mutations cause mis-processing of amyloid β precursor protein (*APP*) and accumulation of $A\beta$, but act at different points in the pathway from *APP* to $A\beta$ aggregates and neurotoxic protofibrils. Moreover, enhancer and suppressor interactions among these genes have been demonstrated in both human and animal models, confirming that they act in the same biochemical pathway. Meanwhile, the search is on for other genes that may interact in this pathway. Family-based association studies suggest that genes on chromosomes 10, 12, and possibly 9 may play a role.

St. George Hyslop maintained that understanding the complex genetics of AD inheritance is important not only as a research tool for identifying new genes and interactions of these genes in the disease pathway, but also as a diagnostic and predictive tool. An individual's risk of developing AD and the subsequent course of the disease, from normal to MCI and from MCI to AD, could be predicted, potentially, by specific genetic factors. More importantly, genetic tests could be useful for identifying at-risk subjects for treatment long before any biochemical, imaging, or clinical changes are evident. Currently, presymptomatic genetic testing is useful only for highly penetrant genes with clear patterns of inheritance and a relatively predictable age of onset, i.e., *PS1*, *APP*, and *Tau*. Knowledge of "risk factor" genes, such as *APOE ϵ 4*, will allow only "fuzzy estimates" of risk, but in the future may be useful for identifying people who should be targeted for primary prophylaxis.

Lindsay Farrer of Boston University Medical School presented data collected in the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, which supports the idea that risk factors for vascular disease are also risk factors for dementia and AD. One family of genes they have investigated are those that encode paraoxonase (*PON*), an enzyme that is expressed in the liver and found in the blood associated with apoA1 and high density lipoprotein. By testing the association of 29 SNPs of *PON1*, *PON2*, and *PON3*, they concluded that polymorphisms in *PON* loci confer susceptibility to AD, and specifically, that a polymorphism in the *PON1* promoter region is likely responsible for the increased risk [18].

They have also been looking at polymorphisms of the *ACE* gene in the Wadi Ara, an inbred Arab community in northern Israel that has a high prevalence of AD. These studies have concluded that two adjacent polymorphisms are highly associated with AD. Farrer said that he believes that vascular genes influence AD as upstream events, possibly involved with $A\beta$ metabolism, or even earlier events.

Venkata Mattay and colleagues at the National Institute of Mental Health have taken a different approach to studying genetic polymorphisms that may be associated with cognitive decline. They use neuroimaging methods to capture the effects of various genes and polymorphisms at the level of neuronal circuitry. This approach, called Imaging

Genetics, provides a more sensitive and objective assessment of changes in the brain than behavioral measures alone. Mattay presented data related to the effects of polymorphisms in the genes for catechol-O-methyltransferase (*COMT*) and brain-derived neurotrophic factor (*BDNF*) on age-related changes in cognition.

Catechol-O-methyltransferase is an enzyme that mediates dopamine catabolism. A common functional polymorphism, val¹⁵⁸met, has been associated with differences in cognitive function in the imaging studies: the met allele confers enhanced cognitive performance, whereas the val allele is associated with impaired prefrontal cognition and physiology. Preliminary results from Mattay's studies in elderly people suggest that *COMT* genotype modulates the effect of age-related changes in cognition.

Brain-derived neurotrophic factor is an important mediator of neuroplasticity in the hippocampus, and thus of learning and memory. Mattay and colleagues have shown that the met allele of a frequent polymorphism (val⁶⁶met) in the gene for *BDNF* is associated with reduced hippocampal engagement during memory processing in healthy individuals, both young and old. Future studies will evaluate the role of the *BDNF* val⁶⁶met polymorphism on age-related changes in cognition as well as in MCI and AD.

Other approaches that are now used extensively to elucidate the biological processes that underlie different disease conditions use cDNA microarray and proteomic technologies. Giulio Pasinetti, from the Mt. Sinai School of Medicine in New York, described studies using both of these technologies to clarify the molecular mechanisms involved in the progression from MCI to AD [19]. Although high throughput DNA microarrays are capable of identifying candidate genes that are altered as the disease progresses, they cannot identify posttranslational modifications of proteins and so may not provide a complete picture of the changes that mediate progression. Thus, Pasinetti uses a combination of cDNA microarrays to study gene expression in brain tissue, and SELDI-Mass spectrometry protein chips to quantify protein expression in the serum and cerebrospinal fluid of MCI and AD patients.

