

Short Communication

Serum antineuronal antibodies in patients with post-COVID-19 condition – association to intensive care

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ABSTRACT

Post-COVID-19 condition (PCC), characterized by persistent symptoms following SARS-CoV-2 infection, is a global health challenge. Neurological symptoms are common in PCC, and immune-mediated mechanisms have been proposed as potential contributors. We set out to systematically explore serum antineuronal antibodies in patients with PCC and clinical factors associated with seropositivity.

Our prospective, single-center cohort study included adult patients with a confirmed SARS-CoV-2 infection at least three months prior and a diagnosis of PCC. Serum and cerebrospinal fluid (CSF) samples were analyzed for the presence of antineuronal antibodies. A control group with confirmed SARS-CoV-2 infection but without PCC symptoms was included, age-, sex- and time from acute infection to sampling –matched to seropositive cases of PCC.

Among 314 consecutive patients with PCC, 38 (12.1 %) tested positive for serum antineuronal antibodies. CSF analysis was performed for a subset; however, no intrathecal autoantibodies were detected. The most prevalent serum autoantibodies targeted CASPR-2 (n = 7, 18.9 %), neurofascin-186 (n = 5, 13.2 %), and glycine receptor (n = 4, 10.8 %). Multinomial logistic regression identified intensive care unit (ICU) admission during acute COVID-19 as the only significant predictor of autoantibody positivity (OR 3.4; 95 % CI: 1.0–10.4). Of the 35 control subjects, two (5.7 %) tested seropositive: one with low titer myelin oligodendrocyte glycoprotein antibodies and another with borderline myelin antibody levels. None of the patients met criteria for autoimmune encephalitis, and neurological assessments and brain magnetic resonance imaging were unremarkable. Neuropsychological testing showed a trend toward impairments in attention and executive functions among seropositive individuals.

Thus, there was no significant difference in the prevalence of serum antineuronal antibodies in PCC compared to post-infection controls, and the association between seropositivity and ICU admission suggested systemic immune activation rather than a specific autoantibody-mediated mechanism. It remains unclear whether observed neuropsychological deficits are attributable to autoantibodies or the effects of critical illness.

1. Introduction

Post-COVID-19 condition (PCC) is defined by the World Health Organization (WHO) as a clinical syndrome affecting individuals with a history of probable or confirmed SARS-CoV-2 infection, in which symptoms typically emerge around three months after the acute phase and cannot be explained by an alternative diagnosis (Soriano et al.,

2022). These symptoms persist for at least two months and commonly include chest pain, dyspnea, musculoskeletal pain, anosmia or ageusia, paresthesia, limb heaviness, and general fatigue (Ballering et al., 2022). The risk of developing PCC is estimated to be around 5 % following infection with the Omicron variant and 10–20 % for earlier variants (Antonelli et al., 2022; The, 2023), by which millions globally have been affected by PCC during their recovery.

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Neurological symptoms are among the most frequently reported in patients with PCC (pwPCC) (Haidar et al., 2022; Romoli et al., 2020) and include cognitive impairment, headache, dizziness, neuropathic pain, hyposmia, hypogeusia, and movement disorders. Several mechanisms have been proposed to explain these symptoms. One hypothesis is that the immune response to SARS-CoV-2 triggers an inflammatory cascade affecting the nervous system, possibly through the generation of antibodies that target neuronal antigens and induce autoimmune-mediated neurological dysfunction (Valencia Sanchez et al., 2021). A recent study identified antibodies against brainstem proteins in patients with acute COVID-19, which could influence cognition and respiratory control (Lucchese et al., 2022). Other proposed mechanisms include central nervous system (CNS) metabolic disturbances (Yin et al., 2024; Klein et al., 2023), endothelial dysfunction leading to microvascular injury and disruption of the blood–brain barrier (Heneka et al., 2020), and the presence of persistent viral reservoirs in neural tissue. Direct viral invasion of neural cells has also been suggested (Meinhardt et al., 2021). Psychological stress and complications related to critical illness, such as hypoxia and prolonged immobility, may further contribute to neurocognitive sequelae in pwPCC. In addition, dysautonomia—manifesting as orthostatic intolerance, palpitations, and gastrointestinal disturbances—has been observed in pwPCC and reflects autonomic nervous system involvement (Astin et al., 2023). Autoimmune encephalitis following SARS-CoV-2 infection has been reported in the literature, with for example targeting of the NMDA receptor (Valencia Sanchez et al., 2021; Payus et al., 2022). However, the prevalence and role of antineuronal antibodies in PCC remains unclear. An association between the presence of autoantibodies in serum and/or cerebrospinal fluid (CSF) and cognitive deficits in this condition has been reported (Franke et al., 2023).

