INTRODUCTION

What characterizes a comprehensive approach to dementia? Gary J. Kennedy, MD, opened the symposium with a discussion of the six elements which make the clinical approach to dementia comprehensive. First is early and accurate diagnosis, which directs the choice of interventions to forestall the disability associated with cognitive decline as well as efforts to optimize treatment of conditions such as diabetes, hypertension, or cardiac arrhythmias which might accelerate the progress of dementia. Recognition of the disease prior to the onset of impaired capacity allows the person and family the full range of considerations for immediate and long-term care planning. Second is collaboration with the family caregivers both to reduce their burden as well as the patient’s morbidity. Indeed, cognitive-behavioral family interventions for Alzheimer’s disease reduce the costs of care. As such, they should be considered the cornerstone of dementia care despite the lack of availability and little or no insurance coverage for the intervention.

Third is the pharmacologic palliation of impaired cognition. Depending on preferences of the patient, family, and practitioner, pharmacotherapy can be cautious to minimize risk or aggressive to maximize the benefit. A very cautious approach might focus exclusively on behavioral, environmental, and caregiver issues and forgo any risk associated with dementia medications. Alternatively, a single trial of a cholinesterase inhibitor might be considered in addition to the nonpharmacologic approach with the understanding that the trial would be brief, lasting only long enough to demonstrate benefits at which time a decision to continue would be addressed. If benefits were not apparent or if an adverse reaction occurred, the trial would be terminated and no further trials proposed. A more aggressive approach might include successive trials of cholinesterase inhibitors until one is found to be both tolerable and beneficial. The addition of memantine to the cholinesterase inhibitor would then be proposed.

Fourth is the treatment of psychological and behavioral symptoms of dementia to reduce the caregiver’s burden and the patient’s disability. Syndromes of depression and psychosis are common among people with dementia. Most distressing to the caregivers are agitation, aggression, and sleep disturbances. In each case, interventions to bring the environment and caregiver into a better equilibrium with the patient’s needs should precede pharmacotherapy. The goal of reducing the distressing behavior to manageable levels is more realistic than outright elimination.
The fifth element is advance planning. This encompasses steps to preserve the person's safety past the time when cognitive capacities no longer support independent decisions, and to honor preferences for end-of-life care. Practitioners may be hesitant to address the topics early on in the course of care. However, patients and their families more often appreciate the foresight and opportunity to exercise control over future choices. Cardiopulmonary resuscitation, use of a respirator, dialysis, and feeding tubes are medical interventions that may extend the patient's life but not preserve cognition or independence. Social interventions such as appointment of a primary and secondary (backup) durable power of attorney for financial matters and medical decisions (healthcare proxy) set the stage for reasoned decisions which would otherwise be made in desperate circumstances. This includes deciding when the person should retire from driving or when the person should accept help at home or in an assisted living or nursing facility. Finally, advanced planning may also mean directives empowering the proxy to enroll the impaired person in research studies past the point when informed consent is possible.

The sixth element is access to advocacy groups such as the Alzheimer's Association, the Geriatric Mental Health Alliance, and the Geriatric Mental Health Foundation. Without the organized advocacy of healthcare consumers, policy to support the comprehensive approach and the training it will require will never emerge.

PRESENTATIONS

From Basic Science to Treatment

The effect of advocacy in accelerating research was evident in Davies's presentation, "From Basic Science to Treatment." The development of neurofibrillary tangles and the deposition of amyloid plaques in the brain are considered to be central to the cause of Alzheimer's disease. In the amyloid cascade hypothesis, the deposition of the protein β-amyloid leads to the formation of tangles, astrocytosis, glial cell reactivity, and neuronal death. However, amyloid is a naturally occurring component of the aging human brain. The secretase enzymes associated with amyloid processing are part of a broad family of proteins critical to health. Moreover, tangles more often are seen in regions separate from amyloid plaques. Tangles are the major pathologic finding associated with the non-Alzheimer's dementias and several developmental disorders. The tangles are rich in tau protein which stabilizes microtubular filaments within the axon. Tau also stabilizes mitotic spindles during cell division. In Alzheimer's disease, tau is abnormally phosphorylated, leading to conformational changes in the molecule and cell death. However, as with amyloid, tau is essential to neuronal health and there may be multiple enzymes responsible for the abnormal phosphorylation.