The microarray studies have identified genes that are differentially regulated in the brains of patients spanning all Clinical Dementia Rating (CDR) levels. Among these, expression of mRNAs for caspases 1, 3, and 7 were upregulated in the entorhinal cortex of MCI patients coinciding with increased poly (ADP-ribose) polymerase cleavage but appear to precede apoptotic cell death [20]. This finding may provide clues about possible therapeutic targets for MCI and AD. Another gene that may be differentially regulated in patients with MCI is the gene for a HuD, a strictly neuron-specific ELAV-like RNA binding protein. This association has been confirmed in proteomic studies. Interestingly, in mice trained in the Morris water maze, HuD levels increase and other genes involved in memory trace formation, such as *GAP-43*, are activated [21], suggesting a pos-

sible mechanism for preservation of cognitive reserve in MCI.

Pasinetti's proteomic studies have investigated candidate proteins that may serve as biomarkers of disease progression across different CDR levels. He has identified one such protein, a novel Cu^{++} -binding protein called S100A7, which is elevated in the CSF of early AD patients. He further showed that mRNA expression of this protein is increased in the brain as a function of the progression of AD dementia and neuritic plaque pathology but not related to neurofibrillary tangles. Finally, he showed in transgenic cell culture experiments that expression of S100A7 results in decreased levels of $\text{A}\beta_{1-42}$ and increased sAPP- α in the conditioned medium. Taken together, these experiments suggest that MCI-related changes in gene expression may influence APP processing and amyloidosis, and thus these may be therapeutic targets in patients with MCI.

The final speaker in this mini-symposium, Steven Younkin of the Mayo Clinic in Jacksonville, Florida, returned to the topic of $\text{A}\beta$ and suggested that lowering plasma or CSF $\text{A}\beta$ levels may represent a preventive treatment strategy for AD, similar to lowering cholesterol to prevent cardiovascular disease. Younkin and colleagues have conducted a longitudinal study in normal (at baseline) white elderly subjects over a 13-year period. In this study, the ratio of $\text{A}\beta_{42}/\text{A}\beta_{40}$, rather than simply elevated $\text{A}\beta_{42}$, was a good biomarker for identifying those who will have MCI or AD over the next 3 to 5 years. He suggested that in a mixed population, or in one in which the disease develops rapidly, such as that studied by Mayeux, elevated $\text{A}\beta_{42}$ alone may indicate increased risk. Younkin's studies also suggest that people at high risk start out with high levels of both plasma $\text{A}\beta_{42}$ and $\text{A}\beta_{40}$, but that $\text{A}\beta_{42}$ starts to deposit in the brain as the disease progresses, leading to declining levels in the plasma. Further, he has shown that in individuals who carry the *APOE* $\epsilon 4$ allele, the ratio of $\text{A}\beta_{42}/\text{A}\beta_{40}$ predicts who will have MCI and AD. A larger longitudinal study will be needed to verify the relative importance of these different forms of $\text{A}\beta$.

After Younkin's presentation, Fiona Crawford of the Roskamp Institute in Sarasota, Florida, moderated a panel discussion about the genetics and proteomics of cognitive decline. She asked whether discrepancies in genetic association studies might be clarified through proteomic studies of candidate genes. Steven Younkin responded that although such studies could provide additional valuable information, because so many genetic and environmental factors play roles in complex conditions such as cognitive impairment, sample sizes for these studies would need to be extremely large.

Crawford also asked whether identification of protein biomarkers might lead back to the identification of genetic risk factors. Richard Mayeux cautioned that the problem with biomarkers is that they are only markers. A genetic association study that identifies a biomarker may lead to

identification of a gene, but it may not explain how that gene predicts the disease. Steven Younkin noted that the value of genetic markers (as opposed to protein markers) is that a strong association indicates that the gene is the driving force. Any protein marker associated with this gene is a result of the effects of this gene and not vice versa.

