Do cross-reactive antibodies cause neuropathology in COVID-19?

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Neurological symptoms are seen in patients with COVID-19 and can persist or re-emerge after clearance of SARS-CoV-2. Recent findings suggest that antibodies to SARS-CoV-2 can cross-react with mammalian proteins. Focusing on neurological symptoms, we discuss whether these cross-reactive antibodies could contribute to COVID-19 disease pathology and to the persistence of symptoms in patients who have cleared the initial viral infection.

During the early months of the COVID-19 pandemic, intense clinical and basic scientific research has helped us to understand the pathogenic potential of SARS-CoV-2 and the spectrum of clinical phenotypes it causes, which range from asymptomatic infections to respiratory failure and multi-organ dysfunction. Promising results have emerged from passive immunization, therapeutic intervention and active vaccination trials. It has also become clear that successful clearance of SARS-CoV-2 cannot guarantee the complete remission of symptoms and that severe symptoms can occur in the absence of virus.

Recent findings suggest that pathological inflammation may be one mechanism of disease that leads to severe respiratory symptoms, cardiovascular events and coagulopathies, potentially explaining the clinical benefit seen in patients treated with corticosteroids[1]. Another mechanism could be virus-induced autoimmunity, which may — owing to the persistence of autoreactive T cells and antibodies — endure after the acute phase of infection or even develop after viral clearance. In increasing numbers of patients with COVID-19 or post-COVID-19, neurological complications have been observed that include disabling fatigue, anosmia, Guillain–Barré syndrome and encephalopathy[2,3]. It is well known that anti-pathogen antibodies that cross-react with host proteins can cause neurological symptoms, and this is exemplified in Guillain–Barré syndrome, a post-infectious neuropathy in which antibodies cross-react with self-glycolipids on peripheral nerves. Could similar mechanisms be involved in the neurological symptoms seen in patients with COVID-19?

Emerging clinical reports (some of which are yet to be peer reviewed) suggest that self-reactive antibodies are present in some patients with COVID-19 and can reach the brain[4–6]. In a series of critically ill patients with COVID-19 who had neurological symptoms — including myoclonus, seizures, delirium and encephalopathy — we detected blood–brain barrier dysfunction, neuronal damage and high levels of autoantibodies in cerebrospinal fluid that target endothelial, glial and neuronal epitopes[4]. Similarly, other groups have detected autoantibodies that target different brain areas in SARS-CoV-2-infected patients who are suffering from autoimmune encephalitis[5,6].

In a recent study designed for an entirely different purpose — namely for the generation of patient-derived virus-neutralizing monoclonal antibodies to treat infected patients — we identified a fraction of high-affinity SARS-CoV-2-neutralizing antibodies that cross-react with mammalian self-antigens, including self-antigens found in the central nervous system[7] (FIG. 1). High-affinity SARS-CoV-2-neutralizing antibodies typically have low levels of somatic hypermutations[8], suggesting that extensive germinal centre reactions are not required for the generation of potent antibodies. However, fewer cycles of affinity maturation can increase the risk of antibody auto-reactivity. The emergence of post-viral neuropathological autoimmunity has precedent in neurology. For example, herpes simplex virus encephalitis can promote the development of autoantibodies targeting the NMDA-type glutamate receptor, resulting in autoimmune encephalitis that can manifest with psychosis, epileptic seizures, amnesia or vegetative symptoms[9,10].

The identification of autoantibodies in neurologically ill patients with COVID-19 together with the demonstration of mammalian cross-reactivity of some SARS-CoV-2 monoclonal human antibodies raises important questions. Can cross-reactive SARS-CoV-2 antibodies be pathological and cause post-COVID-19 neurological symptoms? Prospective studies should aim to determine the frequencies and levels of their occurrence and any correlation with clinical phenotypes. Generation of monoclonal SARS-CoV-2 antibodies should be expanded to patients with neurological symptoms and involve B cells and antibody-secreting cells in the cerebrospinal fluid. Further necessary experiments will include the identification of target antigens, electrophysiology and functional assays using neuronal and glial cell cultures or the administration of monoclonal human antibodies into the brains of experimental animals.

It remains to be seen whether the same cross-reactive antibodies cloned from convalescent donors are present in

