Prevalence and characteristics of systemic autoimmune diseases-related autoantibodies in convalescent patients after SARS-CoV-2 infection

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COVID-19 has been associated with systemic symptoms that do not appear to be directly caused by SARS-CoV-2. The generation of autoantibodies has been proposed as one of the possible mechanisms that explain this phenomenon. Transient, typically low titer autoantibodies may be detected in a variety of viral illnesses (1). Furthermore, infections have been implicated as an initial environmental trigger of autoimmune diseases (AD) (1). However, the progression of such an immune state to an established AD is rare and usually virally induced autoantibodies typically resolve over time. Although the mechanisms responsible for generating autoantibodies as a result of viral infection remain unclear, molecular or antigenic mimicry between microbial proteins and self-components remain the most likely mechanism (2). To investigate any potential links between SARS-CoV-2 infection and the generation of autoantibodies we examined sera from severely ill convalescent COVID-19 patients.

Convalescent patients aged ≥18 years diagnosed with COVID-19 between March 14 and December 31, 2020 and who required admission to our hospital (6.3% in the Intensive Care Unit, ICU) were studied. Specimens were obtained an average of 89±9 days after diagnosing COVID-19. Patients with a history of systemic AD were excluded. The diagnosis was made based on compatible symptoms confirmed by a positive polymerase-chain-reaction test (81%) or a positive SARS-CoV-2 IgG/IgM rapid test. Patients were tested for the presence of antinuclear antibodies (ANAs), antibodies directed against DNA (anti dsDNA), extractable nuclear antibodies (ENA) and anti-phospholipid antibodies (aPL). Autoantibody determinations were performed with the validated immunoassays and algorithms routinely used by our hospital's laboratory, following the manufacturers' recommendations. Our hospital's Ethics Committee approved the study. 189 patients (105 men) with a mean age 59±7 years were studied. They were discharged after an average of 12±11 days. Six patients had thromboembolic events (4 pulmonary embolism; 2 deep vein thrombosis) after a COVID-19 diagnosis, all were negative following aPL screening. Other data of interest are shown in Table I. We detected ANAs (≥1/160) in 22% of patients, the speckled pattern being the most frequent (54%). Only 2.6% patients had ENAs. No anti-dsDNA antibodies were detected. Finally, 45 patients (24%) had aPL (3 were double positives and 3 triple positives). Lupus anticoagulant (LA) was the most common (10%), followed by anti-beta 2-glycoprotein I (B2GPI) antibodies (8%) and anticardiolipin (aCL) antibodies (5%). However, only 53% (8/15) of patients with B2GPI and 40% (4/10) with aCL had moderate-to-high titres (≥40 UI/mL) (Table II). There were no significant differences between genders.

In our study, we assessed systemic AD-related autoantibodies in specimens from convalescent patients with severe COVID-19 post-hospitalisation. As far as we know, of all the studies of this kind, it is the one with the largest number of patients. In addition, unlike most studies that include newly diagnosed patients and do not yet know whether the detectable autoantibodies will persist after COVID-19 resolution and viral clearance, we analysed samples from patients infected with SARS-CoV-2 after a long period of convalescence (3 months on average). For that reason, the frequency of ANAs (+) and titers found in previous studies during the acute phase of infection were higher than those observed in ours (4, 5), supporting the hypothesis that a decrease in autoantibodies also occurs over time after infection with SARS-CoV-2. Severely ill patients, especially those requiring care in the ICU, are more likely to generate autoantibodies (3-5). Although the severity of COVID-19 in our patients was high, it was lower than that observed in other studies in which some patients died and a high percentage of them required intensive care. Despite this, the frequency of ANAs (+) after 3 months of follow-up was significantly higher than expected in a "healthy", general population from our region (<7.5%) (6). The frequency of ENAs (+) was relatively low and zero for anti-dsDNA, suggesting that future development of systemic lupus erythematous may be relatively rare, although exceptional cases have been described (7). The frequency of aPL in patients diagnosed with COVID-19 reported in the literature is variable (8, 9) and depends on the characteristics of the patient, disease severity, the method used for the determination, the threshold that defines positivity and the moment the sample is obtained, among other factors, since aPL emerge ~35-39 days after disease onset (10). Furthermore, usually, as in our study, they are only determined once. Earlier studies suggest that positivity for aPL may be associated with the thromboembolic complications that occur in many patients with COVID-19. However, in our series none of the 6 patients who presented thrombotic events had aPL. This result is consistent with other studies that suggest that the presence of transient aPL in the context of COVID-19 is not clearly pathogenic (8, 9, 11). Longer-term follow-up could reveal whether the generation of autoantibodies after SARS-CoV-2 infection is long-lasting and whether the occurrence of AD among these patients is greater than expected in the general population.

Table I. Characteristics of the participants.

	All participants (n=189)
Age, years	59 ± 7
Days after (+) for SARS-CoV-2 tests	89 ± 9
Smokers, n (%)	11 (5.8)
pre-COVID-19 TED, n (%)	9 (4.8)
post-COVID-19 TED, n (%)	6 (3.2)
Hs-C reactive protein, mg/L	6.5 ± 15.0
Erythrocyte sedimentation rate, mm/h	16.3 ± 17.6
C3 complement, mg/dl	115 ± 33
C4 complement, mg/dl	31 ± 24
Fibrinogen, mg/dL	292 ± 103
D-dimer, mg/L	0.58 ± 0.62
Haemoglobin, g/dl	14.2 ± 1.5
White cell count, /mm^3	6183 ± 1692
Platelets, x10^3/mm^3	240 ± 75
Ferritin, ng/mL	1073 ± 1160

Table II. Autoantibodies found in convalescent patients with COVID-19.

	All participants (n=189)
Positive for ANA (n, %)	41 (21.7)
Titres	
1/160	34 (18)
1/320	6 (3.2)
>1/320	1 (0.5)
Patterns (n, %)	
Speckled	22 (11.6)
Homogeneous	4 (2.1)
Nucleolar	6 (3.2)
Peripheral and others	9 (4.8)
ENA (n, %)	5 (2.6)
Anti-Ro 52	1
Anti-centromere	1
Anti-PM-Scl100	1
Anti U1-RNP/PCNA	1
No specific	1
Anti dsDNA	0
Antiphospholipid antibodies, n (%)	45 (24)
Lupus anticoagulant	20 (10.6)
IgM Anticardiolipin antibodies	7 (3.7)
IgG Anticardiolipin antibodies	3 (1.6)
IgM anti-β2 -glycoprotein I	9 (4.8)
IgG anti-β2 -glycoprotein I	6 (3.2)
Double positivity (n, %)	3 (1.6)
Triple positivity (n, %)	3 (1.6)

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