Lindsay Farrer commented that although genetic and proteomic studies have refocused attention on the role of vascular factors in cognitive impairment, markers that have thus far been identified, such as ApoE, may represent "low-picking fruit" and may not have direct effects on the important pathways involved. He predicted that as more genes and proteins are identified, critical upstream events in vascular and inflammatory pathways will show that multiple genes, layered on top of environmental factors, are involved in the disease process.

4. Pathogenesis of Vascular/Metabolic Cognitive Impairment

The third mini-symposium returned the focus to vascular disease and its relation to dementia and again showed how the concepts surrounding these issues have evolved over time. Gustavo Roman from the University of Texas Medical School began his talk with an overview of how the pendulum has swung back and forth over the last 40 years. Most dementia was originally thought of as being caused by vascular lesions, with AD considered a relatively rare disease. Gradually, neurodegeneration with plaques and tangles began to be seen as the major cause of dementia, and the concept of vascular dementia (VaD) was largely replaced with the term multi-infarct dementia (MID), or dementia caused by multiple, repeated small or large strokes. Now, said Roman, the pendulum is beginning to swing back. Vascular components are seen as increasingly important, and VaD is now seen as more than MID. Single strategic strokes, white matter ischemia, or cerebrovascular disease coexisting with AD are also significant causes of cognitive impairment in the elderly. And a new player has emerged on the scene. Last year, Wu et al [22] showed that expression of the *MEOX2* homeobox gene is low in individuals with AD and that this contributes to neurovascular dysfunction by arresting growth, causing apoptosis of vascular cells, increasing the numbers of abnormal microvessels, and decreasing $\text{A}\beta$ clearance.

The pathogenesis of cognitive impairment after stroke can take many forms based on the location of the stroke, but the common element is an interruption of the memory circuit caused by ischemic injury of any portion of the circuit. For example, 25% of patients with infarcts in the posterior cerebral artery territory present with memory problems. Other strategic areas include the anterior cerebral artery territory and the basal ganglia and thalamus. Silent lacunes, particularly in the thalamus, more than double the risk of dementia. White matter ischemia brought on by

hypoperfusion can result from cardiac or circulatory factors and may also be an important source of cognitive and memory impairment through interruption of prefrontal-basal ganglia circuits. Ischemia can also cause a loss of cholinergic innervation, which in itself can cause cognitive dysfunction and can also alter cerebral blood flow regulation.

Moreover, cerebrovascular disease is an important component of AD. A recent study [23] found that both VaD and AD patients have similar levels of small vessel disease, which can lead to a decline in information processing speed, executive function, and memory. Roman suggested that what is needed is a redefinition of dementia that would give equal prominence to executive dysfunction and loss of functional capacity as it currently does to memory dysfunction.

The heterogeneity in terms of the underlying causes of vascular cognitive impairment extends beyond stroke and cerebrovascular disease, as was described earlier by Monique Breteler and reiterated in a presentation by Lenore Launer, Chief of the Neuroepidemiology Section at the National Institute on Aging. Both cardiovascular disease and diabetes are associated with an increased risk of cortical atrophy, which is often considered a marker of AD. Moreover, in the Honolulu-Asia Aging Study (HAAS), Launer and colleagues have shown that elevated blood pressure in midlife is associated with greater numbers of neuritic plaques in the neocortex and hippocampus, as well as increased neurofibrillary tangles in the hippocampus [24]. These studies, as well as others that have attempted to differentiate between VaD and AD based on cognitive profiles or functional impairments, point to the difficulty of defining vascular cognitive impairment as distinct from AD. Launer concluded that “pure” cognitive impairment syndromes are the exception rather than the rule. Nonetheless, because vascular-based dementia may be more treatable than that owing to classic AD pathology, it remains an important concept to take into account in the clinical management of people with dementia and in prevention.

