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What Does the Pediatrician Need to Know About Alzheimer Disease?

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Senescence describes the alterations in anatomy and physiology of the organism that begins with maturity and continue through later life. These age-related changes occur more slowly in mid-life, but then become more rapid in the later years of life. Accompanying senescence is the increased incidence and prevalence of neurodegenerative disorders. Recent work has emphasized the influence of early life events (including the prenatal, perinatal, and postnatal periods) on both senescence and age-related disorders. As populations around the world are experiencing rapid aging in both developing and developed countries, and because Alzheimer disease (AD) incidence and prevalence doubles every 5 years after the age of 65, it is projected that there will be a monumental increase in the number of AD cases worldwide in the next 50 years.¹ The Communicable Disease Center (CDC) has estimated that although death rates have declined in the United States for heart disease, breast cancer, prostate cancer, and stroke, AD death rates have increased 45% from 2000 to 2005. This is a global problem, as the 10/66 Research Group of the Alzheimer Disease International (www.alz.co.uk/1066) reports that more people with dementia live in developing as compared with developed countries (60% in 2001, rising to 71% by 2040).²

Although important genetic influences on the development of AD are well known, they do not account for all of the risk of developing the disease. Environmental exposures and lifestyle factors beginning in early life are also important. This commentary focuses on these developments to assist the pediatrician in helping patients and families adopt lifestyles that lead to successful aging.

Over 160 mutations on 3 genetic loci have been shown to be responsible for familial early onset autosomal dominant AD (with onset before age 65) (Chromosome 14, presenilin 1; Chromosome 1, presenilin 2; chromosome 21, β amyloid precursor protein [β APP]).³ However, these early onset forms are responsible for less than 1% to 2% of cases. The β APP gene on Chromosome 21 is cleaved by 3 enzymes known as α , β , and γ secretases to produce amyloidogenic ($A\beta$) or nonamyloidogenic breakdown products. The activity of these alternative pathways of β APP catabolism as well as the rate of β APP expression is controlled by genotype as well as environment. The most important genetic risk factor for sporadic AD is the apolipoprotein E ϵ 4 allele.³ However, apolipoprotein E ϵ 4 allele is not necessary or sufficient for AD, and ~50% of the inherited risk of getting the disease is currently unknown.

³ Apolipoprotein E is a lipid handling gene that is responsible for binding lipids in the blood

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and delivering them into the liver and cells throughout the body, as well as to growing nerve fibers. The strong association of apolipoprotein E genotype to AD is a potent indicator of the importance of lipid metabolism and diet in the pathogenesis of the disease.

Work in humans and animal models has shown that AD is associated with the accumulation in the brain of an abnormally folded fibrillar protein called amyloid β ($A\beta$), a breakdown product of the β APP. Amyloid β deposits form neuritic (senile) plaques in the brain parenchyma, which are accompanied by degenerating nerve terminals, death of neurons, and intracellular deposits of the abnormally folded microtubule associated protein tau in paired helical filaments called neurofibrillary tangles. People with Down syndrome all get neuropathological evidence of AD past the age of 35 to 40 (they have 150% of the gene dosage for the β APP found on Chromosome 21). Physiological and neuropathological changes of AD have been shown in early life in Down syndrome with increased cerebrospinal fluid $A\beta$ protein in early childhood, and early stage plaques are found in Down's brain as early as the third decade of life.⁴ This and other evidence from metabolic and behavioral studies have led to the understanding that AD is a very chronic disease, which develops over several decades before the onset of symptoms.

Pathological processes in AD causing loss of neuronal dysfunction involve the interacting actions of $A\beta$, inflammation, vascular factors, and oxidative stress. The brain's inflammatory response to $A\beta$ deposits includes activation of microglia, cytokines, and other inflammatory elements. Amyloid β deposits are also found in blood vessels (cerebral amyloid angiopathy), and may cause ischemia and bleeding and white matter changes, presumably of vascular origin, are commonly found on magnetic resonance imaging in AD.⁵ Activation of reactive oxygen species is an early event in AD and produces free radicals that harmfully modify nucleic acids, proteins, lipids, and carbohydrates.⁶ Lipid metabolism, influenced by genotype and diet, is also important, as the cleavage pathways responsible for production of $A\beta$ from β APP are influenced by plasma lipids.

