Editorial

Memories Are Made of This: Recent Advances in Understanding Cognitive Impairments and Dementia

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“... during the paroxysms of fever, patients are delirious and talk nonsense (desipere et loqui ali-ena). But insanity is really when a continuous dementia begins, when the patient, although up until then in his senses ... (continua dementia ess accepit).”

Celsius, 1st Century AD

C OGNITIVE impairment becomes more common with advancing age. In a study of over 1000 physicians, there was an 18% decline in the total cognitive score between 40 to 70 years of age (1). However, variability within the group was 60% greater in the 70-year-olds compared to the 40-year-olds. Areas in which age-related declines are often more prominent are learning of new information with practice and the speed of motor performance. Cognitive decline represents a major factor involved in the pathogenesis of age-related frailty (2–6) and functional decline (7–12). Intellectual disability is associated negatively with life expectancy (13,14).

When a person has had a decline in cognitive dysfunction they become more vulnerable to the development of delirium when they develop physical illnesses. Persons with delirium often present with new-onset falls (15–17), and thus new-onset falls should be considered a delirium equivalent. Delirium is poorly recognized by health care professionals (18) and often has more than one cause (19–21), and, as such, requires the health care physician to carefully evaluate the patient with delirium for multiple etiological factors. Persons with delirium often have an elevated circulating level of anticholinergic activity (22). As acetylcholine is an important neurotransmitter involved in the genesis of learning and recall, this suggests that inhibition of acetylcholinergic pathways may be an important end pathway in the pathogenesis of delirium. Many drugs that are not classically considered to be anticholinergic, such as digoxin, theophylline, and amantidine, are highly anticholinergic in in vitro assays (23). This explains why polypharmacy, which remains a major problem in older persons (24,25), is such a potent cause of delirium. Infection produces its cognitive impairment predominantly by the release of cytokines. Cytokines produce cognitive impairment by inhibiting acetylcholine function in the central nervous system, both by directly crossing the blood–brain barrier and by stimulating ascending autonomic nervous system fibers (26,27). The major causes of delirium along with the causes of reversible dementia are listed in Table 1. Recent studies have suggested that an interdisciplinary team focused on delirium (28) or a delirium intensive care unit (29) can greatly improve the outcomes of patients with delirium.

Over the last decade, the understanding that a number of persons have mild cognitive impairment (MCI) has become well established (30). These individuals have complaints and objective evidence of memory problems without deficits in activities of daily living. While classically these persons are not supposed to have depression, recent studies have suggested that neuropsychiatric complaints are not rare in MCI (31). Thus, treatment of depression is a key component of the management of MCI and early dementia (32). Patterns location association learning is a test that appears to be particularly sensitive to diagnosing MCI (33). Mild cognitive impairment is not benign, with death occurring in approximately one third of patients and another third progressing to dementia of the Alzheimer’s type within 5 years of diagnosis (34). Persons with MCI who have a major event such as a hip fracture, myocardial infarction, or coronary artery bypass surgery tend to have poorer functional recovery than persons with normal age-related cognitive impairment. Figure 1 provides the Saint Louis University Mental Status (SLUMS) examination developed to help recognize MCI.

A number of attempts have been made to increase the diagnostic accuracy of persons with MCI who are going to progress to Alzheimer’s disease (AD). Utilizing neuroimaging, persons with MCI who have smaller hippocampal volumes (35) or decreased blood flow to the posterior cingulated gyrus (36) are more likely to progress to AD. Persons with an increase in tau protein and a decrease in beta-amyloid [1–42] in the cerebrospinal fluid (CSF) have an increased likelihood of developing AD (37). The recent demonstration that tau levels in oral epithelium are reflective of CSF tau levels may provide an easy noninvasive method to detect those at risk for AD (38).

