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Subject Area - Health

Dementia

Introduction

Dementia is a clinical syndrome of loss or decline in memory and other cognitive abilities. It is caused by various diseases and conditions that result in damaged brain cells. To be classified as dementia, the syndrome must meet the following criteria: It must include decline in memory and in at least one of the following cognitive abilities:

- (1) Ability to generate coherent speech and understand spoken or written language;
- (2) Ability to recognize or identify objects, assuming intact sensory function;
- (3) Ability to execute motor activities, assuming intact motor abilities, sensory function, and comprehension of the required task
- (4) Ability to think abstractly, make sound judgments, and plan and carry out complex tasks.

The decline in cognitive abilities must be severe enough to interfere with daily life. Different types of dementia have been associated with distinct symptom patterns and distinguishing microscopic brain abnormalities. Increasing evidence from long-term epidemiological observation and autopsy studies suggests that many people have microscopic brain abnormalities associated with more than one type of dementia. The symptoms of different types of dementia also overlap and can be further complicated coexisting medical problems.

Alzheimer's disease is the most common cause of dementia. In Alzheimer's disease as in other types of dementia, increasing numbers of nerve cells deteriorate and die. A healthy adult brain has 100 billion nerve cells, or neurons, with long branching extensions connected at 100 trillion points. At these connections, called synapses, information flows in tiny chemical pulses released by one neuron and taken up by the receiving cell. Different strengths and patterns of signals move constantly through the brain's circuits, creating the cellular basis of memories, thoughts, and skills.

Dementia deprives the patient from the ability of valid perception of objects, of understanding their relationship, of comparing them, of keeping full memory of them, resulting in the impossibility of proper reasoning. (Esquirol) This can have devastating consequences for the patient and his family. It may lead to disastrous effects on the whole social tissue in ageing countries where the prevalence of dementia rapidly increases. The prevalence of dementia has been much debated. Following the Diagnostic and Statistic Manual of Mental Disorders of the American Psychiatric Association, it is characterized by multiple cognitive deficits severe enough to interfere with social or occupational activities. Impairment in short- and long-term memory is considered mandatory.

Prevalence of Alzheimer's disease

Alzheimer's disease is by far the most prevalent form of dementia in those aged 65 years and older (Small, Rabins, Barry,

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Buckholtz, DeKosky, Ferris, 1997). The prevalence of dementia increased dramatically with age: 0.8% in the group age 65 to 69 years and 28.5% at age 90 years and older. Incidence of dementia and Alzheimer's disease continues to increase with age up to age 85 years, after which rates increase in women but not in men (Kukull, Higdon, Bowen, McCormick, Teri, Shellenbert, 2002).

African Americans are more likely than whites to have Alzheimer's disease and dementia, but further analyses of this relationship indicate that it is primarily explained by factors other than race. Most analyses that have combined age, gender, years of education, African American versus white race, and other factors show that African Americans do not have a statistically significant increased risk of dementia or that their increased risk in comparison with whites is greatly reduced once these factors are taken into account (Plassman, Langa, Fisher, Heeringa, Weit, Ofstedal, 2007).

Incidence

Current estimates suggest that as many as 5 million people are affected with the disease in the U.S., a number that is expected to almost double by 2050 as the elderly population continues to grow (Brookmeyer, Gray, Kawas, 1998). However, because course and progression of Alzheimer's disease are often infrequent and slow, this will delay the onset or retarding pathologic deterioration has the potential to substantially reduce the incidence of the disease. It has been estimated that delaying the onset by 5 years could cut in half the incidence of Alzheimer's disease by 2047. This results in a major impact on public health among older adults. More women than men have Alzheimer's and other dementias, primarily because women live longer, on average, than men, and their longer life expectancy increases the time during which they could develop Alzheimer's or other dementias. The prevalence of Alzheimer's and other dementias also differs for people with fewer versus more years of education and for African Americans versus whites. The number of Americans with Alzheimer's and other dementias is increasing every year because of the steady growth in the older population (Callahan, Hall, Hui, Musick, Unverzagt, Hendrie, 1996).

