

University of Vermont Update in Dementia and Neuropsychiatry

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The University of Vermont, College of Medicine (VT, USA) hosted a 3-day conference for neurologists, psychiatrists, geriatricians and primary care practitioners in September 2006. The meeting, held on the lakefront in Burlington Vermont, featured national and local faculty and attendees from 14 different states. The goal of the conference was to provide a broad overview of basic science and clinical practice relevant to the care of patients with dementia. For this report, I've chosen to summarize eight of the 13 presentations, selecting those topics less commonly covered.

Normal cognitive aging & mild cognitive impairment

Julie Dumas, PhD (Assistant Professor of Psychiatry and Investigator in Clinical Neuroscience Research Unit, University of Vermont, Burlington, VT, USA).

Dumas reviewed current models of memory encoding and storage. Information comes in through sensory systems into short-term storage then long-term storage. Long-term memory consists of implicit, nondeclarative memory, such as learned skills, and sensory images, such as sights and smells. Implicit, nondeclarative memory is generally unconscious and relies on cortical association areas that are little affected by normal aging. In contrast, explicit, declarative memory is comprised of semantic and episodic experiences that must be actively recalled into consciousness. Explicit, declarative memory relies on the medial temporal lobe and hippocampus and is very sensitive to age effects.

Declarative memory is further subdivided into semantic and episodic memory. Semantic memory (general knowledge) suffers little change with aging. Some forms, such as vocabulary, actually improve with age. Episodic memory (event memory or one-time exposure), on the other hand, is very sensitive to aging. Free recall is affected more than cued recall and cued recall more than recognition, implying that encoding is more affected by age than retrieval, although both are affected. The efficiency of encoding and speed of retrieval show the most age effect. Subtle declines in attention and concentration are thought to account for some of the age-related decline in episodic memory.

Episodic memory is especially sensitive to pathological aging, such as Alzheimer's disease (AD). Impairments in episodic memory are generally used to define the amnesic form of 'mild cognitive impairment' (MCI), considered a precursor to AD. Functional imaging studies indicate that older adults with MCI utilize a larger brain area to achieve similar performance as healthy older adults. These compensatory abilities fail as the condition progresses to dementia phase. Dumas and others have shown that anticholinergic drugs can create similar impairment in healthy older adults, suggesting cholinergic system dysfunction accounts for some of the memory problem in MCI patients.

Clinical neurobiology of cognitive aging & Alzheimer's disease: focus on the cholinergic system

Paul Newhouse, MD (Professor of Psychiatry and Director, Clinical

Neuroscience Research Unit, University of Vermont).

Newhouse noted that the cholinergic system's two divisions, muscarinic and nicotinic, each have a high degree of anatomic and functional specificity. Both muscarinic and nicotinic systems contain several acetylcholine receptor subtypes modulating different functions and subject to specific pharmacological probes. Nicotinic receptor systems operating through ascending cholinergic projections from the basal forebrain to prefrontal cortex appear to be critical in both sustained and divided attention tasks.

These are the very same tasks that are so sensitive to age effects and are implicated as key targets in the pharmacological treatment of AD. In fact, a reduced number of cholinergic neurons was one of the first neurochemical signatures of AD to be identified and cholinergic therapies remain the mainstay of treatment. Healthy older control subjects show densities of nicotinic receptors that are intermediate between those of young adults and the very low levels seen in age-matched AD subjects. It is probable that age-related declines in these nicotinic receptors may account for the intermediate performance level in sustained and divided attention tasks seen in healthy, older adults. There is evidence that estradiol can improve this cholinergic function in postmenopausal women.

Neuropathology of frontotemporal dementia

William Pendlebury, MD (Professor of Pathology and Neurology, University of Vermont).