The objective of our study was to assess the prevalence of serum antineuronal antibodies in a consecutive, unselected cohort of pwPCC followed at a population-based post-COVID-19 outpatient clinic. In a subset of patients, CSF was analyzed to evaluate the presence of intrathecal autoantibodies. Clinical characteristics were compared between seropositive and seronegative pwPCC, and a control group of individuals with a confirmed SARS-CoV-2 infection but no PCC symptoms were also included.

2. Methods

2.1. Data collection

This prospective single-center cohort study was conducted at the Clinic for Long-Term Effects of COVID-19 at the Helsinki University Hospital from June 2021 to May 2023. The study included consecutive patients who met the following inclusion criteria: diagnosis of PCC, age ≥ 16 years and by a PCR or antibody testing confirmed COVID-19 diagnosis at least 3 months prior. All patients gave informed consent. Patients who were unable to complete the forms in Finnish, had ongoing drug abuse issues, or found participation unreasonably inconvenient were excluded from the study. The cohort primarily consisted of pwPCC evaluated at the referral letter to have a need for rehabilitation and thus a moderate to severe presentation, most of whom were of working age.

All patients underwent a comprehensive clinical interview and examination based on their presenting symptoms. When necessary, consultations were held with specialists, including pulmonologists, cardiologists, physiatrists, neurologists, endocrinologists, and psychiatrists, among others. Appropriate diagnostic tests were ordered, such as brain magnetic resonance imaging (MRI), spirometry, and assessments of the autonomic nervous system. Additionally, all patients underwent standardized laboratory investigations (including the serum neuronal autoantibodies screening test) according to protocol to rule out other potential causes of their symptoms. Furthermore, all patients completed structured questionnaires that included screening for possible depression and anxiety. All patients reported symptoms typical

of PCC.

A control group of 35 individuals with confirmed prior SARS-CoV-2 infection but without PCC symptoms was also included. Controls were matched to seropositive PCC cases by age, sex, and time interval from acute infection to sample collection.

2.2. Antineuronal antibodies

To determine the presence of antineuronal antibodies targeting specific antigens, the sera samples and CSF samples, if available, were subjected to testing. This was performed by the diagnostic grade laboratory of Stöcker laboratory, Lübeck, Germany, using fixed cell-based assay of transfected HEK293 cells that expressed the recombination target antigens, and using rat brain slices. The antibodies tested included those directed against Hu, Ri, ANNA3, Yo, Tr/DNER, myelin, Ma (Ma1, Ma2/Ta), GAD65, amphiphysin, aquaporin 4, NMDA receptor, AMPA receptor, GABA- a receptor, GABA b receptor, LGI1, CASPR2, Zic4, DPPX, glycine receptors, mGluR1, mGluR5, Rho-GTPase activating protein 26, ITPR1, Homer 3, MOG, recoverin, neurochondrin, GluRD2, flotillin 1/2, IgLON5, CARPVIII, neurexin-3a, ERC1, Sez6I2, AP3B2, contactin 1, neurofascin 155, neurofascin 186, AT1A3, KCNA2, dopamine receptor 2, with all three immunoglobulin isotypes (IgA, IgG, and IgM) evaluated, the prevalence of antineuronal antibodies using this methodology in healthy controls is 0–2 %.

2.3. Clinical parameters

We compiled a comprehensive set of clinical data for our study cohort, including brain MRI, neurological evaluations, medical history assessments, medication records and neuropsychological assessments encompassing attention and executive control, processing speed, psychomotor skills, visual-spatial reasoning, memory, and language functions. The following assessment methods were used in neuropsychological testing: Verbal fluency test (Benton, 1994); WAIS-IV (Wechsler Adult Intelligence Scale, Fourth edition; block design, similarities, digit span) (Wechsler, 2008); WMS (Wechsler Memory Scale; logical memory, immediate and delayed) (Wechsler, 1997); TMT (Trail Making Test) A & B (Reitan and Wolfson, 1985); Boston naming test (Kaplan et al., 1983); CNSVS (Computerized Neurocognitive Screening Vital Signs): verbal memory test (VBM), visual memory test (VIM), symbol digit coding (SDC), finger tapping test (FTT), Stroop test (ST), shifting attention test (SAT), continuous performance test (CPT), four-part continuous performance test, non-verbal reasoning (Gualtieri and Johnson, 2006) and psychologist interview on cognitive symptoms and history (Virrantaus et al., 2023).