Mortality Rates of Alzheimer's Disease

Alzheimer's disease is among the top 10 leading causes of death for people of all ages and is number 5 for those aged 65 and older. Alzheimer's disease was listed as the underlying cause of death for 71,696 Americans in 2005. It was the seventh leading cause of death for people of all ages and the fifth leading cause of death for people ages 65 and older (US Centers for Disease Control and Prevention, Sep. 2007). The total number of deaths attributed to Alzheimer's disease has increased over the last 15 years. In 1991, only 14,112 death certificates recorded Alzheimer's as the main cause (Hoyert, 1996). From 2000 to 2005, deaths attributed to Alzheimer's disease increased by 44.7%, whereas the number 1 cause of death, heart disease, decreased by 8.6%.

In cases where Alzheimer's is not listed as the cause of death, it might not even be listed as a contributing factor. But, people with Alzheimer's disease in all age groups generally have decreased survival when compared with survival in the general U.S. population. One 2004 study noted that people newly diagnosed with Alzheimer's survived about half as long as those of similar age who did not have the disease (Larson, Shadlen, Wang, McCormick, Bowen, Teri, 2004). Average survival time is 4 to 6 years after diagnosis of Alzheimer's, but survival can be as long as 20 years from the first symptoms. Another study reported that when persons with Alzheimer patients were hospitalized for pneumonia or hip fracture, more than half died within 6 months, compared with about 13% of cognitively intact patients, after receiving

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the same types of treatments (Morrison, Siu, 2000).

Trends for mortality

Women are more likely than men to have Alzheimer's disease and dementia. Fourteen percent of all people age 71 and older have dementia (Plassman, Langa, Fisher, Heeringa, Weit, Ofstedal, 2007). In 2004, age-adjusted death rates for Alzheimer's disease varied by ethnicity, with white women having the highest rates at 24.7 per 100,000 persons. Black women were next, with a death rate of 19.9 per 100,000. Hispanic persons had the lowest death rates, with male Hispanics rate being the lowest of all groups at 10.8 per 100,000 (US Centers for Disease Control and Prevention, 2007).

Quality of Life Issues from Alzheimer's Disease

Alzheimer's disease can affect different people in different ways, but the most common symptom pattern begins with gradually worsening difficulty in remembering new information. This is because disruption of brain cells usually begins in regions involved in forming new memories. As damage spreads, individuals also experience confusion, disorganized thinking, impaired judgment, trouble expressing themselves, and disorientation to time, space, and location, which might lead to unsafe wandering and socially inappropriate behavior. In advanced Alzheimer's, people will need help with bathing, dressing, using the bathroom, eating, and other daily activities. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones, and become bed-bound and reliant on 24/7 care. In the end, Alzheimer's disease is fatal.

Costs of Alzheimer's and other dementias

People with Alzheimer's disease and other dementias are high users of health care and long-term care services, and all people who have these conditions will eventually need end of life care unless they die suddenly of another cause. Almost all older people with Alzheimer's and other dementias have Medicare and their high use of hospital and other health care services translates into high costs for Medicare. Medicaid pays for nursing home and other long term care services for some people with very low income and assets. The direct costs to Medicare and Medicaid for care for people with Alzheimer's and other dementias amount to more than \$148 billion. This includes \$91 billion in Medicare costs for care of beneficiaries with Alzheimer's and other dementias in 2005; this figure is projected to increase to \$160 billion by 2010 and \$189 billion by 2015(Lewin Group, 2004).

In 2000, total Medicare costs per beneficiary for Medicare beneficiaries ages 65 and older with Alzheimer's and other dementias were three times higher, on average, than for other older Medicare beneficiaries which is \$13,207 versus \$4,454 per beneficiary. Average Medicare costs per beneficiary for hospital care for those age 65 and older with Alzheimer's and other dementias were 3.2 times higher, on average, than for other older Medicare beneficiaries; which is \$7,074 versus \$2,204 (Alzheimer's Association, 2003). Most people with Alzheimer's and other dementias have one or more serious medical condition. For example, 30% of Medicare beneficiary's age 65 and older with Alzheimer's and other dementias also have coronary heart disease, and 28% have congestive heart failure (Bynum, Rabins, Weller, Niefeld, Anderson, Wu, 2004).