In contrast to AD, frontotemporal dementia (FTD) is not a distinct diagnosis but a group of diseases that preferentially affect anterior brain regions (frontal and temporal lobes). FTD includes Pick's disease, primary progressive aphasia, semantic dementia, progressive supranuclear palsy, corticobasal degeneration, FTD with parkinsonism linked to chromosome 17, FTD with motor

neuron disease and several others. These diseases tend to start in middle, rather than old age and cause greater impairment in thinking, behavior and language than in memory. Motor findings, such as parkinsonism and paratonic rigidity, are more common than in AD. The primary pathological finding is hyperphosphorylated tau protein within intracellular filamentous clusters. The normal tau protein is part of the microtubular structural and transport system of neurons. The abnormally phosphorylated tau deposits are associated with neuronal structural collapse and cell death. The tau deposits are also observed in AD, but owing to their prominence in FTD, these conditions are classified pathologically as 'tauopathies'. However, it has recently become evident that many patients with FTD have severe lobar atrophy without the prominent tau pathology. The precise nature of these degenerative conditions remains unknown

Vascular dementia

Lisa Silbert, MD (Assistant Professor of Neurology, Oregon Health and Science University, Portland, OR, USA).

Vascular dementia (VaD) is the second most common cause of old-age dementia, responsible for 20% of cases and in many more cases there is comorbidity with AD. The prevalence varies with sex and culture, being more prevalent in men, Japan, China and Russia. Various subtypes are diagnosed: cortical VaD (multi-infarct dementia), subcortical small-vessel dementia, strategic infarct dementia, hypoperfusion dementia, hemorrhagic dementia, hereditary VaD and AD with cerebrovascular disease (mixed dementia).

Cortical or multi-infarct VaD generally produces the classic 'step-wise' decline, in which new strokes are associated with abrupt changes in cognition and function. Executive function (attention, processing speed, verbal fluency, reasoning, initiative and motivation) are more affected than memory, although the exact nature of the cognitive deficits depends on the location and size of the infarcts. Subcortical small-vessel disease results from multiple lacunar infarcts and

periventricular leucoencephalopathy. Executive dysfunction and slowed cognition are hallmark features. A classic type of periventricular small-vessel VaD is Binswanger's disease, diagnosed by the characteristic pattern of severe periventricular white matter disease on magnetic resonance imaging and clinical symptoms of executive dysfunction, gait disorder, urinary incontinence, bradykinesia and depression.

Strategic infarct VaD results from a single, large lesion in a location in which damage inflicts impaired memory and thinking for example occipital-temporal and thalamic infarcts. Hereditary forms of VaD are caused by underlying cerebral angiopathy and other vascular lesions in arterioles and capillaries.

Clinical trials provide evidence supporting symptomatic treatment with cholinesterase inhibitors and memantine, whereas cohort studies suggest antiplatelet agents and the control of vascular risk factors, including hypertension, diabetes, hyperlipidemia, elevated homocysteine and smoking, can slow progression by reducing the risk of a new stroke.

Driving & dementia

Brian Ott, MD (Professor of Clinical Neurosciences, Brown University Medical School and Director, Alzheimer's Disease and Memory Disorders Center, Rhode Island Hospital, Providence, RI, USA).

Aging brings changes in vision, cognition and neuromuscular function that contribute to motor vehicle accident (MVA) rates that are 10-times those of middle-aged adults and comparable with those of teenagers. MVA fatality rates for older drivers are much higher than either young adults or teenagers. Older adults with dementia pose the highest risk for accidents, with a 2.5–5-fold increase in MVA versus the already high rate of age-matched controls.

Clinical consensus guidelines are unanimous in stating that patients with moderate-to-severe dementia should not be allowed to drive. The American Academy of Neurology Practice Parameters (2000) state that even patients with mild dementia (Clinical Dementia Rating = 1) should not drive.

However, many patients with mild dementia may be safe drivers and there is good evidence that clinicians are not good at predicting performance on a standardized road test. However, it is unclear whether a road test is a valid 'gold standard' and no validated method of prospective risk assessment exists.

At Brown University, the predictive value of standardized road tests and neuropsychological batteries assessing working memory, visual scanning, attention to detail and selective attention are being studied. Computerized driving simulators are also proving valuable. Simple computerized maze-navigation performance tests may also provide a fast method of risk assessment in the future. Studies of fear and tension before and after road tests may add to our ability to identify at-risk drivers. Unsafe AD drivers have higher anxiety levels than safe drivers.

These studies indicate that patients with mild dementia may be able to drive safely for at least 1 year, but need close monitoring and planning for gradual termination of driving privileges.