As an alternative to the amyloid cascade and tauopathy hypotheses of Alzheimer's disease, Davies pointed to the more basic mechanism of cell cycle reactivation. This cycle represents the division and replication of cells from conception to maturity to build the tissues of vital organs. Neural stem cells divide and migrate into the hippocampal region of the brain in adult life, but once mature they never again replicate. The cell cycle is permanently deactivated. Oncogenes cause cancer by reactivating the cell cycle to produce the unregulated growth of cancerous cell lines. In mice models, both tau and amyloid pathologies can be induced by activation of an oncogene. A variety of insults, including hypoxia due to stroke, also reactivate the cycle in the brain but without cell replication. Instead, hyperphosphorylated tau filaments accumulate into tangles and result in programmed cell death or apoptosis. This observation in rats may explain the overlap between Alzheimer's disease, stroke, and vascular dementia. This alternative hypothesis suggests that both amyloid and neurofibrillary tangles are merely tombstones indicating an as yet uncovered cause of dementia. An undetected agent, perhaps an oncogene, provokes the mature neuron into a failed attempt at mitosis leading to a proliferation of tau and death of the cell. Of note, neuronal apoptosis is required for the modeling of neuronal circuitry during brain development early in life. Davies did not argue that cell cycle reactivation answered the question of what causes Alzheimer's disease. Rather, he pointed out how findings from basic science are expanding avenues to treatment.
ated into the change point models, excessive variability within subjects was in itself predictive of subsequent dementia.

By implication, much of the normative data on age and cognitive performance is based on mixed samples of older people, some of whom were experiencing the accelerated decline of preclinical dementia but were assessed as normal. The result is an underestimation of normal cognition with advanced age and an overestimation of the performance variability on measures of cognition. Although the intensive annual assessments on which the change point modeling was based in the Einstein Aging Study exceed the capacities of most practitioners, the model is ideal for the assessment of biomarkers, genetic and neuroimaging risk factors, and the early detection of dementia.

Because the offspring of parents with exceptional longevity have a reduced risk of developing Alzheimer’s disease, they present an opportunity to study genetic biomarkers of both risk and protective factors. Genes associated with longevity would be expected to be more prevalent in parents with exceptional longevity than in their offspring. The same genes would be expected to be more prevalent in the children of parents with exceptional longevity than in offspring of parents with average longevity. For example, the VV polymorphism of the cholesterol esterification transport protein (CEPT) is associated with larger lipoprotein size and higher density lipoprotein cholesterol, which protects against heart disease. Centenarians with CEPT VV score significantly higher on the Mini-Mental Status Examination than those without. In the Einstein Aging Study, the risk of dementia was reduced by 25% among people with the VV compared to the II CETP genotype after controlling for age, education, and other illnesses. Efforts to devise CEPT-specific treatments are underway. This is only one example of how population-based clinical studies can promote the identification of risk prior to the onset of symptoms.

**Current and Future Therapy for the Dementias**

Doody’s presentation reviewed “Current and Future Therapy for the Dementias.” Reduction in cardiovascular risk factors remains the leading hypothesis for interventions to prevent Alzheimer’s disease. Exercise as well as control of body weight, blood sugar, cholesterol, and hypertension are all recommended for general health but it is not possible to know if the effects will prevent or only delay the onset of dementia. Even so, because dementia occurs near the end of life, delaying the onset by 5 years would nearly halve the prevalence of the disease over the next 40 years. Current therapies for dementia include cholinesterase inhibitors (donepezil, rivastigmine, galantamine), an N-methyl-d-aspartate receptor agonist (memantine), and possibly high-dose vitamin C 1,000 mg and vitamin E 1,000 IU. The majority of potentially therapeutic agents presently under investigation modulate either neurotransmitters or amyloid. These are followed by drugs or nutraceuticals thought to be promising based on epidemiologic studies. Next in frequency are putative neuroprotective agents and those that modify the activity of tau or glial cells.