Most people with dementia live at home, usually with help from family and friends. As the dementia progresses,

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caregivers provide more and more care, until they can no longer manage their care giving responsibilities on their own. Some families hire home care workers or place their loved ones in assisted living residences or nursing homes. People with dementia make up about one quarter of those receiving home care from governmental programs and half or more of residents in assisted living or nursing homes. Paying for these services for very long is not affordable for most people with dementia and their families, with home care costing \$152 for an 8-hour day and assisted living averaging \$3,000 a month. Nursing home care is even more expensive. Medicaid is the only federal program that will cover the long nursing home stays that most people with dementia require, but this program requires beneficiaries to be poor to receive coverage (Langa, Larson, Wallace, Fendrick, Foster, Kabeto, 2004).

Biological Mechanisms

In Alzheimer's disease as in other types of dementia, an increasing number of nerve cells will deteriorate and die. A healthy adult brain has 100 billion nerve cells, or neurons, with long branching extensions connected at 100 trillion points. At these connections, or synapses, information will flow in tiny chemical pulses released by one neuron and taken up by the receiving cell. Different strengths and patterns of signals move constantly through the brain's circuits, creating the cellular basis of memories, thoughts, and skills.

In Alzheimer's disease, information transfer at the synapses begins to fail, the number of synapses declines, and eventually cells die. In a brain with advanced Alzheimer's, there is dramatic shrinkage from cell loss and widespread debris from dead and dying neurons. Scientists do not yet fully understand the processes resulting in the catastrophic brain damage associated with Alzheimer's disease. According to a leading theory called the amyloid hypothesis, the prime suspect is a tiny protein fragment called beta-amyloid (Gauthier, Panisset, Nalbantoglu, Poirier, 1997). Trouble begins when unknown factors trigger the overproduction of beta-amyloid or reduce the brain's ability to dispose of it. The excess jams signaling at the synapses, blocking information flow and leading to a cascade of damaging events ending in cell death. Beta-amyloid fragments gradually accumulate into the microscopic plaques considered to be one pathologic hallmark of Alzheimer's. Another cause is tangles, formed when a different protein called tau twists into strands inside dead and dying neurons. Other abnormalities seen in Alzheimer's brain tissue include inflammation and oxidative damage due to highly reactive oxygen-containing products of cellular metabolism.

Neurofibrillary Tangles

Neurofibrillary tangles consist of aberrantly phosphorylated fibrillary proteins aggregated within the neuronal cytoplasm. Their presence signifies the failure of the neuron to properly maintain its cytoskeleton, which is required to support the extraordinarily complex branching shape of its numerous processes. A small number of neurofibrillary tangles are a universal consequence of aging. However, it is an increased number and the architectonic distribution of the tangles that promote the cardinal pathology and define the stages of the disease (Braak, Braak, 2006). The development of tangles is a major and possibly the main mechanism of neuronal death in Alzheimer's disease. (Gomez-Isla, Hollister, West, Mui, Growden, Peterson, 1997)

Aging and Alzheimer's disease

Aging is the major risk factor of Alzheimer's disease in the general population. Recent research has identified 2 potential

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mechanisms related to aging that may contribute to the development of the disease. One is the concept that free radicals (reactive oxygen species) produced during cellular respiration may play an important role in the process of aging and in the development of Alzheimer's disease (Smith, Sayre, Monnier, Perry, 1995). Sufficient evidence has accumulated that oxidative damage to proteins and membrane lipids and an up regulation of antioxidant enzymes is associated with Alzheimer's disease (Sayre, Zelasko, Harris, Perry, Salomon, Smith, 1997) (Smith, Richey, Sayre, Beckman, Perry, 2007). The toxic effects of amyloid are mediated, at least in part, through the generation of free radicals by the peptide. The recent demonstration of redox-active iron deposits associated with senile plaques and neurofibrillary tangles is relevant in this respect because iron can catalyze the formation of damaging free radicals.

