APOE, dementia, and COVID-19: What COVID Teaches Us About Dementia.

Apolipoprotein E is a lipid binding protein that circulates as part of chylomicrons, and other lipoprotein particles (HDL and VLDL) is the blood stream. Circulating ApoE is produced mainly in the liver, but also highly expressed in brain, lung, heart, kidney, adrenal, fat, and endothelial cells.[1] In the brain, ApoE is mainly produced by astrocytes, and used to transport cholesterol to the neurons via APOE receptors, APOE also transports fat soluble vitamins such as vitamin D and vitamin K, and other lipids. Cholesterol is an essential component of cell membranes, and the elevated expression observed in some tissues reflects the need for this compound in these tissues, with the exception of the fats cells, wherein APOE serves a storage/distribution function. Cholesterol is an important component of the cell membrane that helps decrease membrane permeability and increase membrane density. This is important for electrical potential development in the heart and neurons.[2]

APOE is polymorphic and has three common genetic alleles in the human population: APOE-ε2, APOE-ε3, APOE-ε4. (For simplicity, herein APOE2, APOE3 and APOE4). APOE3 and APOE4 has only one base pair difference, causing a change of a single amino acid. About 8 percent of alleles in the Caucasian population are APOE2, 78% are APOE3, and about 14% are APOE4. In Nigerians the distribution is about 3%, 67% and 30% APOE 2, 3, and 4 respectively.[3]

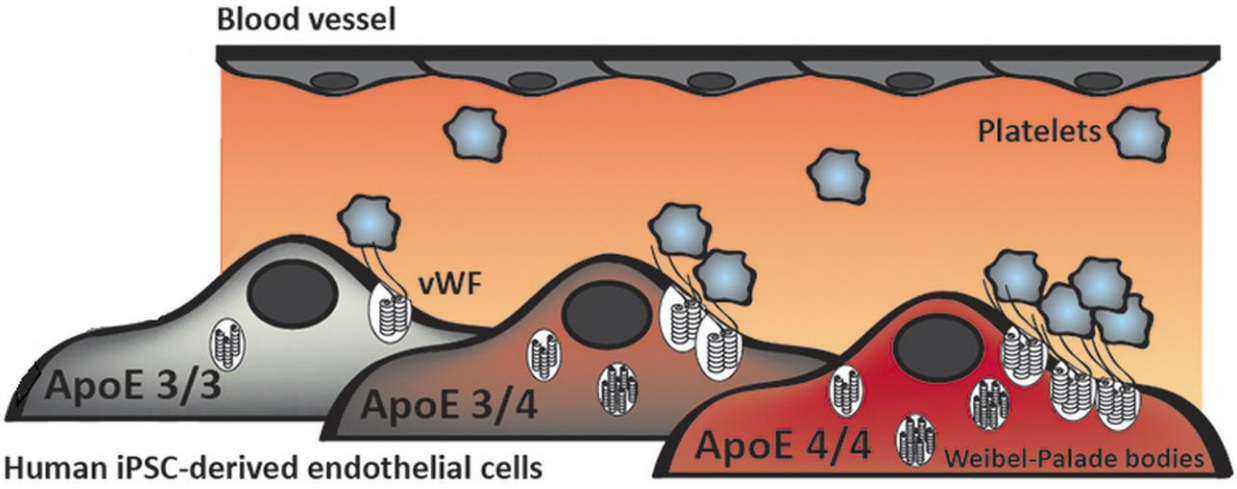
As you are already likely aware, persons with the APOE4 allele are at considerably higher risk for the development of Alzheimer's disease. It is also a risk factor for other brain injury, as it is associated with poorer outcome after traumatic brain injury,[4] ischemic cerebral vascular disease, and sleep disordered breathing.[5] Interestingly, the risk of multiple sclerosis is most elevated with ApoE2 and least in those with APOE3/4,[6] perhaps because of decreased availability of vitamin D and other fat-soluble vitamin delivery among those with APOE2.

APOE is co-dominant, in that both of the copies we inherit, one from our mother and one from our father are expressed and contribute to the APOE function. Thus, those with APOE3/3 are at lower risk of AD than are those with APOE3/4 and those individuals are at lower risk of AD than those with APOE4/4.

APOE4 is has recently been reported to be a risk factor for severe COVID-19 and COVID-19 mortality. Patients with preexisting dementia were three times more likely to die from COVID-19 as were patients with similar non-dementia comorbidities. In a population of individuals aged 48 to 86 years old in the UK, individuals without dementia, but with APOE4/4 were 2.4 times as likely to develop severe COVID-19 as were those with the APOE3/3 phenotype. To put this into perspective, this risk is similar but slightly lower than the risk of severe COVID-19 imparted by hypertension (OR=2.67) type 2 diabetes (OR = 2.73) and coronary artery disease (OR = 2.86).[7]

The risk for those with the APOE3/4 phenotype was not provided, but if the risk spread from APOE 3/3, 3/4, and 4/4 is similar to that for AD, the OR for severe COVID among those with APOE3/4 is likely about 1.5 that of those with APOE3/3. The odds of developing AD is about 10.7 times higher in those with APOE4/4 than those with APOE3/3, and the odds for those with APOE3/4 is 3.2 times higher than those with APOE3/3.