Mary Haan, from the University of Michigan School of Public Health, presented additional information on the link between type 2 diabetes and dementia, cognitive decline, and AD. There has been little research with regard to MCI, said Haan. Studies have shown, for example, that type 2 diabetes affects global cognitive decline as well as specific memory domains and that there is a greater rate of decline in most tests of memory and processing speed among diabetics compared with nondiabetics. In the Sacramento Area Latino Study on Aging, the 5-year risk of CIND (Cognitively Impaired, Not Demented) was higher in diabetics, and diabetics with CIND also converted to dementia at a higher rate. Other research has shown a relationship between obesity, central body fat, and low levels of physical activity with dementia. The mechanisms that could account for these strong relationships have not yet been identified but are related to type 2 diabetes. One study suggested that high

insulin levels may provoke increased $A\beta$ deposition and increases in inflammatory factors [25]. Another study [26] suggested that high body mass index and fat mass are associated with increased levels of plasma $A\beta_{42}$. A third study of brain morphology [27] showed that type 2 diabetes is associated with increased hippocampal atrophy.

Whether treatments for type 2 diabetes may affect cognitive function is not clear, because cognitive function has not been included as an outcome measure in most randomized clinical trials of diabetes treatments. Some observational studies of diabetic treatments suggest that those treated with combination therapy have less cognitive decline than those on monotherapy. A single study of MCI currently in progress will be assessing the effects of insulin-sensitizing treatment on cognitive outcomes and may provide an answer to this question soon. An ongoing study should also help answer the question of whether chronic hyperinsulinemia is associated with an increase in $A\beta$ deposition, and thus, whether insulin is contraindicated for elderly people. Discussants at the mini-symposium agreed that this is a very provocative area for further research.

Helena Chui from the University of Southern California leads a multicenter NIA-funded project that uses neuroimaging and neuropathologic studies to explore both vascular dementia and Alzheimer's dementia. She has developed a method to preserve the postmortem brain and then to coregister neuropathologic findings with in vivo MRI. Preliminary findings using this method indicate a 66% agreement between MRI and pathologic classification, with mismatches occurring mostly for small lesions. Using MRI signal characteristics, she was also able to differentiate between lacunes and perivascular spaces.

Chui's imaging studies show that hippocampal atrophy and cortical atrophy, as determined by MRI, predict cognitive impairment better than lacunes or white matter hyperintensities (WMH). Cortical gray matter volume is the most significant predictor of AD pathology, although vascular pathology (lacunes and WMH) also contribute. In other words, Chui said that hippocampal atrophy is not a specific endophenotype for AD, because it can be caused by hippocampal sclerosis, which may be caused by either ischemia or degeneration. However, among those classified as having vascular dementia, hippocampal atrophy was not found to be a feature. She acknowledged that this point is controversial and that the presence of hippocampal atrophy in a case of dementia did not necessarily imply the presence of AD pathology and the absence of vascular dementia. She did concede that some people believe hippocampal sclerosis is a form of fronto-temporal dementia and is not related to vascular lesions.

Julie Schneider of the Rush University Medical Center studied cerebral infarctions and AD pathology in more than 100 deceased subjects with and without dementia from the Rush Memory and Aging Project, which was described earlier by David Bennett. Schneider and colleagues found

significant overlap between the presence of infarcts and AD neuropathology, with the cognitive effects of the 2 pathologies being additive rather than interactive. Almost all of the subjects with infarctions had some AD pathology, and most of these subjects also met criteria for a coexisting diagnosis of AD. The presence of AD pathology increased the odds of dementia significantly, and the extra presence of one or more infarctions further increased the odds of dementia. Cognitive function across semantic memory and episodic memory was impaired in a similar fashion, with both AD pathology and infarcts lowering cognitive function. With working memory, there was an interactive rather than additive effect of having both pathologies, suggesting that more is going on. Schneider and colleagues are also looking at other vascular factors, such as lipohyalinosis, amyloid angiopathy, perivascular and white matter changes, and inflammatory factors, which may influence cognition. Preliminary studies suggest that lipohyalinosis is related to cognitive impairment, although the mechanism is unclear.

Charles DeCarli of the University of California, Davis, presented data suggesting that there are 2 biologically different subtypes of MCI, one of which is related to cerebrovascular disease, causing WMH; and the other related to AD, causing hippocampal atrophy. Both groups are equally impaired on episodic memory tasks, said DeCarli, but the MCI-WMH group was significantly more impaired on certain working memory tasks that place demands on encoding rather than consolidation. Data from fMRI studies further show that individuals with WMH have dysfunctional dorsolateral prefrontal circuits associated with impairment in working memory.

