Biological Factors Linking ApoE ε4 Variant and Severe COVID-19

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Dear Editor,
The recent review by Moriarty et al. [1] provided a very pertinent analysis of the increased risks from thromboses and other cardiovascular complications of patients with elevated levels of lipoprotein(a) (Lp(a)) following coronavirus disease 2019 (COVID-19). This included an erudite analysis of raised levels of Lp(a) in certain ethnic groups and association with higher frequency of ApoE4 genotypes and risk of severe COVID-19. Whilst this raises the question as to whether ApoE4 genotypes may affect COVID-19 prognosis, recent data is helping to address this issue.

Analysis of data from 382,188 participants of the European ancestry in the UK Biobank [2] revealed a high risk of severe COVID-19, in the 2.36% (n = 9022) of people carrying two copies of the faulty gene variant of ApoE ε4, with 5.13% (n = 37) of the COVID-19-positive participants after hospitalization carrying this gene variant. Compared with the more common ApoE ε3ε3 genotype, the risk of severe COVID-19 for people carrying two ApoE ε4 alleles was doubled (OR = 2.31), including people who had neither developed Alzheimer's disease (AD) (as for the 5.13% COVID-19- positive participants) nor cardiovascular disease (CVD), and for whom two copies of ApoE ε4 also carried increased risk.

Besides raised Lp(a), as highlighted by Moriarty et al., other biological effects may link the ApoE ε4ε4 genotype to severe COVID-19. To explore this, the role of ApoE ε4ε4 in possible risk factors of venous thromboembolism-related mortality, such as extracellular vesicle (EV) release/altered content, von Willebrand factor (vWF) as well as angiotensinconverting enzyme 2 (ACE2), must be considered.

EV Biogenesis Linking ApoE ε4

Variant to COVID-19 Curiously, studying the effect of the ApoE ε4 variant on EV biogenesis in the brain may help us understand the illusive 'biological mechanism' linking it to COVID-19. Analysing human post-mortem tissue and tissue from ApoE ε4 mice (expressing human ApoE4), the ApoE ε4 genotype reduced local EV production but, more importantly in terms of EVs' role in VTE, altered lipid composition [3]. Relative to total brain, EV cholesterol levels were 10× and 50× greater for ceramide and ganglioside, respectively. Lipoproteins from conditioned media of human ApoE4-expressing mouse astrocytes, relative to ApoE3, increased phosphatidylserine (PtdSer) synthesis. If this increase occurred in EVs, where PtdSer is expressed on the outer leaflet of the lipid bilayer, which from blood and vascular cells contributes to thrombotic events, they would be more procoagulant, in a tissue factor-(TF-) independent manner.

vWF Linking ApoE ε4 Variant to COVID-19

Besides AD, the ApoE ε4 allele, as a major genetic risk factor for CVD and stroke, will also affect the vascular system. Upon infection with severe acute respiratory syndrome-coronavirus2 (SARS-CoV-2), the hyperinflammatory response and consequent endothelial dysfunction initiate a local procoagulant environment as suggested by the pulmonary microthrombi observed in COVID-19. Significantly raised vWF [4] released by TNF-α and IL-1β activation of endothelial cells (ECs) is just one feature of the ensuing coagulopathy. Using humaninduced pluripotent stem cell-derived ECs harbouring ApoE ε4ε4, endothelial dysfunction has previously been manifest by increased platelet binding and increased expression of vWF, promoting a prothrombotic condition [5].

ACE2 and a Possible Link Between ApoE ε4 Allele and COVID-19

Demonstration of ε4 as a risk allele in AD is pertinent to ε4 being a risk allele in severe COVID-19, because ACE2 (receptor for SARS-CoV-2) is reduced in individuals that are carriers of ApoE ε4 [6]. As an indirect measure for reduced ACE2 activity, the level of Ang II, which ACE2 converts to the vasodilatory peptide Ang(1-7), was increased, as is found in COVID-19 patients where Ang II levels

are twice normal [7]. Ang II is a powerful vasoconstrictor. Through reactive oxygen species such as superoxide (O2•-) and hydroxyl (OH-), it decreases nitric oxide bioavailability, causes EC dysfunction and promotes a prothrombotic milieu leading to VTE.

Concluding Remarks

In continuing to explore the possible association of the ApoE ε4 allele with COVID-19, it is useful to remember that ApoE is also linked to susceptibility to infection by viruses [8] (as well as bacteria and parasites, including secondary infection), for example, ApoE4 increasing HIV-1 infection, two copies of ε4 aiding accelerated disease development [8]. If the ApoE ε4 allele indeed influences COVID-19 severity, this may explain the prevalence of severe disease amongst certain ethnicities, as in one study the allele frequency was 29.5% for AA versus 12.1% for the Caucasian group [9]. Furthermore, up to midApril 2020, 34% of deaths from COVID-19 in the USA occurred amongst AAs, despite the population representing only 13% of all Americans [10]. In conclusion, ApoE ε4 may have multifaceted effects in COVID-19 which may also be reflected in ethnicity.

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