Citing specific studies and prior presentations, Doody noted that the cholesterol-lowering drugs simvastatin and atorvastatin had failed to slow the progression of Alzheimer’s disease. Neurotransmitter modulators included those that affect cholinergic (muscarinic, nicotinic) transmission, monoamine oxidase activity (dopamine, norepinephrine), the function of γ-aminobutyric acid, glutamate, and glycine, as well as agonists and antagonists of serotonin receptors. Of these, only the agents modulating serotonin receptors have shown promise to date. Of the neuroprotective agents, data from phase III published trials are limited to the dimebon. The results were positive and similar to those seen with cholinesterase inhibitors, but await confirmation from a second study presently underway. Because dimebon is an antihistamine, it may be compatible with the cholinesterase inhibitors and memantine. Of the amyloid-modifying agents, neither tarenflurbil nor tramiprosate were associated with positive results at the end of phase III trials. Immunotherapies, while promising in animal models, have proven problematic in humans. Phase II results with the anti-amyloid monoclonal antibody bupineuzumab are difficult to interpret. Active immunization against amyloid produced microencephalitis in a small number of subjects, terminating the study before efficacy could be determined. The one study of a tau modulator methylene blue also yielded promising but equivocal results. The multitude of intervention studies is cause for optimism, but results to date should temper the enthusiasm of the public and investigators alike. However, in Doody’s opinion, skepticism about the last- ing benefits of medications currently approved for treatment of Alzheimer’s disease is a major public health problem. Given the available science, “persistence of treatment is the most important factor” in the pharmacotherapy of Alzheimer’s disease.

**In the Brain Fitness Software: Consumer Guide to Separating Hope from Hype**

The presentation “In the Brain Fitness Software: Consumer Guide to Separating Hope from Hype” by Fernandez described a burgeoning commercial enterprise promising to preserve cognitive function into old age with mental exercise just as physical exercise can preserve physical fitness. Brain fitness is defined as the result of mental and physical exercise and nutrition that leads to a sense of control, productivity, and alertness, promoting the cognitive abilities required to function in society both at work and in the community. Brain fitness is more a condition
than a skill and is characterized more by attention, memory, emotional self-regulation, inhibition, and planning than intelligence or intelligence quotient. Sophisticated neuropsychological assessments can quantify the various components, but as yet there is no reliable brief test of brain fitness.

Self-regulation of emotion, vocabulary, and the capacity to move from problem solving to pattern recognition improve with advanced age. However, attention, processing speed, memory, mental imagery, and effortful problem solving do not. Vocabulary is an example of consolidated memory which has nearly infinite shelf space in the brain, hence the ever more common phenomenon of people fluent in more than one language. In contrast working memory, the capacity for multitasking, has limited volume and can be fatigued by excessive load. Working memory will support the acquisition of a second language by transferring grammar and vocabulary into consolidated memory, but the process is slowed by brain aging. Nonetheless measures of working memory can be improved with mental exercise. However, mental exercise differs from mental activity. Mental exercise is thought to promote neural plasticity through exposure to novelty, variety, and increasing levels of challenge.

With this background, Fernandez addressed the market of commercially available “Brain Fitness Software.” Although the science of brain fitness is progressing rapidly, the market is growing faster still. He suggests several questions to ask when considering a purchase. First, is the product developed by trained neuropsychologists? Second, are there peer-reviewed scientific publications supporting the product or components thereof? Third, is there a reputable scientific advisory board advising the producers and willing to weigh the risks and benefits to their reputations of being involved? Fourth and fifth, what are the specific benefits and what cognitive processes are targeted? Sixth, how many practice sessions and how many hours or weeks will be needed to demonstrate results? Seventh and eighth, do the exercises teach something new and are they progressively more challenging? Finally, will they meet the purchasers’ personal goals without excessive strain? Annual product assessments are available at the Website for Sharp Brains, a market research and educational publishing company focused on the applications of neuroscience and cognitive science. Fernandez is the co-founder and CEO of Sharp Brains, which neither produces nor sells brain fitness software.

In conclusion, Fernandez argues that the four common sense pillars of brain health are good nutrition, cardiovascular exercise, stress management, and mental exercise. In practice, this means exposure to new things, an array of stimuli, and efforts to improve performance during more familiar cognitive tasks sufficient to stimulate but not strain the mind.