While APOE4 greatly increases risk of AD, not everyone with APOE4/4 gets dementia. There are other risk factors, and a healthy lifestyle decreases AD risk even within these high risk individual. If we understand how COVID-19 risk is elevated by APOE4/4 status, we may be able use that information to lower the risk of severe COVID-19 and risk of Alzheimer's disease for everyone.



(Image adapted from reference 8 below)

In a study evaluating the effect of APOE alleles on endothelial protein expression, it was found that APOE4/4 allele cells grown in cell culture expressed considerably higher levels of von Willebrand Factor (vWF).[8] VWF coils up inside of Weibel-Palade bodies (WPBs), which are unique to endothelial cells. When the endothelial cells are injured or stressed, the VWF is uncoiled but remains tethered to the WPB. Uncoiled, The VWF is sticky, like a spider web, however, it is specifically sticky for both platelets and for collagen. Thus the platelets adhere to each other and to any collagen exposed by endothelial injury. Contact with the collagen activates the platelets to produce thrombin and form clots and microemboli. In Alzheimer's disease, chronic low-level endothelial injury, microthrombi formation with creating local tissue hypoxia and oxidative stress, and the formation of microemboli in the brain likely greatly contribute to disease progression. APOE also mediates clearance of amyloid-β, another important factor in the development of AD. In this study of endothelial cells, there was also increase production of the amyloid-β fragments Aβ40 and Aβ42, which are associated with AD.

SARS-CoV-2, the virus causing COVID-19 specifically infects endothelial cells and causes oxidative stress and injury to these cells and activates VWF release. It is the production of microemboli that are filtered and captured by the fine capillary network of the lungs that causes hypoxia and lung disease.

APOE4 acts as a transcription factor and this study compared the differential expression of endothelial cells with APOE3 and APOE4. They found the greatest alterations in the expression of genes associated with cell adhesion, wound healing, and blood coagulation. VWF not only affects coagulation, but also the blood brain barrier.

It was further determined that APOE3/4 and APOE4/4 endothelial cells contained a significant amount of the inflammatory cytokines IL-1α, INF-γ, Kallikrein 3 and CXCL5, while these cytokines were not present in detectable levels in APOE3/3 endothelial cells. CXCL5 is a chemokine that attracts neutrophils. IL-1α stimulates the release of VWF from the WPBs.

Normally, endothelial cells promote an anti-thrombotic, anti-coagulant balance in the blood vessels. APOE4 causes a shift towards to a less anti-thrombotic, less anti-coagulant balance. With aging and other risk factors this balance can shift to prothrombotic and procoagulant balance where there is the formation of microthrombi, comprise of blood flow in the microvasculature of the brain, and a proinflammatory milieu. APOE4 promotes a reduction in cerebral microvascular flow which results in local hypoxia.[9]

The gene expression study also found that VE-Cadherin (vascular endothelial cadherin, VECad) expression is also increased in endothelial cells with APOE4. VE-Cad helps link neighboring cells together and thus is important for endothelial adhesion, limiting vascular permeability, and for blood brain barrier (BBB) function. Thus, extra VE-Cad would be expected to be helpful in maintaining adherens junction integrity. Nevertheless, APOE4 is associated with poorer BBB function.[8] This suggests that the APOE4-associated increase in VE-Cad expression may be the response to a feedback loop in which barrier function is compromised. This may be the result of loss of intrinsic anti-permeability factors or an increase in non-receptor tyrosine kinase phosphorylation of VE-Cad, perhaps secondary to inflammatory cytokines.[10]

VE-Cad is part of the mechanism for leukocyte transmigration into the tissue and for alterations in the endothelial cell cytoskeletal structural rearrangement that leads to the rupture of adherens junctions in response to inflammatory cytokines such as IL-6. This appears to occur in endothelial during ARDS (acute respiratory distress syndrome), causing leakage of serum proteins into the tissue and the development of hypoalbuminemia, which is known to occur in severe COVID-19.[11]

What does this tell us about prevention of AD and reduction of risk for severe COVID-19.

- N-Acetylcysteine (NAC), which both acts as precursor for glutathione and decreases the stickiness of VWF, may reduce the risk of both these diseases.
- Exercise with increases blood flow also decreases the adhesion of platelets and white blood cells to the endothelium.
- Anti-inflammatory agents that mitigate IL-1α production appear to lower VWF expression,[8] and thus may decrease risk of both of these diseases.
- Very low dose aspirin (40 mg/day) decreases platelet activity and should decrease the risk of both diseases.
- Preventing oxidative stress may be helpful. Thus, lowering homocysteine with 5-MTHF and methylcobalamin may lower risk. NAC and pyridoxal-5′-phosphate (P5P, active vitamin B6)

for those with chronic inflammation, help increase glutathione a key anti-oxidant. P5P is also a key coenzyme for the production of S1P, an important anti-permeability factor for ve-cadherin adherens junction stability between endothelial cells.

- Broccoli and cauliflower consumption induce the production of antioxidant enzymes including those needed for recycling glutathione.
- Avoiding agents that cause sustained inflammation is generally a good bet.

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