Preliminary data from DeCarli's group further suggests that disconnection of specific white matter tracts is responsible for impaired encoding seen in individuals with WMH. Because cerebrovascular disease is potentially modifiable through therapy, DeCarli's findings suggest that treatment may reduce cognitive impairment in a subset of elderly patients.

In the discussion that followed this mini-symposium, Richard Mayeux asked whether the time has come to move from observations about the vascular changes associated with cognitive impairment to identification and clarification of the mechanisms involved. Although data suggest that both clinical and biological risk factors lead to subclinical vascular disease, which eventually leads to cognitive impairment, might these same factors lead to AD and MCI directly, without first causing subclinical vascular disease? Lenore Launer said that although vascular damage can lead to undernutrition of neurons, the pathways leading to vascular lesions and Alzheimer's pathology appear to be independent. Mary Haan added that diabetes may also affect cognitive outcome on a parallel, independent pathway from its effects on vascular pathology, including the possibility that hyperinsulinemia affects A β deposition. David Bennett also noted that vascular researchers are questioning whether

the mechanisms that lead to brain infarcts may contribute independently to cognitive impairment.

Clinical implications of the research on vascular dementia took center stage in this discussion. As mentioned earlier, some findings suggest that treatment for diabetes may influence the development of dementia, although there are conflicting results about the relationship of diabetes to certain cerebrovascular outcomes, such as infarcts. Moreover, there are some data suggesting that dementia may be preventable by addressing the same risk factors as those that are addressed for heart disease. However, as Mary Haan noted, as the risk of cardiovascular disease has gone down, presumably through lifestyle changes, individuals are living long enough to develop dementia, indicating that the relationship between vascular disease and dementia is complex.

5. Systemic (Medical) and Psychiatric Considerations in MCI

In the final mini-symposium, speakers considered more holistic questions about aging and the effects of various diseases on the risk of MCI and dementia. John Starr from the University of Edinburgh presented data collected from the Lothian cohort of the Scottish Mental Survey of 1932. This cohort consists of individuals born in 1921 who, when retested 79 years later, had MMSE scores greater than 23. They also were given other tests of mental ability as well as physical and medical evaluations. Component analysis of both physiologic and cognitive variables identified 2 components that affect functional ability. Component 1, the "common factor" accounts for 35% of the shared variance and posits that higher IQ score was associated with less disability. Component 2, physiologic health, accounts for 20% of shared variance and posits that physiologic health is a more important determinant of disability than mental ability.

The implications of this analysis, said Starr, are that although brawn and brain go together, within the normal or MCI range of cognitive ability, brawn rather than brain limits functional ability.

Jeffrey Wefel, from the University of Texas M.D. Anderson Cancer Center, followed Starr with a discussion of how cancer, chemotherapy, and genetics affect cognitive function. Wefel conducted a prospective, longitudinal study assessing cognitive impairment in women undergoing chemotherapy for breast cancer [28]. At baseline (before beginning chemotherapy), 35% of women showed evidence of impaired cognition. After treatment, testing found a 60% to 70% decline in cognitive function, but after 1 year, 45% had improved, 45% had remained stable, and 10% had mixed results. Although prior studies showed an association suggesting that younger women were more likely to experience cognitive impairment than older women, which may reflect the consequences of undergoing chemical menopause, this was not replicated in Wefel's studies.

Mechanisms for chemotherapy-induced cognitive decline have not been defined; however, Wefel reviewed FDG-PET data from a trial at UCLA that showed hypometabolism at rest in patients who had received chemotherapy. Wefel also reviewed data suggesting that individuals with a history of cancer are less likely to develop dementia, and those with dementia are less likely to develop cancer. The mechanisms behind these observations are unclear at this time.

Mariana Cherner from the University of California, San Diego, discussed cognitive deficits that result from HIV and Hepatitis C (HCV) infections and from comorbid methamphetamine dependence. Although HIV attacks the immune system and HCV attacks hepatocytes, both get into macrophages and likely travel into the brain this way. Most people with HIV infection have mild cognitive problems, and although highly active antiretroviral therapy (HAART) has provided significant benefits overall to people with HIV, it has not reduced the incidence of cognitive impairment. Methamphetamine has an additive effect on cognition among people with HIV. People with all 3 risk factors: HIV, HCV, and methamphetamine dependence fare worst. HCV and HIV cause problems across many cognitive domains; methamphetamine, however, may affect a smaller subset of cognitive domains. Cherner concluded that HCV has been underappreciated as a cause of neurocognitive impairment and may account for some of the deficits that have been attributed to methamphetamine dependence in individuals infected with both viruses.

