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Observational Study

Temporal pattern of humoral immune response in mild cases of COVID-19

Humoral response in mild COVID-19

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Abstract

BACKGROUND

Understanding the humoral response pattern of COVID-19 is one of the essential factors to better characterize the immune memory of patients, which allows understanding the temporality of reinfection, provides answers about the efficacy and durability of protection against SARS-CoV-2, and consequently helps in global public health and vaccination strategy. Most patients who survive infection develop mild COVID-19, so understanding the pattern and temporality of the antibody response of these patients is certainly relevant.

AIM

To investigate the temporal pattern of humoral response of specific IgG in mild cases of COVID-19.

METHODS

Blood samples from 191 COVID-19 RT-qPCR-positive volunteers from the municipality of Toledo/Paraná/Brazil, were submitted to two distinct serological tests, by ELISA, for detection of anti-nucleocapsid IgG. Blood samples and clinical-epidemiological data of the volunteers were collected from November 2020 to February 2021. All assays were performed in duplicate and the manufacturers' recommendations were strictly followed. The data were statistically analyzed using multiple logistic regression; the variables were selected by applying the $p < 0.05$ criterion.

RESULTS

Serum samples from the volunteers spanned a time interval of less than 1 mo to 7 mo between positive diagnosis for COVID-19/symptoms onset and serologic testing for specific IgG. The time periods when the highest number of participants with detectable IgG was observed were 1, 2 and 3 mo. It was observed that 9.42% of participants no longer had detectable IgG antibodies 1 mo only after being infected with SARS-CoV-2

and 1.57% were also IgG negative at less than 1 mo. At 5 mo 3.14% of volunteers were IgG negative, and at 6 or 7 mo 1 volunteer (0.52%) had no detectable IgG. Regarding the period between diagnosis by RT-qPCR/symptoms onset and the date of collection for the study, no statistical significance was observed for any association analyzed. Moreover, considering the age category between 31 and 59 years as the exposed group, the p-value was 0.11 for the category 31 to 59 years and 0.32 for the category 60 years or older, showing that in both there was no association between the pair of variables analyzed. Regarding chronic disease, the exposure group considered was the participants without any comorbidity, so the p-value of 0.07 for the category of those with at least one chronic disease showed no association between the two variables.

CONCLUSION

A temporal pattern of IgG response was not observed, but it is possible suggest that immunological memory is weak and there no association between IgG production and age or chronic disease in mild COVID-19.

Key Words: Humoral response; IgG antibody; Immune memory; Mild cases COVID-19; SARS-CoV-2 infection; Serological test

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Core Tip: This study suggests that there is not until a moment a clear temporal pattern of humoral Response of IgG that indicates a robust immunological memory in mild cases of COVID-19, and in addition, due to the absence of association of IgG responses to the age group, in mild cases the elderly do not seem to be a risk group for infection.

INTRODUCTION

³ COVID-19, a disease caused by SARS-CoV-2, emerged in Wuhan, China, in December 2019 and spread worldwide, very quickly, causing an unprecedented pandemic that impacted healthcare systems, the economy, politics, and social organization. Patients with COVID-19 may present from asymptomatic to critical illness, and symptoms can include fever, cough, sore throat, malaise and myalgia. Some patients may experience gastrointestinal symptoms such as anorexia, nausea, and diarrhea ^[1].

Asymptomatic patients can be assumed to be uninfected, and thus they can be the focus of new outbreaks of the infection by transmitting the virus to healthcare workers or individuals with risk factors ^[1, 2]. According to some studies, risk factors for complications of COVID-19 include advanced age, cardiovascular disease, chronic lung disease, diabetes, obesity and immunosuppression ^[3-7].

Therefore, the influence of comorbidities on the immune response profile and disease susceptibility has been widely discussed. One of the main groups of comorbidities involved in this discussion are diseases of the immune system, such as asthma, rheumatoid arthritis (RA) and autoimmune gastritis (AIG). Although patients with severe asthma have been associated with a higher risk of COVID-19-related death ^[8], studies have indicated that the disease was not statistically associated with increased risk of contracting or being hospitalized due to the disease ^[9, 10].

