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Lipoproteins, Lipids, Cognitive Impairment and Vascular Disease

Introduction

Alzheimer's disease (AD) is a frequent cause of dementia, and affects about 40% of those over 85 years old in developed societies.[1] While a number of cognitive diagnostic tests have been developed and are clinically useful, a definite diagnosis of AD requires an anatomical dissection and the identification of extra cellular amyloid deposits composed of amyloid B (A beta) peptides 40–42 amino acids in length, and intracellular accumulations of abnormally phosphorylated tau protein in neurofibrillary tangles.[2]

The brain is the organ in the body that is richest in cholesterol; containing 25% of the total body cholesterol, in a mass of about 2% of body weight. (3) The brain cholesterol is found in myelin, neuronal and glial membranes. The brain cholesterol is synthesized on site, and since the brain cannot degrade cholesterol, any excess is delivered to the circulation for hepatic excretion. About 6–7 mg of cholesterol leaves the brain daily after conversion to 24S-hydroxycholesterol, which can transverse the blood-brain barrier.[3]

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Apolipoprotein E

Apolipoprotein E (Apo E) is a polymorphic glycoprotein which attached to plasma lipoproteins including chylomicrons, very low density lipoprotein cholesterol (VLDL) and HDL-C.. Apo E's metabolic roles include the transport of lipids from the site of their synthesis or absorption to the tissues, and the transport of cholesterol to the liver for excretion. Apo E also modulates the activity of enzymes such as lipoprotein lipase. [4] Apolipoprotein E is the main apolipoprotein in the brain, in which it is synthesized by astrocytes and microglia.

Human Apo E gene has three common alleles (e2, e3, and e4, coding for the Apo E protein as the three isoforms (E2, E3, and E4) which vary in the amino acid present at position 112 and 158 of the protein and which bind to lipoprotein receptors with differing affinities.[5] Apo E 3/3 is the most common genotype (62% of the population) and Apo E 4 is present in about 25% of the population, including one or two copies of e4. The e 4 allele is associated with an increased risk of coronary artery disease (CAD) and tends to have an exaggerated elevation of LDL-C when the diet is high in saturated fat. Individuals with one or more copies of Apo E 4 tend to have a lower HDL-C level, and higher LDL-C levels. Both Apo E 2 and Apo E 4 are associated with an increased level of triglycerides.[6] Apo E 4 allele is associated with a decrease in LDL particle size and an increased number of small, dense LDL particles.[7]

Apo E4 and Alzheimer's Disease

A great deal of evidence demonstrates that apolipoprotein E4 allele constitutes a significant risk factor for AD. Carriers of apolipoprotein E4 have a greater-than-double risk of developing AD; on the other hand, inheritance of apolipoprotein E2 relates to both a lower risk and a later onset of AD in such individuals.[8] Apo E 4 has been demonstrated to be associated with an increased risk for the development of AD and dementia in Down Syndrome, and a recent study demonstrated that Apo E4 is associated with an increase in mortality risk. In a group of 146 non-demented adults with Down Syndrome, individuals with at least one Apo E4 allele were five times more likely to die in a 7-year period, adjusted for age, gender, BMI, level of mental retardation and level of total cholesterol.[9]

Apo E4 is associated with regional brain atrophy measured by MRI. A volumetric measurement of the amygdale in 32 Apo E4 + AD patients, 23 Apo E 4 – AD patients and 42 cognitively normal elderly controls demonstrated that amygdaloidal volume was significantly smaller (19%) in ApoE4 ($p=0.002$) compared to Apo E4 – individuals.[10]

As we age, neurons are remodeled and repaired to maintain synapto-dendritic connections. Apo E is an important factor in these processes, particularly Apo E3 and Apo E2 are effective in repairing neuronal cells, but Apo E4 is much less effective. Injurious events include oxidative stress, ischemia, excess A beta production, mutations, inflammation, and the aging process itself.[11] Impaired cognition in individuals caring one

