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LETTER TO THE EDITOR

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Significance of IgA antibody testing for early detection of SARS-CoV-2

To the Editor,

Serological detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-specific antibody is usually limited to immunoglobulin M (IgM), IgG, and total antibodies, comprising IgA, IgM, and IgG.[1–3] IgA antibodies are less frequently used for SARS-CoV-2 detection as IgM- and IgG-based assays are the gold standard for serological diagnosis. Traditionally, IgM antibodies are considered as a serological marker of a recent or acute infection. However, SARS-CoV-2-specific IgA, IgM, and IgG can be detected after the onset of symptoms at different time points.[2,3]

The kinetics of seroconversion vary significantly between different antibody detection kits due to differences in SARS-CoV-2 epitopes, antibody isotypes, and variations in analytical sensitivities associated with different chemistries. Antibodies against S protein are generated later than those against the N protein in SARS-CoV-2 infection. Herroelen et al.[4] observed that seroconversion of antibody against S-RBD was earlier than seroconversion against N protein, suggesting that the time of seroconversion being detected depends on the patient's immune condition and the design of the assay. Performance of the antibody kit can be enhanced by the inclusion of IgA with IgG isotypes.[4]

Recent studies showed that IgA might also play an important role in the immune response and disease progression.[5] In a study comparing different assays, it was shown that IgA appeared early in SARS-CoV-2 infection. With a small sample size of patients ($n = 30$), who were IgM-negative and polymerase chain reaction (PCR)-positive for SARS-CoV-2, 26.6% (8/30) of the patients tested positive for IgA at days 5–7 post-onset. Although the samples are limited, these results suggest that the presence of IgA antibodies is superior to IgM as an early serological marker of recent SARS-CoV-2 infections.[6]

Guo et al used an indirect enzyme-linked immunosorbent assay (ELISA) for detection of IgA, IgM, and IgG against SARS-CoV-2 using purified recombinant N protein as antigen.[3] The median duration for detection of IgA and IgM was 5 days after symptom onset and 14 days for IgG.

A commercially available S1-protein-based IgA ELISA assay by Euroimmun was evaluated. The assay had good sensitivity and showed a quantitative relationship with higher neutralizing antibody titers.[1]

Using a SARS-CoV-2 S protein-specific chemiluminescent immunoassay, Yu et al. found that the first day of IgA, IgM, and IgG seroconversion was 2, 5, and 5 days post-symptom onset, respectively. Of 183 samples from 37 patients, the positivity rate of antibodies was 98.9%, 93.4%, and 95.1% for IgA, IgM, and IgG, respectively.[5] The early detection capacity of IgA could be a valuable addition to the IgG assay.[1]

IgA assays showed early detection capacity with low specificity. Not surprisingly, it is puzzling why seroconversion of IgA antibodies can be detected early, sometimes within 2 days of symptom onset.[5] Several possibilities may account for this. Admission time may be mistaken for onset time. Another possibility is a rapidly triggered nonspecific IgA memory response, probably due to previous infections with common cold coronaviruses, resulting in detectable IgA levels within 2 days.[1,7] The third possibility may be rapid T-cell-independent production of IgA in general or by cross-reacting with previously experienced common cold coronaviruses.[8,9]

IgA is abundant in serum, nasal mucus, saliva, breast milk, and intestinal fluids, accounting for 10% to 15% of human immunoglobulins. For acute SARS-CoV-2 infection, IgA detection could be helpful along with IgG in patients with atypical symptoms or when RNA testing is repeatedly negative for a suspected patient.[10]

Low sensitivity renders a saliva IgA assay unsuitable for serological screening of suspected COVID-19 patients.[11] However, it is well-known that IgA plays a central role in mucosal immunity, which is important in protection against respiratory infections. A saliva IgA assay can be of importance to evaluate the level of protective immunity in recovered patients or the efficiency of a vaccine when available in the near future.

Considering the early detection characteristics of IgA, it should be recommended for inclusion in serological test kits. An IgA assay can be valuable when SARS-CoV-2 RNA testing remains negative in patients with suspected chest computed tomography/symptoms or if no PCR facility is available. IgA testing could be a good alternative way to shorten the SARS-CoV-2 diagnosis turnaround time. Importantly, laboratories and clinicians must be familiar with the significance of IgA and know how to interpret the serological testing results. For policymakers, IgA antibody should be given higher priority for implementation in current clinical and public practice.

CONFLICT OF INTERESTS

The author declare that there are no conflict of interests.

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