Regarding the gastrointestinal system, specifically AIG, the data in the literature indicate no relationship between autoimmunity and increased susceptibility to SARS-CoV-2 ^[11]. On the other hand, in relation to RA, a study of patients with rheumatic diseases, 91.89% of whom were autoimmune - with 72.97% referring to RA, and 18.92% of systemic lupus erythematosus showed that cardiovascular manifestations caused by COVID-19 occurred more frequently in patients with rheumatic diseases ^[12].

⁷ According to Chinese data, 81% of individuals infected with SARS-CoV-2 developed mild or moderate COVID-19, 14% developed severe disease, and only 5% developed critical disease ^[13]. Therefore, it is critical to study asymptomatic cases and those with mild symptoms, as they represent a risk of spreading COVID-19 in the world

population. One example is a case in China in which the infection of 71 individuals originated from an asymptomatic case ^[14]. Furthermore, it has been evidenced that mild cases of COVID-19 also cause an increase in the need for primary health care, potentially lasting up to 3 mo ^[15], this can further burden the health care system.

Another point that emphasizes the importance of studying mild cases is the sequelae left by ⁴ the virus. SARS-CoV-2 uses the Angiotensin-converting enzyme 2 (ACE2) as a functional receptor to invade host cells. This enzyme's main function is the regulation of angiotensin 2 and is highly expressed in the lungs, intestine and kidneys ^[16]. This gives the pathogen a high capacity for dissemination ^[16, 17]. Thus, although the main focus of viral infection is the respiratory system, its systemic dissemination can occur, affecting several organs ^[17].

As respiratory sequelae, besides lung damage, the main consequences observed were alterations in taste and smell, such as anosmia, hyposmia, ageusia or dysgeusia ^[17, 18]. Such symptoms were mainly associated with the appearance of symptomatic manifestations of COVID-19, since the gateway of the virus into the body are both the oral and nasal cavities, sites whose epithelial tissue presents receptors for these senses ^[17].

Furthermore, one study demonstrated the high presence of ACE2 in biopsies of the olfactory mucosa, and the enzyme is mainly present in Bowman's glands ^[16]. In addition, other sequelae already reported involve the cardiovascular system, such as heart attack and pulmonary thromboembolism, as well as kidney disease, liver damage, and even neurological changes ^[17].

As for the differences in immune response between mild and severe cases of COVID-19, it was observed that patients with more critical illnesses showed a higher and earlier IgG and IgA response against SARS-CoV-2, as well as high viral neutralization. On the other hand, 75% of patients with mild symptoms developed antibodies and these showed low or even no viral neutralization rate ^[19, 20].

Accordingly, this study set out to evaluate the temporal pattern of IgG anti-SARS-CoV-2 response in mild cases of COVID-19. To this end, the study analyzed data from

patients presenting with the disease between September 2020 and January 2021, prior to the introduction of vaccines.

MATERIALS AND METHODS

Population study and data collection

This study was approved by the Ethics Committee for research with humans of the Setor de Ciências da Saúde - Universidade Federal do Paraná (UFPR)/Brazil (Protocol no. 35872520.8.0000.0102) and all participants signed an informed consent form. Volunteers older than 18 years (393) were tested for COVID-19 by RT-qPCR and 191 were positive. Blood samples and clinical-epidemiological data from the volunteers were collected from November 2020 to February 2021. The clinical-epidemiological data were collected by means of a semi-structured questionnaire. Venous blood was collected from each volunteer in a tube without anticoagulant and the serum was separated by centrifugation (2,000 rpm for 2 min). At this time, COVID-19 vaccines were not yet being applied in Brazil. The 191 individuals diagnosed as positive for COVID-19 by RT-qPCR were included in this study; all were residents of the municipality of Toledo/Paraná/Brazil. Serum samples were submitted to two different serological tests by ELISA: a commercial test - Allserum EIA COVID19 IgG (MBiolog Diagnostics) and a test developed by UFPR/Setor Litoral [21]. Both tests detect anti-nucleocapsid IgG, the secondary antibody is bound to Horseradish peroxidase, chromogenic substrate was Tetramethylbenzidine (TMB) and absorbance reading was performed at 450 nm. All assays were performed in duplicate and the manufacturers' recommendations were strictly followed; assays were analyzed by UV/Vis Multiskan Sky spectrometer (Thermo Fisher Scientific Inc.).