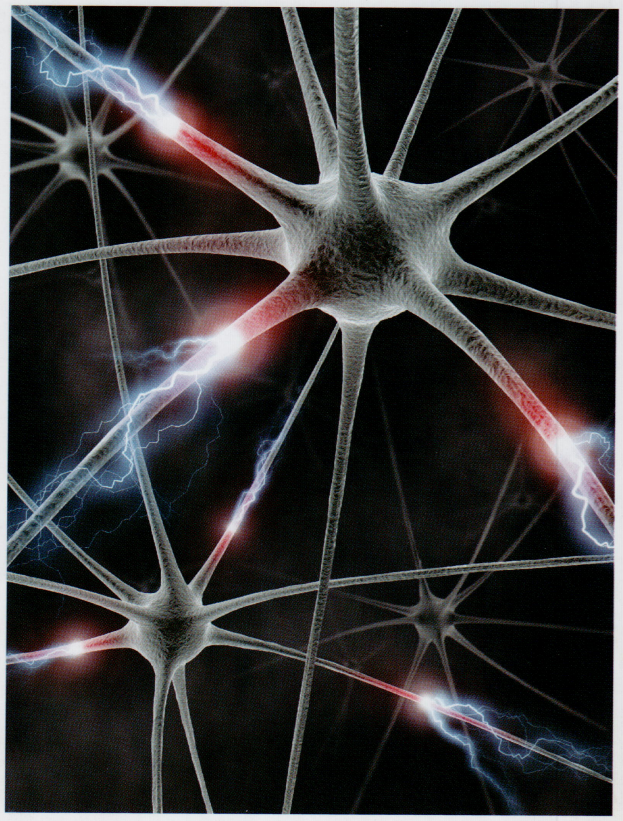
or two alleles of Apo E4 worsens with age.[12] Apo E4 is associated with impaired CNS glucose utilization in both normal and AD patients.[13] In 65–75 year old and 29–39 year old subjects , the Apo E4 allele was associated with lower glucose utilization that the Apo E3 allele , and affected the hippocampus and cortex, area also affected by AD.[14–15]

In the CNS, astrocytes are the major cell types that produce Apo E. Moreover, CNS neurons express Apo E under both physiologic and pathologic conditions.[16] Apo E is the major apolipoprotein in the CNS (LDL-C and Apo B are absent), capable of redistributing lipids the LDL-C receptor related family of receptors.[17] Apo E occurs in the cerebrospinal fluid as a small high density lipoprotein–like particles or phospholipids discs. Apo E-containing lipoproteins can deliver lipids, including cholesterol, to sites of injury for the repair of cells. Decreased A beta clearance or increased A beta deposition has been suggested to play a role in AD pathogenesis.[18] Both *in vitro* and *in vivo* studies demonstrate that Apo E4 inhibits A beta clearance and /or stimulates A beta deposition.[18]

In patients with AD who carry the Apo E4 genotype, mitochondrial dysfunction may occur. The disruption of the electro potential of the mitochondria by Apo E fragments in cultured neurons may affect neuronal function. Mitochondria have a role in synaptogenesis, and Apo E4 expression may impair synapto-dendritic connections.[19] ApoE4-associated neuropathogy can occur through disruption in mitochondrial regulation of glucose metabolism in neurons.[13] In young subjects with no signs of dementia and unlikely to have Abeta deposits, Apo E4 is associated with reduced glucose metabolism.[13]

Cholesterol metabolism may contribute to the pathogenesis of Alzheimer disease (AD). Apolipoprotein E is the main lipid carrier in the brain, and intracellular cholesterol levels influence the generation of A beta peptides, which may be etiologically involved with the cause of AD.[20, 21]

Apo E has functions in distributing lipids among CNS cells for normal lipid homeostasis, repairing injured neurons, maintaining-synapto-dendritic connections, and scavenging toxins.[11] Age-dependent dendritic and synaptic regeneration may be less efficient with Apo E4, and this may unmask age-related neurodegenerative changes.[22] The increased risk of AD associated with Apo E4 may be modulated by diet, vascular disease risk factors, and genetic polymorphisms that affect the function of other transporter functions and enzymes involved in brain lipid homeostasis. Brain plaque deposition in the form of (A beta) peptide is a pathologic component of Alzheimer's Disease. Apolipoprotein E is believed to be involved in plaque formation. Patients with AD who carry Apo E4 have a larger number of A beta plaques than those carrying Apo E3. Apo E4 associated with lipid bound preferentially to an intermediate aggregated form of A beta with a higher avidity than did Apo E or Apo E2.[23] Apolipoprotein E



as well as several members of the adenosine triphosphate cassette transporter family, including ABCA1 and ABCG1 is likely to play a role in lipoprotein homeostasis in the central nervous system (CNS).

