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# Clinical Immunology

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## Letter to the Editor

### Response to “Comment on Mastellos and colleagues and efficacy of complement-targeting drugs in COVID-19”

We read with great interest the comment submitted by Drs. Ferreira de Miranda Santos and Ribeiro de Barros Cardoso. The authors draw their hypothesis from recent evidence that genetic variations in key complement components, such as C4, appear to modulate susceptibility to neuropsychiatric disorders (e.g. schizophrenia) partly by mediating aberrant complement-dependent synaptic pruning and neuroinflammation in a sex- and age-dependent fashion (1, 2). In this respect, the authors speculate on the potential contribution of C4 allelic variants to neuropsychiatric perturbations (e.g. delirium) that affect a proportion of critically ill COVID-19 patients or ICU-admitted patients in general. While this is an interesting hypothesis on its own merit, worth pursuing in an independent study, it is marginally related to the conceptual basis, rationale or scope of our study. Our pharmacologic complement intervention does not emulate the complex genetic landscape that dictates a patient's predisposition to develop neurological manifestations following SARS-CoV-2 infection.

Furthermore, we have transiently treated COVID-19 patients with C3 or C5 inhibitors in an acute clinical setting, with the aim of comparing the biological efficacy of these two therapeutic strategies against key markers of thromboinflammation. It is highly unlikely that transient, systemic delivery of complement inhibitors would result in clinically overt neurological changes in this context.

Testing the hypothesis that complement allelic variations may influence neurological manifestations during COVID19 would require the conduct of a separate study; one that would systematically genotype

COVID-19 patients in multiple susceptibility loci, including complement genes, in order to correlate such genetic variants with the frequency and phenotype of neuropsychiatric manifestations.

We hope that these comments may help clarify the context and scope of this letter.

#### References

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