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Prevalence of Anti-SARS-CoV-2 Antibody in COVID-19 Patients in Japan

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Abstract

The continued spread of coronavirus disease 2019 (COVID-19) has prompted widespread concern around the world, and the World Health Organization (WHO), on 11 March 2020, declared COVID-19 a pandemic. The significance of performing an antibody test against SARS-CoV-2 using serum is to identify asymptomatic SARS-CoV-2 infected individuals. Our research group has been studying the prevalence of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in SARS-CoV-2 infected Japanese individuals. Within 20 days after symptom onset, 100% of patients tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, which was first reported in December 2019 in Wuhan, China. The coronavirus disease 2019 (COVID-19) has been declared a public health emergency of international concern by the World Health Organization (WHO), progress to a pandemic associated with substantial morbidity and mortality. SARS-CoV-2 is genetically related to SARS-CoV, which caused a global epidemic with approximately8100 confirmed cases in more than 25 countries in 2002–2003 [1].The epidemic of SARS-CoV was successfully contained through public health interventions, including case detection and isolation. Airborne transmission of SARS-CoV occurred mainly after days of illness [2] and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset [3].

Immunoglobulins are immunity that protects the body from pathogens such as viruses. Five types of antibodies are working as a biological defense mechanism, but immunoglobulin-M(IgM) and IgG are working as a biological defense action in infectious diseases. IgM is the first antibody produced after a pathogen invades the body. Approximately one week after infection with the pathogen, the amount of IgM in the body increases, and the serum test becomes IgM positive. On the other hand, pathogen-specific IgG becomes positive 3-4 weeks after infection.

Diagnosis of COVID-19 is performed by Polymerase Chain Reaction (PCR) test and antigen of SARS-CoV-2 test [4]. In particular, the prevalence of anti-SARS-CoV-2 IgG(note 1) is 100% in cases 15 days or more after SARS-CoV-2 infection. Therefore, the anti-SARS-CoV-2 IgG test has extremely high diagnostic ability for COVID-19. The results show that in clinical practice, the test for anti-SARS-CoV-2 IgG may be useful especially as a "rule out" test for individuals infected with SARS-CoV-2 and/or COVID-19 cases.

In Japanese individuals with SARS-CoV-2 and/or COVID-19 cases, the expression of anti-SARS-CoV-2 IgG often precedes the expression of anti-SARS-CoV-2 IgM(note 2) (Figure 1).In the textbook, the expression of IgG is induced by the IgM class switch, suggesting the presence of cross-immunity against the N protein of SARS-CoV-2. Perhaps IgG and/or IgM against the common cold virus, the coronavirus, is responding to SARS-CoV-2. However, at this time, it has not been clarified that cross-immunity has an immunological role for SARS-CoV-2.

At National Hospitals in Japan, higher levels of IgM, IgG, and IgA(note 3) antibodies against SARS-CoV-2 were observed in moderate and severe cases of COVID-19 compared with mild cases of COVID-19. From this clinical finding, it is considered that the antibody test is useful as one of the severity prediction test systems required in actual clinical practice.

IgM, IgG, and IgA antibody titers to SARS-CoV-2 were found to decrease faster in COVID-19 severe cases compared to COVID-19 moderate cases. From these clinical findings, it is considered that the antibody against SARS-CoV-2 is not sufficiently produced and maintained as one of the mechanisms of COVID-19 aggravation. Therefore, in Japan as well, it is possible that people with a history of COVID-19 will be infected with SARS-CoV-2 again. Testing for IgA, which is mucosal immunity against SARS-CoV-2 may also be useful in early diagnosis of COVID-19 and determination of severity.

Confirming suspected cases infected with SARS-CoV-2 as early as possible with the help of serological testing could reduce exposure risk during repeated sampling and save valuable reverse transcription PCR (RT-PCR) tests. In our small-scale survey, seven cases with negative nucleic acid by

RT-PCR results and no symptoms showed positive IgG and/or IgM. This highlights the importance of serological testing to achieve more accurate estimates of the extent of the COVID-19 pandemic.

Footnote:

Note 1: IgG is a type of antibody. Representing approximately 75% of serum antibodies in humans, IgG is the most common type of antibody found inblood circulation.