Treatment trials of MCI with acetylcholinesterase inhibitors are underway. Despite the generally negative associations of estrogen use with the development of AD, nevertheless biochemical and animal studies suggest a
possible use of estrogen in slowing the progression of MCI (39–45). The gradual decline of testosterone in males with aging has been associated with cognitive decline (46–53). Testosterone replacement has resulted in improvement of age-related memory dysfunction in some (54–56), but not all, studies (57,58). Testosterone improved memory in the SAMP8 mouse, an animal model of cognitive decline associated with overproduction of beta-amyloid protein (59). Other hormones such as pregnenolone and dehydroepiandrosterone (DHEA) have produced dramatic improvement of memory in animals, but minimal effects in humans (60,61).

Alzheimer’s Disease

The first descriptions of a disease similar to AD were published in the 18th century. However, it wasn’t until Alois Alzheimer described the association of cognitive impairment with amyloid plaques in relatively young persons in 1907 that the disease became firmly established (62). These findings suggested that it was the amyloid plaque that was responsible for the disease and generated the amyloidocentric theories of AD. Modern thought processes have moved away from the concept that soluble oligomeric forms of beta-amyloid are neurotoxic to the concept that soluble oligomeric forms of beta-amyloid produce memory disturbance (63–65), and in complex with alpha-secretase or by themselves, generate free radicals and are neurotoxic (66).

Three genes have been associated with early-onset AD. These are amyloid precursor protein (APP) on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1. The mutations on presenilin 1 are the most common cause of familial AD. Presenilin mutations lead to altered processing of APP by activating gamma-secretase, resulting in a disproportionate production of beta-amyloid [1–42]. APP is a type 1 transmembrane glycoprotein that has a small cytoplasmic tail, a transmembrane portion, and a large extracellular region. Mutations that produce AD either reduce alpha-secretase activity or increase gamma-secretase activity, resulting in increased production of beta-amyloid [1–42] (67,68).

Apolipoprotein E is a lipid transport protein whose gene is located on chromosome 19. The E4 allele of apolipoprotein E increases the risk of late-onset AD and the E2 allele decreases the risk (69,70). The E4 allele is also associated with an increase in cardiovascular disease. Apolipoprotein E complexes with beta-amyloid, reducing its transport out of the brain and resulting in formation of insoluble plaques, neuroinflammation, and possibly phosphorylation of tau protein (66,71).

Aside from amyloid plaques, the pathological diagnosis of AD requires the presence of neurofibrillary tangles. In AD, these are produced by hyperphosphorylation of tau protein possibly secondary to overproduction of beta-amyloid. However, tauopathies with neurofibrillary tangles can be seen in other neurodegenerative disorders such as frontotemporal dementia with Parkinsonism linked to chromosome 17 (Pick’s disease). It is characterized by personality changes, altered executive function, personality changes, bradykinesia, and rigidity (72).

There is increasing evidence that decreased clearance of beta-amyloid from the central nervous system plays an important role in the pathogenesis of AD (73). Thus, it is not surprising that genetic mutation of the genes for \( \alpha_2 \)-macroglobulins and lipoprotein-related protein, which are involved in clearance of proteins from the brain, have been associated with AD. At present, studies are ongoing examining the effectiveness of low-flow CSF drainage for the treatment of AD (74).

Animal Models of AD

Mouse models that either spontaneously overproduce beta-amyloid (SAMP8) or are transgenics that overproduce human beta-amyloid have allowed major advances in our understanding of the pathophysiology of AD. The 3 transgenic mice are the “Games mouse” (75), the “Hsiao mice” (76), and the “Novartis mouse” (77). Each of these transgenic models produced beta-amyloid plaques and neuritic changes. They do not develop tau-positive neurofibrillary tangles. Memory impairment occurred at 9 to 10 months. When mice that overexpress human amyloid precursor protein are mated with mice lacking apolipoprotein E, there is a marked decrease in beta-amyloid deposits (78).

