Reviewer's report

Title: Clinical significance of biomarkers and neuropsychological performances in patients with temporal lobe epilepsy

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Reviewer: Ioannis Karakis

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This is a cross sectional study assessing the predictive value of certain serum biomarkers for cognitive performance and radiological abnormalities in patients with non-surgical TLE and lack of psychiatric comorbidities.

The authors concluded that certain biomarkers such as HSP70 could be treated as a stress biomarker in TLE predicting poor memory scores and decreased hippocampal volume and that also extratemporal regions manifesting volume loss are common in this population compared to controls.

There are several advantages to the study:

1) The identification of reliable biomarkers of epileptogenesis and epileptogenicity for research and clinical applications for the epilepsy community is high priority and in that sense this paper addresses an important need.

2) An attempt was made to concentrate on a specific study population and exclude potential confounders in the past medical history.

3) Several serologic markers were checked in a standardized fashion and subsequently correlated with numerous clinical, radiologic and neuropsychologic parameters related to epilepsy

On the other hand:

1) Due to its cross sectional design this study cannot differentiate between reactive and pathogenic changes. In other words it is unclear whether the changes in the serum biomarkers identified are implicated in the process of epileptogenesis and epileptogenicity or represent the outcome of other, under recognized nosogenic processes. Unless a longitudinal follow-up study design is implemented to characterize the evolution of these biomarkers with the clinical and radiological endpoints of interest, safe conclusions cannot be drawn.

2) The current study cannot differentiate between biomarkers of epileptogenesis vs epileptogenicity. The population under study has established TLE and it is unclear how early in the disease genesis or course the biomarker and related abnormalities took place. Risk factors of epileptogenesis (e.g. genetic predisposition, history of childhood febrile seizures, etc) both in the disease and control group that may be linked to the abnormalities identified have not been explored.
3) As mentioned in the limitations, the duration, type and dosing of antiepileptic treatment was not adequately taken into account. That on its own may have a significant impact not only in the levels of the measured biomarkers but also in the neuropsychological and even radiological outcomes. Similarly, comorbidities other than overt psychiatric illnesses that were controlled for may indirectly affect these biomarkers.

4) The biomarker measurements and neuropsychological tests were performed presumably during the interictal state but without concomitant EEG monitoring it is impossible to ascertain that. Moreover, despite certain tools utilized such as the MMSE or the CDR may not necessarily be the most suitable for the epilepsy population.

5) The segregation of disease severity in two groups, while useful, cannot be always representative of the reality since rare but prolonged seizures (i.e. status) may have more impact than more, short lasting events.

A biomarker in epilepsy can be useful if it can predict which risk factors would materialize in epilepsy down the road, if it can predict the course of the disease and response to various treatments and if it can help identify potential surgical candidates and localize their epileptogenic zones.

The currently proposed biomarkers do not seem to serve any of these purposes yet. However they constitute important contributions to our current knowledge in that field, setting the basis for future longitudinal studies to address the paramount issues of epileptogenesis and epileptogenicity.

On the whole, this paper should be accepted and an effort should be undertaken to address some of the aforementioned limitations, acknowledge the rest and discuss about the future perspectives on the topic.

Declaration of competing interests:

I declare that I have no competing interests.