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Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long COVID symptoms

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Abstract

Background Autoimmunity has been reported in patients with severe coronavirus disease 2019 (COVID-19). We investigated whether anti-nuclear/extractable-nuclear antibodies (ANAs/ENAs) were present up to a year after infection, and if they were associated with the development of clinically relevant post-acute sequalae of COVID-19 (PASC) symptoms.

Methods A rapid-assessment line immunoassay was used to measure circulating levels of ANAs/ENAs in 106 convalescent COVID-19 patients with varying acute phase severities at 3, 6 and 12 months post-recovery. Patient-reported fatigue, cough and dyspnoea were recorded at each time point. Multivariable logistic regression model and receiver operating curves were used to test the association of autoantibodies with patient-reported outcomes and pro-inflammatory cytokines.

Results Compared to age- and sex-matched healthy controls (n=22) and those who had other respiratory infections (n=34), patients with COVID-19 had higher detectable ANAs at 3 months post-recovery (p<0.001). The mean number of ANA autoreactivities per individual decreased between 3 and 12 months (from 3.99 to 1.55) with persistent positive titres associated with fatigue, dyspnoea and cough severity. Antibodies to U1-snRNP and anti-SS-B/La were both positively associated with persistent symptoms of fatigue (p<0.028, area under the curve (AUC) 0.86) and dyspnoea (p<0.003, AUC=0.81). Pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and C-reactive protein predicted the elevated ANAs at 12 months. TNF-α, D-dimer and interleukin-1β had the strongest association with symptoms at 12 months. Regression analysis showed that TNF-α predicted fatigue (β=4.65, p=0.004) and general symptomaticity (β=2.40, p=0.03) at 12 months.

Interpretation Persistently positive ANAs at 12 months post-COVID are associated with persisting symptoms and inflammation (TNF-α) in a subset of COVID-19 survivors. This finding indicates the need for further investigation into the role of autoimmunity in PASC.