Statistical analysis

A database containing clinical-epidemiological characteristics and serological results was prepared. To perform multiple logistic regression, variables were selected by applying the $p < 0.05$ adjusted odds ratio criterion and using the Maximum likelihood

estimation. The final model was obtained after testing for all possible multiple interactions with subsequent verification of model fit by the Hosmer & Lemeshow method. A ROC (Receiver Operating Characteristic) curve was done to evaluate the ability of the model created to represent reality.

RESULTS

Serum samples from the volunteers spanned a time interval of less than 1 mo up to 7 mo between positive diagnosis for COVID-19/symptoms onset and serological testing for specific IgG. The majority of study participants (62.83%) had detectable IgG for SARS-CoV-2, of which 37.17% had no antibodies at the time of blood collection. Furthermore, as shown in Figure 1, regarding the residence time of IgG detectable by serological testing, only 1 volunteer (0.52%) was IgG positive for 7 mo. The time periods where the highest number of participants with detectable IgG was observed were 1, 2 and 3 mo, with 46 (24%), 25 (13.08%) and 19 (9.94%), respectively. Twelve participants (6.28%) had IgG antibodies at the end of 4 mo, 4 participants (2.09%) remained IgG positive at the end of 5 mo, 8 (4.19%) had IgG for 6 mo, and 5 (2.61%) were IgG positive for less than 1 mo.

Figure 1 also shows that 18 individuals (9.42%) no longer had detectable anti-SARS-CoV-2 IgG antibodies one month after being infected with SARS-CoV-2 and 3 (1.57%) were negative at less than 1 mo. Seventeen volunteers (8.90%) had no detectable anti-SARS-CoV-2 IgG after 2 mo; the same was observed with 16 volunteers (8.37%) at the end of 3 mo and 9 participants (4.71%) at the end of 4 mo. At 5 mo, 6 volunteers (3.14%) had negative anti-SARS-CoV-2 IgG, and at 6 or 7 mo 1 volunteer (0.52%) had no detectable IgG.

According to Table 1, regarding the period of time elapsed between diagnosis by RT-qPCR/symptoms onset and the date of blood collection for the study, no statistical significance was observed between the variables.

Regarding age, most participants were between 31 and 59 years old; 115 (60.21%) individuals were in this age group, 57 (29.84%) were between 18 and 30 years old, and

19 (9.95%) participants were 60 years old or older. Considering the age group between 31 and 59 years as the exposed group, the p value was 0.11 for the category 31 to 59 years and 0.32 for the category 60 years or older, showing that in the categories there was no association between the pair of variables analyzed.

About the presence of chronic diseases, 135 (70.68%) participants had no comorbidity. On the other hand, 45 (23.56%) individuals had one chronic disease, while 10 (5.24%) had two and one (0.52%) participant had three. Regarding this variable, the exposure group considered was the participants without any comorbidity, so that the p value of 0.07 for the category of those with at least one chronic disease showed no association between the two variables studied.

The statistical model showed adequate fit evaluated by the Hosmer & Lemeshow method ($\chi^2=3.656$; GL= 8; $P = 0.887$). The area under the ROC curve showed that the estimated probability model could predict approximately 67.59% of the factors associated with the outcome.

DISCUSSION

The viral proteins play a striking role in diagnosing COVID-19 and monitoring the production of antibodies against the coronavirus by serological tests. In this regard, tests for COVID-19 can be either nucleic acid amplification tests (RT-qPCR) or serological tests. While RT-qPCR is recommended for active coronavirus infection, serological tests are recommended for antibody response (IgM and IgG) [22]. Thus, serologic testing and antibody analysis are useful to verify whether there has been previous exposure to the virus and to qualify the patient's humoral immunity - levels and types of antibodies produced [23].