Depression can further complicate the diagnosis and treatment of mild cognitive impairment and dementia, because depression itself can cause many of the same cognitive impairments seen in MCI. According to Anand Kumar of the University of California, Los Angeles, depression modifies both the clinical picture and the course of dementia, and both vascular dementia and Alzheimer's dementia may lead to depression. Whether depression hastens the conversion of MCI to dementia is not yet known, and the biological mechanisms that might contribute to this are unclear.

Nonetheless, it is known that late-onset major depression and amnesic MCI are high risk factors for dementia, and more data are needed on the role of less-severe depressive symptoms and non-amnesic MCI. A problem is that all current diagnostic tools for depression have their limitations. Assessing cognition and using neuroimaging studies as a part of the diagnostic workup can provide more clarity as to the relative contributions of vascular problems, depression, and dementia in patients with coexisting MCI and mood symptoms. Moreover, depression should be treated and followed up aggressively, although there are limited data on the use of different types of antidepressants in cognitively impaired patients.

Larry Tune, of Emory University raised another issue relevant to elderly people who are experiencing cognitive

impairment. Among the many drugs that elderly patients are commonly prescribed, many of them are either benzodiazepines or have anticholinergic effects, both of which may lead to toxicity ranging from subtle cognitive impairment to delirium. Moreover, when an individual is taking multiple drugs in these classes, the effect on cognition can be significant. Tune discussed many different studies that have documented the association of high serum anticholinergic activity with delirium and poor performance on tests of cognitive function.

Similar results were seen in a study in which elderly patients receiving ditropan for urge incontinence had their ditropan doses reduced. Although there was no effect on incontinence, there was a significant inverse relationship between ditropan dose and MMSE. In another study on patients receiving donepezil, those on anticholinergics as well showed a greater loss in MMSE score over the 2-year study period.

Tune also showed results of studies of patients on tricyclic antidepressants and antimuscarinic drug treatment for Parkinson's disease. In both studies, patients receiving these drugs had a higher rate of plaques and tangles on neuropathology studies. Tune has extracted data from the AD center database at Emory to assess the relationship between number of benzodiazepine and anticholinergic medications and the conversion from MCI to AD. At this point, no clear effect has been seen; however, Tune said the study is limited by several factors including its small size and retrospective design. Further prospective studies are needed that include measurement of anticholinergic levels.

Discussants for this mini-symposium included Meryl Butters and Mary Ganguli, both from the University of Pittsburgh, and Karine Pérès from the University of Bordeaux. Butters and Ganguli, along with many of the audience participants, discussed the need for an adequate definition of MCI. They favored a distinction between "mci" ("lower case mci") and MCI, with the latter being a subset of the former. The broader category of "mci" applies to all cases, regardless of etiology, in which cognition is mildly impaired compared with the individual's own usual or previous functioning, or compared with others with similar demographic characteristics. The narrower category of MCI would refer to those cases with incipient degenerative or vascular dementing disease. Butters pointed out that we already have a model for this approach with the broad definition of "dementia" and the narrower subcategories of AD, vascular dementia, and other dementing subtypes. Ganguli further emphasized the need to have well-defined and homogeneous categories and subtypes to be diagnostically meaningful. However, there was little consensus on whether MCI, as currently defined, represents a distinct, homogeneous, diagnostically valid entity.

Pérès presented data from the PAQUID study, an epidemiologic study of mental and functional aging in a community-based sample in France. This study has assessed the

effects of restrictions on instrumental activities of daily living (IADL) in patients with MCI. Instrumental activities of daily living restriction is a strong predictor of short-term conversion to dementia and a strong predictor of nonreversibility, according to Pérès. This measure captures early deficits beyond those measured by cognitive tests and reflects an individual's capacity to function in real life. However, consensus is still needed on the usefulness of this measure.