Environmental factors are important in determining AD risk. Studies around the world have documented that increasing years of education are protective against development of the disease.⁷ Two related explanations are likely to be involved: (1) More educated persons have a higher degree of cognitive reserve, so they are more resistant to becoming symptomatically demented in the early stages of brain pathology⁸; and (2) education is linked to lifelong patterns of brain activity, and people who are more mentally active in leisure and work tasks are relatively protected.⁹ It is likely that cognitive activity is protective because of the well-known relationships of brain work to cerebral blood flow, glucose utilization, oxygen metabolism, resistance to endogenous excitatory neurotransmitters, and production of growth factors in the brain. These relationships have also been shown in studies with transgenic mice that have been genetically engineered to have features of AD.

AD has also been linked in several studies to head injuries and cigarette smoking and dietary influences on AD have also been widely reported.¹⁰ Studies have suggested that a diet high in saturated fat increases the risk and diets high in fish and omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, found in fish and nuts and oils, may be protective. Hypertension, heart disease, stroke, diabetes mellitus, hyperlipidemia in mid-life, metabolic syndrome, and obesity have also been linked to AD. The insulin degrading enzyme also degrades $A\beta$, and people with diabetes mellitus with relative insulin unresponsiveness may have less insulin-degrading enzyme available to degrade $A\beta$. Awareness of this complex web of pathological processes is important, because reducing the risk for any reduces the risk for others as well.

Inflammatory factors and early life environmental exposures to poisons and chemicals are also relevant to this discussion.¹¹ Elevated levels of C-reactive protein (a nonspecific marker of inflammation) in mid-life have also been found to be a risk factor for later development of AD, as well as stroke. Wu et al¹² found that lead exposure in early life in Alzheimer model transgenic monkeys influences β APP expression in later life. Other early life exposures likely to have negative consequences in later life include mercury and fetal alcohol syndrome.

The developmental origin of health and disease hypothesis is relevant to AD. Early life factors can influence disease in late life through epigenetic effects, changes in gene expression which are not caused by alterations in the nucleotide sequence of DNA, which are nevertheless inheritable. Mechanisms include alterations of histones which package DNA, methylation of DNA, non-coding RNAs, and covalent modification of DNA and RNA. The fetus adapts to adverse situations in its environment in utero with adjustments in fetal homeostasis to aid survival. These adaptive changes in response to the environment in early life may influence the organism's capacity to respond to changes later—responses may be adaptive in early life but maladaptive later on.¹³ Epigenetic adjustments may become permanent and ultimately have negative effects, increasing the risk of chronic noncommunicable diseases in adulthood. Several studies have reported that both small height and small head circumference are linked to AD. It is thought that nutritional deprivation in childhood (associated with the failure to reach the genetically determined height or head circumference) may enhance AD risk by decreasing cognitive reserve.

There are also undoubtedly nongenetic aspects of behavior, which are inherited through childhood experiences which influence brain aging in late life through memes (a cultural practice transmitted from one person to another, either through words or actions). There are countless aspects of diet, adaptations to stress, response to emotions, and intellectual activities which are passed from parent to child through generations. Studies in animals provide a window to observing the influence of early life events on brain function in aging. Mothering behavior in rats has been reported to influence the epigenome of the glucocorticoid receptor in the hippocampus (both DNA methylation and histone modification). Mothers who devoted more time to grooming had offspring with more hippocampal glucocorticoid receptors (important for memory and learning) and a better regulation of the stress response (enhanced ability to turn it off), leading to enhanced survival of hippocampal neurons into old age. These effects continued into adulthood and were found to persist across generations. This is evidence of a molecular mechanism for the fact that “the style of parenting can influence the sort of adult a child becomes.”¹⁴

It is vital that public policy takes into account the importance of environmental exposures and lifestyle factors beginning in childhood because of their role in influencing neurodegeneration. Childhood is the period of life when lifestyle patterns are established such as diet, physical and mental activity, and risk behaviors such as smoking. There is evidence that public health measures can be effectively applied to early life health behaviors, although more is needed. There is increasing awareness that we need much better evidence about how to modify trajectories of risk which may be initiated in utero. Such understanding requires data ranging from laboratory and animal studies to community and policy intervention programs. This is urgent if we are to bring new generations into a healthier middle age in all economic settings who then would be at lower risk of dementia at later ages. Policies based on such evidence also need to address the fact that a successful outcome will include longer life and that this in itself is likely to result in larger sections of the populations being at higher risk of dementia and disability. This may attenuate benefit but models can be created to explore the potential balance of benefit and risk.¹⁵ This is, of course, particularly critical as life span and risk patterns change. Pediatricians are uniquely well placed to assist patients and families to develop healthy lifestyles in early life to allow for later years to be full of memory and meaning.

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