Roles of the Impaired Patient, the Family and the Professional in Medical Decision-Making

Powell addressed the “Roles of the Impaired Patient, the Family and the Professional in Medical Decision-Making” using the metaphor of “voice.” Even though all clinicians need to assess their patients’ capacity to decide about proposed treatment, few receive training and many feel unprepared for the task. The assessment of capacity represents the most common problem in medical ethics and most common cause for conjoint psychiatric and ethics consultations in hospitals. According to the principle of autonomy, patients have a right to make decisions about their treatment. These decisions reflect personal values and preferences, and are coherent and consistent over time. However, when capacity is lacking, the patient becomes dependent on the beneficence of a surrogate decision maker, usually a family member. It then becomes the responsibility of the surrogate to determine which choice would better serve the patient’s interest and values.

Capacity is a clinically assessed skill that is elastic and decision specific. In contrast, competence is categoric, determined by a judge, and represents a more global determination of one’s ability to meet the demands of personal care and the management of property. There are several components to capacity. First, the patient needs to demonstrate an understanding of the problem and of the decisions necessary to address it. For example, a patient with unstable angina should be able to link the condition to the need to choose between medical management and surgery. Second, the patient needs to be able to weigh the risks and benefits of the various options available. Third, the patient with capacity is expected to appreciate the personal consequences (and, at times, consequences to others) of the selected course of action. Finally, the patient has to be able to express a choice and, in some cases, implement it. If any of these abilities are impaired, the patient might lack capacity. However, capacity is not a binary skill, which is simply present or absent; capacity occupies a continuum, and it varies with different decisions and at different times.

The therapeutic index of a medical decision is determined by the ratio of benefit and risk. The higher the risk the lower the therapeutic index and the higher the capacity level needed to make such a choice. Many physicians will accept consent to treat from a marginally capable patient when the choice exposes the patient to minor risk. However, a much higher level of capacity will be required of a patient refusing treatment with the result being a high risk of morbidity or mortality. It is imperative that physicians maximize the patients’ capacity to understand their medical circumstances and the treatment proposed. Yet, it is also imperative not to impose personal values. The patients need not reason as the professional would to be considered capable; reasoning which is consistent with a coherent value system is sufficient.
Even when cognitive impairment is obvious, its presence is not in itself sufficient to assume the patient is incapable of making any decision. The presence of insight related to diagnosis, prognosis, and symptoms is better correlated with decision making capacity than the Mini-Mental Status Examination score. Memory may be quite impaired yet adequate for the patient to remember the information long enough to make an informed decision. The presence of mental illness is also insufficient to declare a patient incapable unless symptoms of the illness interfere with the patient’s capacity. For example, unless psychotic guilt or suicidal rumination make the patient feel unworthy of care and deserving of punishment, the diagnosis of depression does not necessarily interfere with patients’ ability to make choices about life-saving treatments.

In contrast, patients that appear perfectly able to understand and reason may lack capacity to make a choice because of paralyzing anxiety, denial, or obsessive preoccupation with detail. Professionals need to involve families in the process of helping the patient to make a choice, and at times need to use their professional expertise and moral authority to help the patient decide. Such responsibility is easier to shoulder for more experienced physicians, especially in the context of a longer-term relationship with the patient.

A patient incapable of decision making because of cognitive impairment might maintain a strong desire to have a voice in the process. This need to be heard imposes another challenge on the process of capacity assessment. Even patients with no insight into the seriousness of their deficits and little understanding of the consequences of a decision might be unwilling to cooperate with any decision that would not take their expressed preferences into account. In such circumstances, it is both ethical and pragmatic for the clinicians to involve the family. Families can play multiple roles: they can repeat, validate, and reinforce the value of the information received from the professional. They can provide feedback about consequences that the patient might be unaware of. They can help the physician understand the patient’s decisional style, values, past choices, and preferences. Finally, they can participate in the design of a more creative plan that honors the patient’s voice and makes compliance possible. In summary, collaboration with families and the integration of the patient’s voice in the decision-making process can yield a plan of care that is both medically sound and realistically possible to implement.

CONCLUSION

Commercial interests and public support are leading to unprecedented advances in cognitive neuroscience. However, interventions to cure or prevent Alzheimer’s disease remain beyond the horizon. Nonetheless, research into the care of people with the illness and their families is bringing the ideal of a comprehensive approach closer to reality. If comprehensive care compresses the disability of dementia to the end of the natural life span, we will have conquered this illness without having to cure it.

The 14th Annual Symposium on the Comprehensive Approach to Dementia will be held on March 4, 2010 at the New York Academy of Medicine in New York City. For further information please call 718-920-6674. PP

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