The SAMP8 is a mouse model that spontaneously overproduces beta-amyloid (79–83). The SAMP8 mouse develops memory and learning deficits at 8 to 10 months of age. Beta-amyloid plaques develop late at 15 to 16 months. The memory deficits can be reversed by administration of antibodies to beta-amyloid (84) or by an antisense to the mRNA for amyloid precursor protein that reduces beta-amyloid production (85,86). SAMP8s show abnormalities in acetylcholine function and other neurotransmitters including glutamate, gamma aminobutyric acid, and serotonin (87). SAMP8s also have an increase in oxidative stress (88).

The data from animal models strongly support the concept that overproduction of beta-amyloid is key to the pathogenesis of AD. These models suggest that plaque formation occurs late and may be an epiphenomenon.

Nutrition and Dementia

Protein energy malnutrition is common in older persons and is associated with cognitive decline (89–91). Equally, persons with cognitive impairment are at high risk for
Mental Status (SLUMS) Examination

Name ______________________________ Age ______________
Is patient alert? ______________ Level of education ___________________

1. What day of the week is it?
2. What is the year?
3. What state are we in?
4. Please remember these five objects. I will ask you what they are later.
   Apple  Pen  Tie  House  Car
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
   How much did you spend?
   How much do you have left?
6. Please name as many animals as you can in one minute.
   0-5 animals  1  5-10 animals  2  10-15 animals  3  15+ animals
7. What were the 5 objects I asked you to remember? I point for each one correct.
8. I am going to give you a series of numbers and I would like you to give them to me backwards.
   For example, if I say 42, you would say 24.
   87  1  649  1  8537
9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o’clock.
   Hour markers okay
   Time correct
10. Please place an X in the triangle.

Which of the above figures is largest?

11. I am going to tell you a story. Please listen carefully because afterwards, I’m going to ask you some questions about it.
   Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.
   What was the female’s name?
   When did she go back to work?
   What work did she do?
   What state did she live in?

Scoring

<table>
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<th>High School Education</th>
<th>Normal</th>
<th>Less than High School Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-30</td>
<td></td>
<td>20-30</td>
</tr>
<tr>
<td>20-27</td>
<td>MCI</td>
<td>14-19</td>
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<tr>
<td>1-19</td>
<td>Dementia</td>
<td>1-14</td>
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Figure 1. Rapid screening test for cognitive impairment.
decreasing food intake and weight loss (92–94). Thus, paying special attention to the nutritional needs of older individuals with dementia, such as recognizing the shifts in circadian rhythm of eating patterns (95,96), paying attention to alterations in taste and smell (97,98) [patients with AD develop anosmia (99)], and providing adequate amounts of time to allow them to feed adequately (100), are all key to maintaining cognitive function.

The reasons for cognitive decline associated with malnutrition are multifactorial and include not only vitamin and mineral deficiencies, but also the fact that food releases gastrointestinal hormones that enhance memory (101,102). Thus, cholecystokinin, a gut hormone, is a potent enhancer of memory that produces its effects by activating ascending vagal fibers that, through a number of relays, modulate the ability to recall memories in the amygdala and hippocampus (103–105).

Elevated homocysteine levels are associated with AD. There are a number of causes of elevated homocysteine levels, including vitamin B₁₂ and B₆ deficiency, folate deficiency, renal failure, hypothyroidism, estrogen deficiency, and congenital causes (106). Vitamin B₁₂ replacement in persons with mild cobalamin deficiency improved verbal fluency and electrographic signs of cerebral function (107). These improvements were associated with a decline in homocysteine.

It is now recognized that lipid content of neuronal membranes plays a key role in the function of neurotransmitters. The SAMP8 mouse has a decrease in Δ⁹ desaturase activity, leading to an increase in brain saturated fatty acids compared to unsaturated fatty acids (108). A diet rich in polyunsaturated fatty acids enhances memory function in the SAMP8 mouse (109). Caloric restriction has been demonstrated in rodents to have a number of beneficial metabolic effects that extend life (110–113). In addition, caloric restriction enhances membrane fluidity (114), and this is associated with improved acquisition and memory (115).