Oxidative damage may be an important mechanism in aging has led to a large-scale clinical trial of vitamin E to treat patients with moderate to severe Alzheimer's disease (Sana, Ernesto, Thomas, Klauber, Schafer, Grundman, 1997). Although the results have demonstrated that a daily dosage of 2000 IU of vitamin E slowed the progression of the disease, there was no indication that vitamin E therapy was associated with symptomatic benefit or a reversal of disease effects. It is important to recognize that the redox balance in the brain is complex, and that additional measures will be required to provide more substantive treatment strategies aimed at the attenuation of these disease-related mechanisms.

Treatment of Alzheimer's Disease

There is no treatment currently available to delay or stop the deterioration of brain cells in Alzheimer's disease. The U.S. Food and Drug Administration has approved five drugs that temporarily slow worsening of symptoms for about 6 to 12 months, on average, for about half of the individuals who take them. On the basis of deepening insight into the underlying biology of Alzheimer's and emerging conceptual frameworks for understanding the disease, researchers have identified several new treatment strategies that might have the potential to change its course. A number of experimental therapies based on the amyloid hypothesis and other targets have reached various stages of clinical testing in human volunteers. Despite the current lack of disease modifying therapies, studies have consistently shown that active medical management of Alzheimer's and other dementias can significantly improve quality of life through all stages of the disease for diagnosed individuals and their caregivers. Active management includes appropriate use of available treatment options, effective integration of coexisting conditions into the treatment plan, and utilization of supportive services such as counseling, activity and support groups, and adult day programs.

Many scientists consider the emerging field of prevention one of the most exciting recent developments in the dementia research arena. A growing body of evidence suggests that the health of the brain, one of the body's most highly vascular organs, is closely linked to the overall health of the heart and blood vessels.

FDA Approved drugs for Alzheimer's Disease

The five drugs approved by the FDA for the treatment of Alzheimer's disease are Cognex (tacrine), Exelon (rivastigmine), Razadyne (galantamine), Aricept (donepezil), and Namenda (memantine). The FDA has approved all medications except Namenda for the treatment of mild to moderate Alzheimer's disease. Aricept was just recently approved for severe Alzheimer's disease. Exelon was approved on July 6, 2007, in the form of a transdermal patch. This reduces gastrointestinal side effects compared to the oral form of the medication. All of these drugs except Namenda act by increasing brain levels of acetylcholine, which is a neurotransmitter that is abnormally low in patients with Alzheimer's

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disease. Namenda is approved for the treatment of moderate to severe Alzheimer's disease only. It works differently than the other approved drugs. It interacts with a receptor that is thought to be involved in preventing the death of certain cells in the brains of patients with Alzheimer's disease Alzheimer's disease (von Eschenbach, 2007).

The Role of Physical Activity in Alzheimer's Disease

Recently there has been accumulating evidence that physical exercise offers health benefits for older people. Exercise has been suggested to enhance brain neurotrophic factors and modify apoptosis. Exercise may benefit dementia by preserving muscle mass, preventing falls, and consequent head trauma. Evidence that exercise can preserve optimal cardiovascular function, deter stroke and microvascular disease, and improve regional cerebral blood flow has been offered (Berchtold, Kesslak, Cotman, 2002).

There are very few controlled studies of the effect of exercise on affect or mood in cognitively impaired elders. Most studies have addressed depression, and only 1 study included participants with moderate or severe dementia.

In a randomized controlled trial by MacRae and associates, they studied exercise in mildly impaired elders. Ten weeks of lower extremity resistance exercise 3 days per week was compared with an activity of the subjects' choice (walking, games, discussion groups). Depression scores improved significantly for those in the exercise group. (MacRae, Asplund, Snelle, 1996)

Another study by Teri and associates compared 12 hours of exercise training (endurance, strength training, balance, and flexibility) over 12 weeks to routine medical care in community-dwelling persons with moderate Alzheimer's disease. When compared with usual care, exercise was more effective in reducing depression (Teri, McCurry, 2003).

Physical-activity effects on cognition during older adulthood

The study of exercise and cognition with older adults dates back several decades. Recently the exercise-cognition relation in older adults has been strengthened by the observation, in prospective epidemiological studies, that there are a number of lifestyle factors. This includes social interaction, diet and physical activity. These are associated with the maintenance of cognitive function and a reduction in risk for cognitive disorders, such as Alzheimer's disease.