2.4. Ethical considerations

The study was approved by the Ethical Committee of Helsinki University Hospital (permit number HUS/1493/2021), and the institutional review board of Helsinki University Hospital gave approval for studying the laboratory tests and clinical parameters recorded during diagnostics and follow-up at the Long-Term Effects of COVID-19 outpatient clinic. All patients gave informed consent.

2.5. Statistical analyses

Statistical analyses were performed with SPSS software version 25 (IBM, New York). Demographic data was described by means and standard deviations (SD) for normally distributed variables and medians and ranges otherwise. We compared continuous variables by the Mann-Whitney *U* test and categorical variables by Fisher's exact test. We used logistic regression analysis for continuous variables. A *p*-value of < 0.05 was considered statistically significant.

3. Results

Of the 314 pwPCC included in the study, 38 (12.1 %) tested positive for serum antineuronal antibodies. In this group, seven individuals (18.4 %) also underwent CSF analysis, where no intrathecal antibodies were detected. CSF was also analyzed for 5 of 276 seronegative individuals, with negative findings (Fig. 1).

We saw no differences in age at sampling, sex or time from acute illness to sampling between seropositive and seronegative patients (Table 1). Twelve seropositive patients (31.5 %) were hospitalized during acute COVID-19, which was significantly more than in the seronegative group (7.6 %, $p < 0.0001$). Of the hospitalized seropositive patients, eight (21 %) had been admitted to an intensive care unit (ICU). Common symptoms included fatigue, sleep disturbances, reduced exertion tolerance, cognitive deficits, pain, dyspnea, headache, and cardiovascular issues; no differences between the groups emerged. Brain MRI was performed for 27 seropositive patients (71 %), with no findings consistent with autoimmune encephalitis. One ICU patient exhibited cerebral microhemorrhages and incidental findings included a meningioma and an acoustic neurinoma; age-related vascular changes were seen in older patients. Neurological examinations were unremarkable.

The most common autoantibodies were against CASPR-2 (18.4 %), neurofascin-186 (13.2 %), and glycine receptor (10.5 %) (Table 2). All antibodies belonged to the IgG subclass, with titers ranging from 10 to 320. All detected autoantibodies were verified using fixed CBA; for altogether four patients, there was staining on rat brain slices, but no exact target antigen identified (Table 2). Multinomial logistic regression identified ICU admission as the only significant predictor of antibody seropositivity (OR 3.4; 95 % CI: 1.0–10.4; Table 3). Symptom profiles did not differ according to antibody specificity: patients with the same antibodies exhibited heterogeneous symptoms, most commonly fatigue, reduced exercise tolerance, cognitive impairment, musculoskeletal pain, and cardiac arrhythmias.

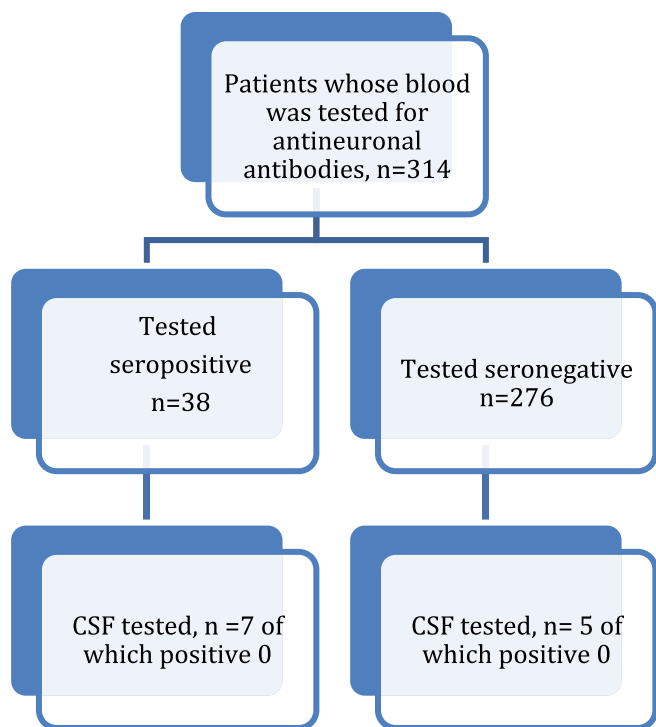


Fig. 1. Flow chart on forming the study cohort. Among the 314 patients tested, 38 (12.1%) had positive serum antineuronal antibodies. Cerebrospinal fluid (CSF) was subsequently analyzed from 7 seropositive patients, but no autoantibodies were detected intrathecally. Similarly, in 5 seronegative patients, no autoantibodies were found in the CSF.