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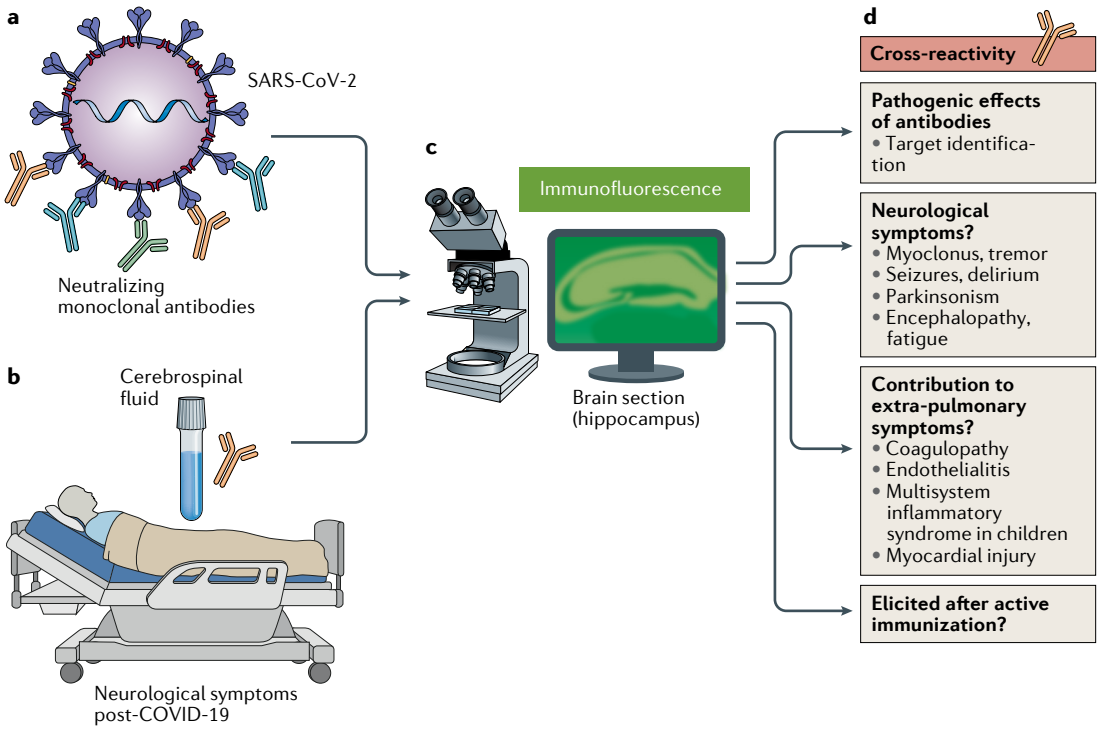

Fig. 1 | **Neutralizing SARS-CoV-2 antibodies can be autoreactive. a** | A fraction of SARS-CoV-2-binding monoclonal antibodies that have been derived from patients with COVID-19 can cross-react with mammalian tissue antigens. **b** | Similarly, antibodies detected in cerebrospinal fluid from patients with COVID-19 can bind to vessel, muscular and neuronal autoantigens. **c** | Indirect immunofluorescence using mouse brain (and further organ) sections has demonstrated specific autoantibody binding. **d** | Potential implications of antibody cross-reactivity that require urgent research.

the cerebrospinal fluid of patients with COVID-19-associated neurological abnormalities. Likewise, the potential role of self-reactive antibodies in further extra-pulmonary symptoms, such as coagulopathy, endothelialitis, multisystem inflammatory syndrome in children and myocardial injury, awaits investigation and will need to be differentiated from already established mechanisms, such as hyperinflammation and cytokine storm, as well as direct viral damage. If confirmed, new treatment strategies including immunotherapy might be used to treat virus-associated autoimmunity.

Could post-COVID-19 autoimmunity become a long-term health issue? The current pandemic and the emergence of multiple post-COVID-19 neurological abnormalities including fatigue or movement disorders are strikingly reminiscent of 'encephalitis lethargica', a severe unexplained brain disease that affected more than one million individuals during the 1918 'Spanish flu' pandemic. Thus, prospective cases should be collected in clinical registries, paralleled by immunological phenotyping including the role of self-reactive antibodies. Moreover, it will be important to examine whether cross-reactive virus-neutralizing antibodies can also occur after active immunization. Given the lack of self-reactivity seen with the majority of SARS-CoV-2-neutralizing monoclonal antibodies, the development of efficacious and safe vaccines is clearly possible. However, ongoing vaccination trials should closely investigate the induction of potential tissue-reactive antibodies and related clinical signs.

In summary, cross-reactive antibodies generated in response to SARS-CoV-2 may contribute to some of the clinical phenotypes seen in COVID-19 and could provide a mechanistic explanation for the persistence of symptoms in patients who have recovered from initial viral infection. Although preliminary, these findings suggest that monitoring for self-reactive antibodies and post-challenge autoimmunity should be incorporated into vaccination trials.

1. Horby, P. et al. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2021436 (2020).
2. Helms, J. et al. Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med.* **382**, 2268–2270 (2020).
3. Paterson, R. W. et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* https://doi.org/10.1093/brain/awaa240 (2020).
4. Franke, C. et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Preprint at *medRxiv* https://doi.org/10.1101/2020.07.01.20143214 (2020).
5. Mulder, J. et al. Autoimmune encephalitis presenting with malignant catatonia in a 40-year-old male patient with Covid-19. Preprint at *medRxiv* https://doi.org/10.1101/2020.07.23.20160770 (2020).
6. Delamarre, L. et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *Neurol. Neurosurg. Psychiatry* **91**, 1004–1006 (2020).
7. Kreye, J. et al. A therapeutic non-self-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 hamster model. *Cell* https://doi.org/10.1016/j.cell.2020.09.049 (2020).
8. Kreer, C. et al. Longitudinal isolation of potent near-germline SARS-CoV-2-neutralizing antibodies from COVID-19 patients. *Cell* **182**, 843–854 (2020).
9. Armangue, T. et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol.* **17**, 760–772 (2018).
10. Prüss, H. et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann. Neurol.* **72**, 902–911 (2012).

Competing interests
The DZNE and Charité – Universitätsmedizin Berlin have filed a patent application on therapeutic SARS-CoV-2 monoclonal antibodies on which J.K., S.M.R. and H.P. are named as inventors.