Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Immunology 222 (2021) 108618

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Letter to the Editor

Commentary on "Complement C3 vs C5 inhibition in severe COVID-19: Early clinical findings reveal differential biological efficacy" by D.C. Mastellos et al.

To the Editors,

We read with great interest the report by Mastellos and colleagues on the efficacy of complement-targeting drugs for abrogating various components of hyper-inflammation responses in cohorts of patients presenting with severe COVID-19 [1].

These findings obviously point to an important role for complement in the physiopathology of COVID-19. They also raise the hypothesis that complement is involved in the manifestation of delirium, a clinical symptom and a medical complication observed in typical severe cases of COVID-19 [2], but also in 80% of patients under treatment in intensive care units [3,4]. Confirmation of this hypothesis will justify examining if genotypes of complement components, especially C4, and the clinical symptom of delirium itself are useful as prognostic markers that can guide certain interventions for ICU patients presenting with severe COVID-19. The facts that support this hypothesis and the candidate biomarkers are as follows.

Both schizophrenia [5] and delirium [6], including the delirium of critically ill COVID-19 patients [7] have recently been shown to be heritable conditions. While changes in mental functions in psychiatric diseases such as schizophrenia do not, by definition, meet the criteria for delirium, psychotic symptoms are components of delirium. Indeed, Charlton and Kavanau [8] have proposed a model that integrates delirium and psychosis and that also places delirium as a spectrum of manifestations in psychiatric disease.

Importantly, through a meta-analysis of genome-wide association studies on schizophrenia, Sekar and colleagues found an association between phenotype, i.e., schizophrenia or health, and alleles of the complement component 4 (C4) genes [9]. Also importantly, these alleles generate levels of C4 expression in the brain that vary widely and are associated with phenotype. Furthermore, those authors also showed that C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. Of even further interest is the fact the genetic variants of C4 explain sex biases for many diseases in men [10], of which COVID-19 is probably the most recent and currently notorious example.

It is therefore reasonable to hypothesize that complement may participate in the generation of delirium that frequently occurs in critically ill patients, including severe COVID-19. Mastellos and colleagues did not address delirium in the report involving their cohorts and it would be interesting to make this observation in future clinical trials of the C5-targeting monoclonal antibody eculizumab and of the compstatin-based C3-targeted drug candidate AMY-101, both being components that are downstream from C4 in the complement cascade.

Acknowledgments

The authors acknowledge funding for their COVID-19 studies by the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP, grant numbers 2020/09093-5 and 2020/05270-0.

Declaration of Competing Interest

None.

References

[1] D.C. Mastellos, B.G.P. Pires da Silva, B.A.L. Fonseca, et al., Complement C3 vs C5 inhibition in severe COVID-19: Early clinical findings reveal differential biological efficacy, Clin Immunol. 220 (2020) 108598.
[2] S.R. Beach, N.C. Praschan, C. Hogan, et al., Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement, Gen. Hosp. Psychiatry 65 (2020) 47–53.
[3] E. Wesley, A. Shintani, B. Truman, et al., Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit, JAMA 291 (2004) 1753–1762.
[4] J.I. Salluh, M. Soares, J.M. Teles, et al., Delirium Epidemiology in Critical Care Study Group. Delirium epidemiology in critical care (DECCA): an international study, Crit. Care 14 (2010) R210.
[5] K.S. Kendler, S.R. Diehl, The genetics of schizophrenia: a current, genetic-epidemiologic perspective, Schizophr. Bull. 19 (1993) 261–285.
[6] N. Stoicea, S. McVicker, A. Quinones, et al., Delirium - biomarkers and genetic variance, Front. Pharmacol. 5 (2014) 75.
[7] M.K.F. Williams, M. Freydin, M. Mangino, et al., Self-reported symptoms of COVID-19 including symptoms most predictive of SARS-CoV-2 infection, are heritable, medRxiv (2020). https://doi.org/10.1101/2020.04.22.20072124.
[8] B.G. Charlton, J.L. Kavanau, Delirium and psychotic symptoms - an integrative model, Med. Hypotheses 58 (2002) 24–27.
[9] A. Sekar, A.R. Bialas, H. de Rivera, et al., Schizophrenia risk from complex variation of complement component 4, Nature 530 (7589) (2016) 177–183.
[10] N. Kamitaki, A. Sekar, R.E. Handsaker, et al., Complement genes contribute sex-biased vulnerability in diverse disorders, Nature 582 (7813) (2020) 577–581.

Isabel Kinney Ferreira de Miranda Santos[a,*], Cristina Ribeiro de Barros Cardoso[b]

[a] *Department of Biochemistry and Immunology, Ribeirão Preto School of Medicine, University of São Paulo, Brazil*

[b] *Department of Clinical Analysis, Toxicology and Food Sciences, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil*

[*] Corresponding author.
E-mail address: imsantos@fmrp.usp.br (I.K.F. de Miranda Santos).

DOI of original article: https://doi.org/10.1016/j.clim.2020.108617.

https://doi.org/10.1016/j.clim.2020.108618
Received 10 October 2020; Accepted 23 October 2020
Available online 27 October 2020