Note 2: IgM is one of severali so types of antibody (also known as immunoglobulin) that are produced by vertebrates. IgM is the largest antibody, and it is the first antibody to appear in the response to initial exposure to anantigen. IgM is used to diagnose infectious diseases. If IgM is found in the patient's serum, it means that he has an infection.

Note 3: IgA, also referred to as sIgA in its secretory form is an antibody that plays a crucial role in the immune function of mucous membranes. The amount of IgA produced in association with mucosal membranes is greater than all other types of antibody combined. In absolute terms, between three and five grams are secreted into the intestinal lumen each day. This represents up to 15% of total immunoglobulins produced throughout the body.

Methods

Study design

A total of 41 COVID-19 patients were enrolled in this cross-sectional study from three designated hospitals belonging to the National Hospital Organization in Japan. These national hospitals affiliated to National Hospital Organization were assigned by the Japan Ministry of Health, Labor and Welfare to admit patients from the three designated areas. All enrolled patients were confirmed to be infected with SARS-CoV-2 by RT-PCR assays on nasal and pharyngeal swab specimens. The median age of these enrolled patients was 48 years (IQR, 34-56 years) and 58.7% were males.

Performance evaluation of the SARS-CoV-2-specific IgG/IgM detection assay

The precision and reproducibility of the SARS-CoV-2 IgG/IgM Test Kit were first evaluated by Sanyou Biopharmaceuticals Co., Ltd. (Shanghai, China). Moreover, 35 serum samples from patients with COVID-19 showing different titers of IgG (range 0.54-169.91) and IgM (range 0.36-89.46) were tested. Each individual sample was tested in three independent experiments, and the coefficient of variation (CV) was used to evaluate the precision of the assay. Finally, 32 serum samples from patients with COVID-19 were assessed using different batches of the diagnostic kit for SARS-CoV-2-specific IgG or IgM antibody; reproducibility was calculated based on the results from two batch experiments.

Ethics statement

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization of Japan (Meguro, Tokyo, Japan). The approved number for this study is 50-201504. In order to carry out this research, the authors attended a research ethics education course (e-APRIN) conducted by Association for the Promotion of Research Integrity (APRIN; Shinjuku, Tokyo, Japan). The approved numbers of e-APRIN are AP0000151756, AP0000151757, AP0000151758, AP0000151769.

Author contributions

T.H.wrotethemanuscript.I.K.carefullyreviewedthemanuscript andcommentedonaspectsofclinicalmedicine,sharedinformati ononclinicalmedicine.

Data availability and Consent to publish

This manuscript is an editorial and does not contain research data. Therefore, there is no research data or information to be published or opened.

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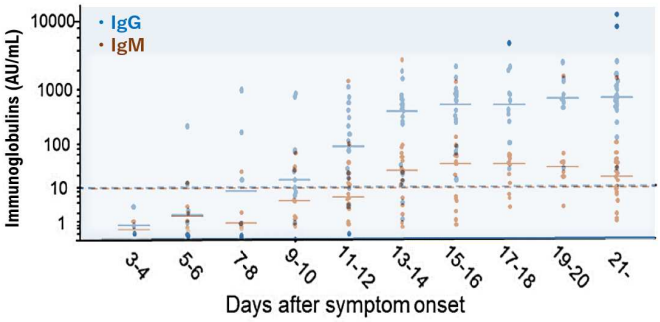

Figure 1.The time courses of serum titers of anti-SARS-CoV-2 antibodies in COVID-19 patients after symptom onset. The titers of SARS-CoV-2 IgM and SARS-CoV-2 IgG were measured with 125 sera collected from RT-PCR-positive patients (n = 41) by using the SARS-CoV-2 IgG/IgM Test Kit. The data are plotted for days 1–2, 3–4, 5–6, 7–8, 9–10, 11–12, 13–14, 15–16, 17–18, 19–20, and ≥ 21 since symptom onset. The bars show the median titers at each timepoint. The broken line shows the manufacturer's cutoff value (10AU/mL). RT-PCR-positive patients, IgM (brown color). RT-PCR-positive patients, IgG (blue color).