Table 1

Demographic and clinical characteristics of seropositive and seronegative pwPCC.

Variable	Seropositive (N = 38)	Seronegative (N = 276)	p value
Age at sampling, mean in years (SD)	44.5 (10.4)	43.6 (10.6)	NS
Female, n (%)	23 (60.5 %)	149 (53.9 %)	NS
Time from acute illness to sampling, mean in days (SD)	253 (161)	263 (174)	NS
In-hospital treatment during acute illness, n (%)	12 (31.5 %)	21 (7.6 %)	0.0001

SD standard deviation, NS not significant.

Table 2

Detected serum antineuronal antibodies in the cohort. Titers and reference values for all the autoantibodies are given.

Antibody target	Number of patients (% of seropositive)	Titers (N)	Reference value
CASPR2	7 (18.4 %)	10 (N = 5); 32 (N = 2)	<10
Neurofascin-186	5 (13.2 %)	32 (N = 1); 100 (N = 4)	<10
Glycine receptor	4 (10.5 %)	10 (N = 1); 32 (N = 3)	<10
GABA-B	3 (7.9 %)	10	<10
Hippocampus and cerebellum (rat brain)	3 (7.9 %)	100	<10
GFAP	2 (5.2 %)	100; 320	<100
NMDAR	2 (5.2 %)	100	<10
mGluR5	1 (2.6 %)	32	<10
ITPR1	1 (2.6 %)	100	<100
Neurochondrin	1 (2.6 %)	100	<100
MOG	1 (2.6 %)	10	<10
Purkinje cells (rat brain)	1 (2.6 %)	100	NA
VGlut2	1 (2.6 %)	320	<100
mGluR2	1 (2.6 %)	100	<10
AQP4	1 (2.6 %)	32	<10

CASPR2 contactin-associated protein-like 2; GABA-B gamma-aminobutyric acid B receptor; GFAP glial fibrillary acidic protein; NMDAR N-methyl-D-aspartate receptor; mGluR metabotropic glutamate receptor; ITPR1 inositol 1,4,5-trisphosphate receptor type 1; MOG myelin oligodendrocyte glycoprotein; AQP4 aquaporin 4; N number of patients; NA not available.

Table 3

Multinomial logistic regression to assess factors associated with antineuronal antibody seropositivity.

		N	OR	95 % CI
			0.1	0–0.4
Age	40–50 (ref)	121		
	18–40	94	0.9	0.4–2.2
	40–50	99	0.9	0.4–2.1
Sex	Male (ref)	98		
	Female	216	0.6	0.3–1.4
Time from infection	Under 180 days (ref)	82		
	Over 180 days	232	1.1	0.5–2.5
Comorbidities	No comorbidities (ref)	231		
	One comorbidity	41	1.6	0.5–4
	Two or more comorbidities	42	2.2	0.8–5.4
Covid-19 treatment	Managed at home (ref)	281		
	Hospitalization	16	0.4	0–2.5
	Intensive care	17	3.4	1–10.4

OR odds ratio, CI confidence interval, ref reference value.

An external control group of 35 individuals with prior SARS-CoV-2 infection but without PCC symptoms was also tested. Age at sampling was for the controls mean 47.4 (SD 9.1) years and for the seropositive

pwPCC mean 44.5 (SD 10.4) years (NS). Time between sampling and positive PCR test was mean 380 (SD 206.1) days for the controls and mean 253 (SD 161) for the seropositive pwPCC (NS). Percentage of females of the controls and seropositive pwPCC was similar (54.3 % vs 60.5 %, respectively; NS). None of the controls had been hospitalized for acute infection. Of the control group, two individuals (5.7 %) were positive for antineuronal antibodies: one with MOG antibodies (titer 32, reference value < 10) and another one with borderline myelin antibodies (titer 100, reference value < 100). Notably, these myelin antibodies do not represent defined antigens such as MOG, MAG, or MBP, but rather present a broader, non-specific staining pattern without a clearly identified autoantigen and are thus regarded of uncertain clinical relevance by the diagnostic laboratory. There was no significant difference in the occurrence of seropositivity between the groups (5.7 % vs 12.1 %, respectively; NS).

In our study of a consecutive, unselected population-based cohort of pwPCC, serum antineuronal antibodies were identified in 12.1 % of participants. The most frequently detected antibodies targeted CASPR-2 (18.4 %), neurofascin-186 (13.2 %), and the glycine receptor (10.5 %). CSF analysis was conducted for a subset of pwPCC where no intrathecal autoantibodies were found. Furthermore, none of the patients showed MRI abnormalities or clinical features consistent with autoimmune encephalitis. Symptom profiles of pwPCC showed no correlation to autoantibody detected, and ICU admission was the only significant predictor of antibody seropositivity, which together suggest a potential link between disease severity and systemic immune activation rather than targeted autoimmunity.