A small but growing number of randomized intervention studies have examined whether fitness training has a positive effect on different aspects of perception and cognition in older adults. These studies will usually enroll healthy but sedentary adults between the ages of 60 and 85 years and ask them to participate in an exercise regime several times per week over the course of several months to several years. Cognition and fitness is assessed before and after the intervention. The main question is whether individuals who participate in an aerobic training regime show larger gains in cognition than wait-list control subjects or control subjects who participate in non-aerobic regimes, such as toning and stretching.

Although a number of intervention studies have found improvements in performance on cognitive tasks for aerobically trained but not control subjects, other studies have found equal performance improvements for both aerobic and control subjects across cognitive tests. Given that the number of randomized intervention trials that have examined fitness

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training effects on cognition is small. There are a number of factors that are responsible for a mixed pattern of results. Some of these factors include: the cognitive processes examined; the length, intensity and type of exercise program; the age range, health and education of participants; and the manner in which fitness improvements were measured. Several results have been obtained from these meta-analyses, which examined partially overlapping sets of studies. Most important was that in all of the studies; physical activity had a positive effect on cognition. Second, a significant relationship between physical activity training and improved cognition was kept for both normal adults and patients with early signs of Alzheimer's disease. It appears that physical activity can have a positive effect on a wide range of cognitive functions. Physical activity training appears to have both broad and specific cognitive effects. Broad in the sense that various different cognitive processes benefit from exercise participation, and specific in the sense that the effects on some cognitive processes, especially executive control processes (this includes scheduling, planning, working memory, multi-tasking and dealing with ambiguity. This is particularly interesting as executive control processes, and the brain regions that support them do show substantial age-related deterioration. The findings suggest that even processes that display substantial age-related change are amenable to intervention. Additionally, the relationship between physical activity training and cognition was also influenced by program duration, age, and gender.

Recommendations for Physical Activity

Another important issue relating to the public health message is what specific type of physical activity and what intensity, duration, and frequency of exercise should be recommended. The public health message on physical activity from the Center for Disease Control and Prevention and the American College of Sports Medicine recommends that all adults (including older adults) should exercise most, preferably all, days of the week for at least 30 minutes or more of moderate intensity. The recommendation that the physical activity should be 30 minutes or more is compatible with findings suggesting that bouts of exercise of 30 minutes or less have little impact on cognitive function. This research also reports that brief, 3-month exercise training programs can result in significant effects on cognitive performance, suggesting that positive gains can appear in a relatively short timeframe. This encouraging finding related to program duration should be built into the public health message. Observational studies have linked a variety of physical activities, or lack thereof, with clinical expression of dementia. Low levels of walking in men and limited leisure-time activity have been reported to increase risk for cognitive decline.

Position Stand

The position stand by the American College of Sports Medicine states that "By the year 2030, the number of individuals 65 yr and over will reach 70 million in the United States alone; persons 85 yr and older will be the fastest growing segment of the population. As more individuals live longer, it is imperative to determine the extent and mechanisms by which exercise and physical activity can improve health, functional capacity, quality of life, and independence in this population. Aging is a complex process involving many variables (e.g., genetics, lifestyle factors, chronic diseases) that interact with one another, greatly influencing the manner in which we age. Participation in regular physical activity (both aerobic and strength exercises) elicits a number of favorable responses that contribute to healthy aging." (ACSM, 1998)

Conclusion

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In conclusion, Alzheimer's disease is the most prevalent form of dementia in ages 65 and older. There is no exact cure for Alzheimer's disease. Although there are a multitude of unanswered questions regarding Alzheimer's disease, there is evidence of a relationship between fitness training and improvements in various aspects of cognition across a broad range of ages. Also, the findings suggest that physical activity is beneficial across the human lifespan. While the minds of children are continuing to develop and undergoing organization, the minds of adults are not. Physical activity during younger adulthood might encourage optimal cortical development, promoting lasting changes in brain structure and function. Despite the wealth of knowledge that has been obtained concerning the effects of exercise and physical activity on brain and cognition, there are a multitude of important questions that remain to be answered about Alzheimer's disease.

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