Apathy: the hidden syndrome

William Reichman, MD (Professor of Psychiatry and Neurology, Senior Associate Dean for Clinical Affairs, University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School, New Brunswick, NJ, USA).

Apathy is a prominent feature of AD. An early development in many patients, apathy may precede diagnosis and grows more severe as AD progresses. Apathy is disabling, affecting grooming and hygiene, work and household tasks. Apathy affects relationships, causing loss of interest in activities, sexuality, ability to experience and express feelings and lost interest and concern for others.

While apathy can be a symptom of depression, producing an overlap in the symptomatology of depression and dementia, apathy in dementia produces a vacancy that is distinct from the dysphoric hopelessness of depression.

Neuropsychological studies of AD indicate that apathy is strongly associated with impaired executive and expressive language skills. Functional imaging and

histopathological studies suggest that apathy relates to dysfunction in the anterior cingulate-subcortical circuits, involving the nucleus accumbens, globus pallidus and thalamus. Hypometabolism of the mesial and orbitofrontal cortex has also been reported on both single photon emission computed tomography and positron emission tomography.

No large, placebo-controlled clinical trial with apathy as a primary outcome has been reported in AD patients. Studies of cholinergic therapies with behavioral symptoms as secondary outcomes indicate that these drugs may reduce apathy, among other symptoms. Small, open-label studies with psychostimulants suggest some benefit. Psychosocial interventions, including music therapy and activity therapy, have shown modest benefit in controlled trials.

Omega-3 fatty acids for mood & memory

Lynne Shinto, ND, MPH (Assistant Professor of Neurology, Oregon Health and Science University).

Derived from α -linolenic acid, the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are critical for healthy brain function. Plant oils are a good source of α -linolenic acid, but contain little or no EPA or DHA. By contrast, fish contains no α -linolenic acid but high amounts of EPA and DHA. Salmon and white tuna are excellent sources.

There is evidence that EPA is anti-inflammatory, whereas DHA has neurotropic properties necessary for brain development and function. Both cohort

and double-blind placebo-controlled studies have demonstrated a relationship to mood disorders. Several cohort studies have shown a correlation between increased consumption of fish and lower levels of depression. Out of six small, controlled intervention trials of adjunctive EPA, EPA plus DHA, or DHA as monotherapy, five have shown a significant reduction in depression-rating scores relative to placebo. Depression is associated with increased inflammatory markers and omega-3 free fatty acids can decrease inflammatory cytokines *in vitro*, but we do not yet know whether treatment with EPA or DHA reduces these markers in humans. Several National Institute of Health-funded studies are currently underway in the USA to study omega-3 supplementation as adjunctive or monotherapy in several subtypes of depression.

Three epidemiological studies found a 60–70% reduction in AD from eating fish once or more a week. DHA has been found to reduce oxidative damage and β -amyloid production in a transgenic mouse model for AD. A small pilot study of DHA administered at a dose of 0.72 g/day for 1 year found a significant increase in cognitive measures relative to placebo. Larger prospective studies are needed to define the dose, safety and efficacy of omega-3 fatty acids in both mood and cognitive disorders of aging.

Dementia in depression: cause or effect?

Clifford Singer, MD (Associate Professor of Psychiatry, University of Vermont).

Of patients with MCI, 26% suffer from major depression and up to 60% of

patients with AD will be depressed during the course of their illness. The prevalence of depression is even higher in non-AD dementia.

Depression increases the risk of all-cause dementia by 2–13-fold over 1–21 years follow-up. The risk for AD itself is at least doubled by a history of depression.

The relationship between depression and dementia is complicated by the fact that the memory is impaired in non-demented, younger patients with histories of recurrent depression. Late-life onset depression is associated with more executive dysfunction than memory impairment. Decreased speed of mental processing is especially prominent. Late-onset depression with cognitive impairment is associated with greater cerebrovascular disease than age-matched patients with early-onset depression. Both early and late-onset depression are associated with hippocampal atrophy, but only late-onset is strongly correlated with subcortical microvascular disease and vascular risk factors. Both may increase the risk of AD, but late onset appears to increase risk of non-AD dementia as well.

Cognitive impairment predicts a poor outcome for both mood and cognition. Future work will help to determine whether or not more effective prevention of depression will also reduce the risk of developing AD.

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