The prevalence of serum antineuronal antibodies in the general population is not well established and may vary depending on the antibody and population studied. Some studies report that up to 5 % of individuals may test positive without clinical signs of autoimmune encephalitis (Flanagan et al., 2023; Lang and Pruss, 2017), while the diagnostic laboratory (Stöcker laboratory, Germany) estimates a prevalence of 0–2 % in healthy controls. In our control group—individuals with prior SARS-CoV-2 infection but no PCC symptoms—the seropositivity rate was 5.7 %, aligning with the upper range of previous estimates. Our finding of 12.1 % seropositivity for pwPCC was not statistically different from the control group although a trend of higher detection was seen, possibly driven by preceding ICU treatment, which was only recorded for pwPCC.

Specific prevalence data for antibodies such as CASPR-2, neurofascin-186, and glycine receptor in healthy individuals are limited. CASPR-2 antibodies are typically associated with autoimmune encephalitis characterized by seizures and memory impairment (Flanagan et al., 2023), neurofascin-186 with chronic inflammatory demyelinating polyneuropathy (CIDP) (Notturmo et al., 2014), and glycine receptor antibodies with motor disorders such as stiff person syndrome (SPS) (Matsui et al., 2018). Our three most common autoantibody-targets were extracellular; Membrane-bound antigens are more likely to be targeted by autoantibodies due to their extracellular accessibility, which may play a role in immune-mediated neurological dysfunction. However, in our study, seropositivity to these antibodies was not accompanied by corresponding clinical syndromes, supporting the hypothesis of bystander activation rather than pathogenic autoimmunity.

Our findings align with the theory of broad immune activation following critical illness. The presence of multiple autoantibody targets in individual patients further supports nonspecific immune responses rather than focused autoimmune pathology. Thus, our data does not support antineuronal antibody-mediated mechanisms as drivers of neurological symptoms in PCC but support a link to critical illness during acute COVID-19, consistent with previous findings (Nersesjan et al., 2023). Additionally, the presence of serum autoantibodies in PCC may reflect broader immune phenomena, such as elevated T follicular helper (T_{fh}) cells that promote antibody affinity maturation (Yin et al., 2024; Kudryavtsev et al., 2022).

Neuropsychological assessments revealed a trend toward deficits in

attention and executive functions among seropositive pwPCC. However, similar cognitive deficits have been observed in post-ICU COVID-19 patients irrespective of antibody status (Ollila et al., 2022). Given the correlation between ICU treatment and seropositivity, it remains unclear whether observed neurocognitive impairments are a consequence of autoantibodies or ICU-related factors. A prior study demonstrated a link between CSF brain-binding antibodies and cognitive dysfunction in pwPCC (Nersesjan et al., 2023), but differences in study design, patient selection, and rates of ICU treatment may explain the divergence in findings.

A major strength of our study is the use of a consecutive, unselected cohort encompassing patients with a range of disease severities—from ICU-treated individuals to those who managed COVID-19 at home. All participants underwent uniform antibody testing, independent of clinical presentation, which minimizes selection bias. However, a limitation is that CSF sampling was declined by many participants due to the invasive nature of lumbar puncture. Further studies are needed to assess the presence of CSF antineuronal antibodies in larger cohorts. The prevalence of antineuronal antibodies in ICU treated patients for any cause should also be investigated.

4. Conclusions

We observed a low prevalence of serum antineuronal antibodies in pwPCC and a significant association with ICU treatment, pointing toward broad systemic immune activation rather than targeted autoimmunity. Our findings do not support antineuronal antibody-mediated mechanisms as a cause of PCC-related neurological symptoms. From a clinical perspective, broad screening for antineuronal antibodies in pwPCC should be approached with caution, and positive results must be carefully interpreted to avoid unnecessary or potentially harmful treatments. It remains, however, unclear whether observed neuropsychological deficits are attributable to autoantibodies or to the effects of critical illness.

CRediT authorship contribution statement

Tatiana Posharina: Writing – original draft, Formal analysis. **Mikko Varonen:** Visualization, Formal analysis, Data curation. **Hanna Jarva:** Methodology. **Mari Kanerva:** Writing – review & editing, Supervision. **Helena Liira:** Supervision, Project administration, Funding acquisition, Data curation. **Sini M Laakso:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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