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Letter to the Editor

Correspondence on "Age, Anticoagulants, Hypertension and Cardiovascular Genetic Traits Predict Cranial Ischaemic Complications in Patients with Giant Cell Arteritis"

[1] Carla Alexandra Scorza, [2] Fulvio Alexandre Scorza, [3] Josef Finsterer
[1, 2] Federal University of Sao Paulo (UNIFESP/EPM). São Paulo, Brazil
[3] Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

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Corresponding Author: **Josef Finsterer**

We read with interest the article by Chaddock *et al*. on whether pre-existing cardiovascular risk factors, cardiovascular disease, or genetic predisposition to cardiovascular disease predicted ischemic stroke in 1946 patients with giant cell arteritis (GCA) [1]. Using an elastic net, it was found that 17% of the included patients had developed ischemic stroke at presentation, that univariate analysis revealed 10 variables associated with ischemic stroke, that multivariate analysis revealed age and anticoagulation as the strongest risk factors for ischemic stroke, and that after excluding anticoagulation from the multivariate analysis, age and hypertension were found to be the strongest predictors of ischemic stroke [1]. The study is convincing, but some points should be discussed.

The first point is that the risk of cerebrovascular disease in patients with GCA depends not only on age, anticoagulants, hypertension and genetic cardiovascular disease, but also on many other risk factors for ischemic stroke. These include diabetes, hyperlipidemia, smoking, comorbidities other than hypertension, atrial fibrillation, concomitant medications other than anticoagulants, and genetic conditions other than cardiovascular disease. Other risk factors include male gender, coronary artery disease, atherosclerosis, aortic aneurysm, and aortic dissection, [2, 3, 4]. Were these additional risk factors for ischemic stroke included in the multivariate analysis?

The second point is that it is incomprehensible why transient ischemic events were evaluated separately from ischemic cerebral events. Transient ischemic attacks are a subgroup of ischemic events and should be included in this group in the analysis.

The third point is that the age range was relatively small (age 66 to 77 years) [1]. Therefore, the result of the multivariate analysis that age predicts ischemic stroke in GCA patients must be considered with reservation.

The fourth issue is the discrepancy between the aims of the study (to identify associations between preexisting cardiovascular risk factors, cardiovascular disease, or genetic risk for cardiovascular traits and cranial ischemic complications at presentation of GCA) and the methodology section, which states that a composite of extracranial ischemic manifestations, which includes extracranial ischemic traits, was included as a secondary outcome [1]. As the study aimed to identify risk factors for cranial cerebrovascular events, it does not make sense to include extracranial events as a secondary outcome. It is also not clear what is meant by non-ocular cranial ischemic events [1].

The fifth point is that the number of genes studied that are involved in cerebrovascular events was small. Many more genes associated with cerebrovascular risk could have been studied, and a test using whole-exome sequencing (WES) would definitely have been more informative than a test only for *IBTK; CLTA, TEK, CD96* and *MROH9* [1].

The sixth point is that according to the American College of Rheumatology (ACR) only 93% of patients meet the diagnostic criteria for GCA and that only 95% meet the criteria of the European Alliance of Associations for Rheumatology (EULAR) [1]. Why were these 5% and 7% of patients who did not meet the established diagnostic criteria not excluded from the analysis?

Overall, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and reinforce the study's message. Predictors of ischemic stroke in patients with GCA may not only be age and arterial hypertension, but also other classic risk factors for ischemic stroke such as diabetes, smoking, hyperlipidemia, atrial fibrillation, acquired or hereditary coagulopathies, and others that were not included in the analysis.

Declarations
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