Apolipoprotein E binds A–beta in an isoform and lipidation–dependent manner, co-localizes with amyloid deposits and participates in the uptake and degradation of A beta by astrocytes and microglia.[24, 25]

While there are few absolute answers to the pathogenesis of AD, and the roles that apolipoprotein play are still a matter of some discussion, it appears that there are some "yang and ying" aspects to individual alleles. The detrimental effects of apoE4 include an inhibitory effect on neurite outgrowth, a disruption of the neuronal cytoskeleton, a stimulation of tau phosphorylation, a relationship to cognitive decline, neurodegenerration caused by apo E4 fragments, and enhanced A beta deposition.[26,27,28,29]

A potentially positive role is played by Apo E3, including: stimulating neuritic outgrown, protection from neurodegeneration, protection from cognitive decline, protection from tau phosphorylation, antioxidative effects, stimulation of cholesterol efflux, and stimulation of A beta clearance.[30,31,32,33,34,35]

Apolipoprotein D (Apo D) is elevated in AD, in the cerebral

cortex, localized to cells, blood vessels and plaques. Apo D immune-reactivity with special staining processes has been detected in AD tissue.[36]

An understanding of the significance of apolipoproteins in the process of cognitive decline is important and vital as a background for a number of important diagnostic and therapeutic advances waiting in the wings as a diverse and intense interest in the forthcoming epidemic of cognitive decline has spawned a cornucopia of imaginative research studies currently in planning or already underway. While currently available drugs appear to have limited value in preventing AD or even prolonging its development, this is not to say that there are no current therapeutic modalities of interesting potential.

The lack of a major or dramatic effect of the currently available drugs lends further credence to the non-pharmacologic approach discussed above, which can be applied safely and at minimal cost.

Significant data are already available to point the way to a variety of non-pharmacologic approaches which may alter the progress of dementia and AD, and perhaps limit its development in compliant "at risk" individuals.

A hygienic approach to reducing the toll of cognitive impairment

The KAME project measured the food intake of 1836 Japanese-Americans prospectively followed with repetitive neuro-psychologic testing.[37] Their average age was 72 years and 20% possessed one or two apolipoprotein E4 alleles. After a 6-year follow-up, the subjects had an inverse relationship between the intake of fruit and vegetable juices and the risk of AD. The association was stronger in those who were positive for the Apo E4 allele. Compared to those whose intake was less than one time a week, those individuals who drank fruit and vegetable juices more than three times a week had a hazard ratio of 0.24 (CI 0.09–0.61; P< 0.01).[38]

Another study followed individuals older than 65 years with a semi-quantitative food frequency questionnaire and cognitive testing. Fish intake was associated with a slower rate of cognitive decline when infrequent fish consumers were compared to consumers of more than 2 fish meals a week. (P= 0.04).[39]

The Mediterranean diet (MD) is characterized by a high intake of vegetables, fruits, cereals, unsaturated fatty oils and fish. It is low in saturated fats and meats. Adherence to the MD was measured in 2558 older individuals who were followed with repetitive neurological testing. There were 262 incident cases of AD, and those with the highest adherence had the lowest hazard ratio for the development of AD: 0.60 (95%, CI 0.42–0.87, P for trend .007).[40]

A study of dietary fat and the risk of dementia in Holland demonstrated that a fish intake of more than once a week reduced the risk of developing AD by 60 %.[41] In addition, several animal studies demonstrated beneficial effects of other dietary components. In one, an increased intake of Omega-3 fatty acids was protective against the deposition, accumulation and toxicity of A beta.[42] Joseph and his colleagues suggested that foods rich in anti-oxidants including spinach, strawberries, and blueberries may be beneficial in age-related cognitive impairment.[43] They used transgenic mice and demonstrated a protective mechanism derived from blueberries, which enhanced memory-associated neuronal signaling.