6. Clinical Trials in MCI

In the second keynote address, Murali Doraiswamy of Duke University Medical Center reviewed the design and execution of clinical trials in MCI. Currently, said Doraiswamy, there are no drugs approved for MCI; hence, any treatment used for MCI in practice would be viewed as off-label. Most of the randomized, clinical trials that have been conducted have focused on amnesic MCI, and most have looked at either symptomatic cognitive benefits or a delay in "conversion" to AD. A few studies have also taken on the challenge of assessing a disease-modifying effect by measuring rates of brain atrophy. Comparing results of different trials is complicated by the fact that they use different memory criteria for entry into the trial and different outcome measures. Although none of these trials yielded primary outcomes that were predicted, Doraiswamy said that much has been learned from these trials.

The initial 24-week donepezil MCI trial was a randomized, double-blind, placebo-controlled study of 270 patients with MCI who were given 5 mg/d donepezil for 6 weeks and then force titrated to 10 mg/d. No significant effect was seen in the primary outcome variables; however, secondary outcomes improved, including ADAS-Cog scores and patient perception of greater improvement in memory. Transient and mild to moderate adverse events were relatively higher after the dose escalation in this study (compared with AD trials). This study led to a second study that evaluated the effectiveness of Donepezil, Vitamin E, and placebo [29]. Donepezil treatment resulted in a reduced likelihood of progression to AD during the first 12 months of the study, but the rate of progression at 3 years was not changed. One important finding of this study related to *APOE*ε4 status. The presence of 1 or more of these alleles was a strong predictor of conversion to AD, and these subjects did benefit from donepezil treatment through the study period. Vitamin E had no benefit in patients with MCI.

Doraswamy also considered nondrug trials, including lifestyle interventions. However, very few of these studies have been conducted in amnesic MCI.

Ronald Petersen, the principal investigator of the donepezil study commented on some of the difficulties encountered in conducting clinical trials for MCI. In the Merck trial of Rofecoxib, slow recruitment led the investigators to

adapt their criteria for entry into the trial such that a milder group of patients were included. This compromised their ability to detect an effect on conversion to AD. Another problem was seen in the international rivastigmine trial, where language and cultural differences led to inconsistency in defining conversion. A third problem cited by Petersen is the difficulty in retaining subjects over a long clinical trial. These little problems add up to significant difficulty in conducting clinical trials, he said. Doraiswamy added that different metrics and more objective outcomes are needed to measure efficacy in people with MCI. With soft outcomes, power is lost, and the need for large numbers of subjects is exaggerated. For example, MRI and MRS measures may increase the ability to detect effects on brain atrophy and neuronal function directly, although they also can increase the cost and patient burden.

7. Revising the Diagnostic Criteria for MCI

John Morris of Washington University School of Medicine in St Louis, Missouri, chaired a special session to consider whether the time has come to revise current diagnostic criteria for Alzheimer's disease. The session was predicated on an editorial recently published in the *Archives of Neurology* [30], in which Morris argued that a recognizable subset of individuals with amnesic MCI show the pathologic characteristics of early-stage AD, and that revised diagnostic criteria would allow inclusion of these individuals in therapeutic trials at a time when interventions might have their greatest impact.

Ronald Petersen, who was in large part responsible for characterizing amnesic MCI as a transitional stage between normal aging and AD, suggested that requiring memory impairment in the definition of MCI may limit the term's usefulness. Any change in cognitive function that affects daily activities constitutes dementia, he argued. Richard Mayeux, however, argued that it may be premature to revise the criteria because there are no gold standards for risk, diagnostic, or prognostic markers. Lenore Launer emphasized the need for more quantitative measures of disease that reflect the underlying pathology and symptomatology.

Petersen and Morris emphasized that they were not themselves proposing new criteria, but instead were suggesting that the time may have come to consider whether a revision would be valuable and, if so, how to go about gathering the data to support a revision. Ranjan Duara noted that in 1984, when the current criteria were developed, little was known about the relationship between pathology and cognitive decline but that much more is understood at this point. Duara suggested that the 2007 MCI Symposium might be a good forum for further discussion of whether revision of the diagnostic criteria for MCI is warranted.

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