Recent studies have demonstrated that treatment with 3-hydroxy-3-methylgluarcyloenzyme A reductase inhibitors (statins) are associated with a lower prevalence of cognitive impairment (116). Whether these effects are due to enhanced membrane fluidity or secondary to a reduction in vascular disease remains to be determined (117,118). Apolipoprotein E is a cholesterol-lowering protein, and this provides a link between cholesterol lowering and AD.

Persons with diabetes mellitus have cognitive and functional impairment (119–121). While in many cases this is due to vascular disease, it has also been demonstrated both in animals (122) and humans (123,124) that elevated glucose levels per se can cause a decline in cognitive function.

Finally, much data has accumulated to implicate oxidative stress and free radical damage in the progression of dementia (72). Vitamin E slows progression of dementia (125). Alpha-lipoic acid is a particularly potent free radical scavenger that may prove of use in delaying progression of AD.

Management of AD

The majority of persons with dementia will have AD, with lesser numbers having reversible dementias (Table 1) and vascular dementia. It is likely that dementia of the frontal lobe type and Lewy-body dementia are underdiagnosed. Figure 2 gives a simple approach to the diagnosis of dementias. Persons with frontal lobe dementia, besides having more behavioral problems, perform worse on letter and category fluency and better on memory and clock drawing tests than do patients with AD. A number of tests to help confirm the diagnosis of AD show promise. These include hippocampal volume, elevated levels of tau in the CSF and lips, measurement of ALZAS (Alzheimer Associated Protein), imaging of beta-amyloid plaques, and PET (positron emission tomography) scan measurement of frontal lobe metabolic activity (38,126–129). Chan (130) has suggested that dementia could be recognized earlier if the rate of decline in cognitive function is taken into account.

Most of the drugs presently used to treat AD were developed in response to the cholinergic hypothesis as outlined in the article by Grossberg and Desai in this issue of the Journal (131). These drugs produce small improvements in cognition (somewhat less of an improvement than the gain seen when earwax is removed from a demented person), delay the progression of the disease, and possibly decrease behavior disturbances: It is important to recognize that although not tested with similar batteries, studies have consistently reported that ergot alkaloids such as nicergoline and hydergine appear to be equally effective in the treatment of dementia (132–136).
Memantine is a drug approved in Europe for the treatment of AD (137). This drug works by modulating the glutamate/n-methyl-D-aspartate system. Preliminary results suggest that it may function as well or slightly better than the acetylcholinesterase inhibitors. Trials of a vaccine against AD produced brain inflammation (138,139). A pilot study utilizing vagal nerve stimulation has reported a positive effect in persons with AD (140).

Many older persons utilize complementary medicines (141–145). One of these is ginkgo biloba, which appears to have positive effects according to an article in the Journal by Andrieu and colleagues (146). Wittstein, in a meta-analysis, concluded that ginkgo special extract is equivalent to donepezil and rivastigmine (147). Other studies have found efficacy for ginkgo (148).

As has been chronicled in the pages of the Journal, appropriate therapy for dementia includes not only treatment aimed at the dementia but also treatment of medical comorbid conditions (149), appropriate nutritional and exercise support (150–152), care of pain management (153,154), caregivers (155–157), and appropriate end-of-life care (155). Thus, hip fracture is classically associated with functional decline (158,159). However, a recent study showed that intensive therapy in hip fracture patients with dementia can result in a high proportion returning to the community (160). Finally, it is important to recognize that antipsychotic agents only have small effects on behavioral disturbances in demented individuals, and in many individuals have no effect at all on behavior (161–163). The appropriate first line of management of behavioral abnormalities is education of the caregivers and behavioral management. Programs such as the Eden Alternative and pet therapy can be far more effective in modifying behavior than antipsychotics (164–166).

REFERENCES


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