Finally, recent research has suggested a completely new approach that is undergoing further testing. The New York University researchers tested blocking of the apoE/A beta interaction *in vivo* as a therapeutic target.[44] They developed a new compound A beta 12-28 P, which is a blood-brain barrier permeable, nontoxic, nonfibrillogenic synthetic peptide homologous to the apo E binding site on the full-length A beta. A beta 12-28 P binds with high affinity to apoE, preventing its binding to Abeta. This was useful in preventing memory deficit in two AD transgenic mouse models. Of course, further and more intense research will be necessary even before human controlled trials can be initiated.

Any discussion of the drugs available for the treatment of AD or other dementias requires a comment on the available drugs already in use by many patients. Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are currently approved by the FDA for the treatment of AD. Clinical trials have demonstrated limited efficacy of these treatments in other forms of dementia, including vascular dementia.[45,46,47] However, these agents fail to provide a disease-modifying effect or a preventive role. They provide brief symptomatic treatment, currently.

The lack of a major or dramatic effect of the currently available drugs lends further credence to the non-pharmacologic approach discussed above, which can be applied safely and at minimal cost. Hygienic measures, including dietary modification, require a strong effort to achieve compliance. Involvement, interest, and an enthusiastic approach provided by the physician will be vital for the patient to achieve successful adherence to these measures, which have been successfully documented in published trials.

It is apparent that there have been great strides made in furthering our understanding of the role of various

apolipoproteins in cognitive impairment, dementia and vascular disease. There is room for optimism, but a sober assessment requires that we accept that there is currently no magic bullet, and there may not be such medication for a considerable period. There is enough information to initiate a response to a forthcoming epidemic of cognitive impairment, which will be global in scope and enormous in incidence. A number of studies suggest that dietary modifications can be helpful, and as they will also reduce cardiovascular disease risk factors and are inexpensive, they should be implemented now. At the very least, they appear to offer no significant toxicity risk.

Summary

- Alzheimer's disease is a common cause of dementia in the elderly and there is increasing evidence that apolipoproteins play an important role in its development.
- Apo E4, an isoform of apo E which plays a major role in modulating brain cholesterol metabolism, and which is present in about 25% of the population has been strongly linked to Alzheimer's disease.
- Apo E4 has been shown to stimulate the deposition and slow the clearance of the A beta protein that accumulates deposits in plaques, a pathological hallmark of Alzheimer's disease.
- Apo E also plays a role in the remodeling and repair of synapto-dendritic connections related to aging and apo E4 is less effective in this process.
- Although the development of effective preventive treatment for Alzheimer's disease is still evolving, dietary modification, especially reducing animal fats by increasing fish, fruit and vegetables are associated with a reduced risk.

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Lipoprotein management consensus statement released by ADA, ACC

The American Diabetes Association (ADA) and the American College of Cardiology (ACC) issued a consensus statement regarding the role of lipoproteins in the evaluation of cardiometabolic risk (CMR). This reinforces the idea that LDL cholesterol (LDL-C) may not be the optimal method of quantifying patient risk for cardiovascular disease (CVD).

There is little disagreement with the general idea that low LDL-C is desirable, but the ADA and ACC consensus conference report took a closer look at the sorts of patients with CMR, such as those with Type 2 diabetes, central obesity and insulin resistance, and noted that "measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles."

ApoB and LDL particle concentration seem to be more closely associated with these markers of CMR than LDL-C or non-HDL-C, and lipoprotein abnormalities are commonly found in patients with CMR. Thus, the consensus statement finds that ApoB and LDL particle number may be more useful in determining the adequacy of LDL-C lowering therapies than traditional measurements. Because this is a new area of interest, the NLA has invited Allan Sniderman, MD, a professor of cardiology who has published a number of papers in support of making ApoB a target, to present the findings of the ADA/ACC consensus statement at the NLA Scientific Sessions in Seattle.

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