Therefore, the production of specific antibodies is essential, since they are responsible for effective protection against the severe forms of the disease, even though there are other cells, such as TCD4+ and TCD8+, that act in the immunity process [24]. In addition, IgM antibodies provide the first line of defense during infections, while IgG production provides immunity and long-term memory [25].

The level of antibody production depends on the elapsed time of infection, the severity of the disease, the viral load to which the patient has been exposed, and individual patient characteristics such as age, sex, and pathogen elimination [26]. There may also be variations in the detection of antibody levels according to the sensitivity of the serological test used.

Regarding the elapsed time of infection, while IgM antibodies can be detected at about five days of infection and reach higher rates between two and three weeks of illness, IgG antibodies begin to be produced about 14 days after the symptoms onset and individuals with more severe disease have higher antibody levels [27, 28]. Regarding COVID-19, the observation period for most studies on the production of specific anti-SARS-CoV-2 antibodies is 12 wk, and it is still unclear how antibody titers may change in subsequent periods [29].

In a study conducted in Wuhan, China, after confirmation of coronavirus infection by RT-qPCR, asymptomatic individuals were recruited to detect levels of anti-SARS-CoV-2 antibodies. Of a total of 63 individuals with asymptomatic infections, 38.1% (24 patients) produced no antibodies and 61.9% (39 patients) produced only small titers. Six (11.8%) out of 51 patients with mild symptoms, produced no antibodies and 88.2% (45 patients) produced higher levels of antibodies when compared to asymptomatic patients.

In the same study, in asymptomatic individuals, antibody production started seven days after exposure, peaked between 10 and 25 days, and decreased rapidly thereafter. On the other hand, in individuals with mild symptoms, one day after the onset of symptoms, antibodies were already produced, even at a low level, and titration increased persistently up to 22 days, maintaining high levels for at least 65 days [30].

In a study of 164 participants in Singapore, 19 patients (12%) did not develop neutralizing antibodies against SARS-CoV-2; 44 patients (27%) produced antibodies early (approximately 20 days after symptoms onset), but disappeared in less than 180 days; 46 patients (28%) had neutralizing antibodies for more than 180 days after symptoms onset; 52 patients (32%) had minimal decay of neutralizing antibodies; and

three patients (2%) who had increased neutralizing antibodies 90 days after symptoms onset [31].

Similarly, 140 patients COVID-19 RT-qPCR - positives were recruited for a study in France, in which 44 were admitted to the Intensive Care Unit (ICU), 42 were hospitalized without the need for ICU, and 54 received outpatient treatment only (including eight asymptomatic cases). It was observed that most patients in the different groups produced neutralizing antibodies, but the neutralizing activity was variable, i.e. higher in the group of patients admitted to the ICU, so that only one patient in this group did not develop a neutralizing antibody response at the time of collection. In contrast, 21.9% of hospitalized patients and 25% of outpatients treated did not develop neutralizing antibodies at the time of the study [32].

This study supports the hypothesis that seroconversion is observed more frequently in individuals with severe symptoms and that they have higher antibody titers than mild and asymptomatic cases. This means that plasma titers are approximately eight times higher for severe cases [33].

Therefore, this study focused on understanding humoral immunity in mild cases of COVID-19 and regarding the time period of IgG detection in the serum of patients, similar results were obtained to previous studies. This finding contributes and adds data to the current knowledge about the humoral response against mild COVID-19 as it is a study conducted in a western country with a larger sample size.

However, the temporal profile of the antibody response raised a concern - also cited by other authors [34, 35, 36] - humoral immunity against SARS-CoV-2 does not appear to be durable, especially in individuals with mild or asymptomatic symptoms, which make up the majority of COVID-19 cases. This fact is corroborated by the several doses of the SARS-CoV-2 vaccine, which is currently in its fourth dose in Brazil. On the other hand, it was also found that individuals with low titers or even undetectable levels of neutralizing antibodies can still be protected from subsequent infections, considering that memory B cells are still present in recovered patients [37, 38].

