THE 6TH ANNUAL HEART IN DIABETES
CME CONFERENCE • JUNE 24-26, 2022
LOEWS PHILADELPHIA HOTEL, PHILADELPHIA, PA
Where the Heart, Kidney and Diabetes Meet in Clinical Practice

Coagulation and cognitive function - science behind the scenes

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Introduction - Cardiovascular diseases and neurodegenerative diseases are age-related diseases. Epidemiological studies suggest that cardiovascular risk factors are related to the development of the most common neurodegenerative disease worldwide - Alzheimer's disease (AD), which is characterised by progressive cognitive impairment. In addition, accumulation of the beta-amyloid peptide (Aβ), the key distinguishing neuropathological feature of AD, was detected in human hearts and blood vessels. It has been suggested that AD is, in fact, a vascular disorder, and that other molecules that regulate endothelial cell function can become dysregulated and, at least in part, contribute to the development of AD. NRP-1 is a type I transmembrane protein that is implicated in cardiovascular and neuronal functions. NRP-1 is a receptor for vascular endothelial growth factor (VEGF) and other members of the VEGF family of proteins expressed in endothelial cells where it appears to play an important function in VEGF-dependent intracellular signalling, cell migration and angiogenesis. NRP-1 is also a receptor for semaphorin 3A (semaphorin 3A), a protein that is involved in axonal guidance. In addition, studies suggest that NRP-1 plays a role in the functions of the vascular smooth muscle cells where it is also expressed and where it is sensitive to fibroblast growth factor 2 (FGF-2) and platelet-derived growth factor (PDGF) (1,2). Recently, NRP-1 was identified as one of the receptors that allows entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes COVID-19, to the host cells (3).

Aim - The aim of the study was to investigate a relationship between vascular endothelial growth factor (VEGF), VEGF-interacting protein, NRP-1, and blood coagulation/anticoagulation proteins with cognitive decline associated with AD.

Methods - Data from the AddNeuroMed's Alzheimer's disease biomarker project were used (4). They were obtained through authorised access from the Synapse Data Platform, which is hosted by Sage Bionetworks (https://www.synapse.org/), following ethical approval from the Sarajevo Medical School Bioethical Committee from the 07/01/2020. Plasma levels of VEGF, NRP-1, fibrinogen, coagulation factors (V, VI, VII, IX, X, Xa, XI) and anticoagulation proteins (C, S), and activated protein C were measured by using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array called SOMAscan, in cognitively healthy volunteers (N=193), patients diagnosed with mild cognitive impairment (MCI) (N=126) and patients diagnosed with probable AD (N=365). The results between the three groups of subjects were compared by using Kruscal-Wallis non-parametric ANOVA method with all pairwise comparisons.

References - 1) Pellet-Many C et al., Biochem J., 2008; 2) Mahmoud M et al., Am J Physiol Cell Physiol., 2019; 3) Cantuti-Castelvetri L, et al., Science, 2020; 4) Sattlecker M, et al., Alzheimer's Dement., 2014.

Results - Fibrinogen and coagulation factor XI levels were the highest in the probable AD group (median 247264.0, range 1756.8-331735.0, and median 2021.5, range 904.7-3217.3, respectively), but they were significantly different only from the values in the group of healthy volunteers ($p = 0.035$ and $p = 0.002$, respectively). On the other hand, coagulation factor X, coagulation factor Xa and protein C were the lowest in the probable AD group (median 10497.9, range 4406.5-16113.0, median 7929.8, range 3450.2-12338.3, and median 30764.1, range 11497.2-49766.5, respectively), but the differences were significant only when compared with the values in the group of healthy volunteers ($p = 0.043$, $p = 0.003$ and $p = 0.008$, respectively). Other measured biomarkers were not significantly different among the study groups.

However, there was significant non-parametric correlation between VEGF and NRP-1 and coagulation/anticoagulation factors: NRP-1 and protein C ($r = -0.274$, $p = 0.000$), NRP-1 and fibrinogen ($r = 0.209$, $p = 0.000$), NRP-1 and coagulation factor X ($r = -0.220$, $p = 0.000$), NRP-1 and coagulation factor Xa ($r = -0.247$, $p = 0.000$), VEGF and protein C ($r = -0.191$, $p = 0.000$) (Table 1).

Variable	Healthy (N=193)	MCI (N=126)	Probable AD (N=365)	*p* (Probable AD *versus* Healthy)
Fibrinogen	239975.4	244437.0	247264.0	0.035
Factor XI	1873.2	1884.4	2021.5	0.002
Factor X	10984.0	10812.2	10497.2	0.043
Factor Xa	8348.2	8150.7	7929.8	0.003
Protein C	31768.6	30327.5	30764.1	0.008
VEGF	2008.2	2057.3	2054.0	ns
NRP-1	2527.5	2511.8	2531.4	ns

Table 1: Results of the study. All values represent median values. (MCI = mild cognitive impairment, AD = Alzheimer's disease, ns = not statistically significant)

Conclusion - Our results demonstrate significant differences in plasma levels of some coagulation/anticoagulation proteins between AD patients and healthy individuals, indicating a specific pattern of hypercoagulability risk in the AD patients. Further investigations are warranted in order to make evidence-based decisions regarding the inclusion of anticoagulation pharmacotherapies towards the improvement of the key clinical symptom of AD - cognitive decline.