The effect of age on immunity against SARS-CoV-2 has been widely discussed. A cohort study developed by the University of Virginia analyzed the antibody responses in individuals who received two doses of the vaccine BNT162b2 (Pfizer®) or mRNA-1273 (Moderna®) and had a blood sample collected seven to 31 days after the second dose. The results showed that participants aged 50 years and older who received BNT162b2 had lower pre-boost IgG levels than participants younger than 50 years who received the same vaccine. Individuals aged 50 years and older who received BNT162b2 had post-boost IgG levels that were also lower than levels found in younger participants [39].

Another study examined the immune response in elderly participants and younger healthcare professionals following immunization with the BNT162b. The results showed that after the first dose of the vaccine, IgG or IgA levels were lower in older individuals. In addition, elderly participants showed lower IFN- γ and IL-2 production by T cells specific against SARS-CoV-2 when compared to younger individuals [40].

Furthermore, a cohort study conducted in Greece analyzed the IgG response against the protein S of SARS-CoV-2 in a group of individuals after immunization with two doses of the BNT162b2 vaccine. The results revealed that younger patients (21-30 years old) had the highest antibody levels in both periods. [41].

On the other hand, some studies have observed that older patients have been related to higher levels of antibodies against SARS-CoV-2. A study from Union Hospital (Huazhong University of Science and Technology, Wuhan, China) conducted with convalescent patients identified the presence of anti-SARS-CoV-2 antibodies one year after infection, in addition to a difference in IgG response according to the age of the patients. It was observed that the mean IgG antibody level was relatively low in younger convalescent patients (21 to 35 years old), and gradually increased to about 60% in older patients. The mean anti-SARS-CoV-2 IgG level was significantly higher in patients older than 35 years when compared to those younger than or equal to 35 years [42]. In our study, however, we found no statistical significance in the association

between age and anti-SARS-CoV-2 IgG antibody levels. Seroconversion in the group of older individuals was not lower when compared to younger participants, demonstrating that age is possibly not a risk factor when analyzing mild cases of COVID-19.

Regarding the association between COVID-19 and pre-existing comorbidities, those with the highest association are hypertension and obesity, followed by metabolic disease, cardiovascular disease, neurological disease, chronic lung disease, kidney disease, asthma, immunosuppression, gastrointestinal or liver disease, and finally autoimmune disease [43]. According to some authors, COVID-19 has also been associated with type 2 diabetes mellitus (DM2), cancer, and chronic kidney disease [44].

It has been found in numerous studies that individuals with DM2 may have higher severity and mortality from COVID-19. This fact is due to the existing inflammatory condition in these patients, with higher levels of pro-inflammatory molecules, such as cytokines - especially IL-6. In addition, the presence of DM2 causes the response to SARS-CoV-2 to show a large amount of interferon and a delayed Th1 and Th17 response, which contributes to a more intense inflammatory response [45]. An example of this is a study showing that increased viral replication and production of pro-inflammatory cytokines may be related to high glucose concentration [46].

Coronaviruses bind to ACE2 reducing the activity of this receptor and increasing vascular permeability [47]. However, in individuals with systemic arterial hypertension (SAH) and DM, there is a higher number of these receptors when compared to the general population, which may explain the more severe cases of COVID-19 in these patients. Furthermore, SARS-CoV-2 produces endothelial injury, causing an inflammatory vascular state, pro-coagulant state, and a cellular infiltrate, also clarifying the more severe symptoms in individuals with these chronic diseases [48, 49]

In addition, the presence of SAH also determines a pro-inflammatory state - arising from the endothelial dysfunction caused by this disease - leading to excessive activation of coagulation and platelets, in addition to the production of cytokines, antimicrobial peptides, and reactive oxygen species. This excessive activation may not

only cause damage to the respiratory epithelium, but also reduce lung function and increase the local inflammatory response, contributing to further complications from COVID-19 [50, 51].

An important question of the study is how COVID-19 affects patients with autoimmune diseases, such as RA. In a study of 11,122 individuals with COVID-19, patients with RA were found to have a higher chance of hospitalization or death than healthy individuals, and the study used an unadjusted model. However, when adjusting for age, sex, and comorbidities, no greater chance of unfavorable outcomes was observed [51]. Thus, AR is associated with a higher risk of infection and death in patients with COVID-19 when taking into account active AR, the presence of other diseases and the use of medications such as Rituximab, sulfasalazine or other immunosuppressive drugs [52].

Regarding the association between AIG and COVID-19, a study conducted at the Foundation of San Matteo Hospital, Italy, analyzed the susceptibility to COVID-19 in 400 drug-free immunosuppressive patients with autoimmune diseases, 100 of whom had AIG. The findings showed that among the individuals with AIG, seven (7%) had already tested positive for COVID-19, one (1%) required hospitalization for COVID-19, and 43 (43%) were vaccinated for SARS-CoV-2.

Furthermore, considering all investigated autoimmune diseases, molecular nasopharyngeal swabs and/or serology for SARS-CoV-2 testing showed that 33 (8.2%) tested positive [53]. These data are similar to those reported in the general population in the same geographical area in Italy [53], suggesting that the risk of COVID-19 in individuals with autoimmune diseases appears to be the same as in the general population.

Asthma is still being studied as a risk factor for COVID-19. The proposed hypothesis about the occurrence of more severe complications caused by COVID-19 in patients with asthma is due to a possible interaction between the pathobiology of SARS-CoV-2 and asthma. Thus, since the virus causes an intense inflammatory response and asthmatic individuals already have narrowed airways with high mucus production,

pneumonia caused by the virus can lead to severe complications [54]. However, asthma can also lead to favorable outcomes, since it induces a negative regulation of ACE-2 - an enzyme that assists in the process of viral entry of SARS-CoV-2 into lung tissue [55]. On the other hand, a meta-analysis study did not identify a statistically significant increase in mortality and a worse prognosis for COVI-19 in asthmatic individuals [56].

Thus, although there are studies indicating the need for more intensive treatment in individuals with DM2, SAH, and other comorbidities [57], in patients with mild symptoms, this association does not seem to materialize, as the presence of previous diseases was not statistically significant for seroconversion in our study participants.

CONCLUSION

This study suggests that in mild cases of COVID-19 it is not possible to establish a temporality relationship of specific IgG production, raising the hypothesis that such a relationship may, in fact, not exist or that perhaps there is more than one type of relationship since there is interference from several factors - such as age, sex, presence of comorbidities, viral elimination, viral load, among others. It is also suggested that the virus generates a weak and non-lasting immune response in mild cases. Furthermore, a lower production of IgG antibodies was not observed in the elderly and in individuals with previous chronic diseases, leading to the conclusion that in mild cases of COVID-19, these patients may not be a risk group for unfavorable outcomes when analyzing the humoral response.

ARTICLE HIGHLIGHTS

Research background

The molecular test used in the diagnosis of COVID-19 is very specific and sensitive, however, it is not able to detect previous exposure to the virus nor to assess immunological memory. Therefore, serological tests that have this capability are used as tools for understanding the course of the humoral immune response to SARS-CoV-2.

Research motivation

The motivation for this study arose from the serological test developed at the Federal University of Paraná, which in the validation process showed better sensitivity results than commercial tests. A more sensitive test allows specific antibodies to be detected even at low titers, and thus to effectively assess whether there is still a protective antibody response in individuals who have been infected by the disease.

Research objectives

The aim of the research was to see if a pattern of SARS-CoV-2 specific IgG production can be determined according to time from the time of infection of the individual. The data could indicate, for example, the interval between vaccination doses.

Research methods

The research was initiated after approval by the ethics committee. The participants were tested by RT-qPCR by the municipal government, which provided us with the data. Only positive cases were included in the study. Blood collection was performed by our research team and the method used for specific IgG antibodies was the indirect enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed by the statistician of the research group, one of the authors of the manuscript.

Research results

The results of the study showed that there is no time pattern for the production of specific IgG. Less than one month after infection some participants no longer have detectable IgG in their serum, while others have the antibodies seven months after infection.

Research conclusions

The conclusion of the study was that, in addition to the impossibility of establishing a temporal pattern of IgG response, the data indicate that SARS-CoV-2 does not appear to induce a long-lasting humoral response.

Research perspectives

The study perspective is to analyze the IgM response of the same volunteers and determine the titers of both IgG and IgM to better understand seroconversion and the robustness of the anti-SARS-CoV-2 antibody response.

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