Investigation of the effect of Severe Acute Respiratory Syndrome Coronavirus 2 pandemic on autoantibody positiveness evaluated by the indirect immunofluorescence assay

İndirekt immünofloresan testi ile değerlendirilen otoantikor pozitifliklerine Şiddetli Akut Solunum Yolu Sendromu Koronavirüsü 2 pandemisinin etkisinin araştırılması

Abstract

Aim: The aim of this study is to determine the possible relationship between Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infection and systemic or organ-specific autoimmune diseases.

Methods: Serum samples sent to a Medical Microbiology Laboratory from patients in various clinics with preliminary diagnoses of autoimmune disease between March 2018 and March 2022 were included in our study. During this period, the indirect immunofluorescent antibody test results studied in our laboratory were obtained from the automation system of our hospital and evaluated retrospectively.

Results: In the two years before the Coronavirus Disease 2019 (COVİD 19) pandemic and the two years during the pandemic anti-nuclear antibody (ANA) positivity was detected in 2256 of 8325 patients who underwent indirect immunofluorescence assay (IIAF) evaluation [single pattern in 2038 patients (1363 speckled), multiple pattern in 218 patients]. When the change in autoantibody positivity over time was examined, it was determined that there was a statistically significant increase in the positivity rates of ANA, anti-double-stranded DNA antibody (anti-dsDNA), antigliadin,anti-islet cell antibody (anti -ICA) and anti-Gliadin autoantibodies in the first two years of the pandemic compared to the previous two years. No difference was observed in the positivity rates of anti-mitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA), anti-endomysium, Antineutrophil cytoplasmic antibody (ANCA) autoantibodies before and during the COVID-19 pandemic.

Conclusion: The increase in the positivity rates of ANA, anti-dsDNA, anti-ICA, anti-Gliadin autoantibodies during the pandemic period suggested that the COVID-19 process may affect some autoimmune diseases.

Keywords: Autoantibodies; autoimmune diseases; indirect immunofluorescence assay; SARS-CoV-2

Öz

Amaç: Bu çalışmanın amacı Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) enfeksiyonu ile sistemik veya organa özgü otoimmün hastalıklar arasındaki olası ilişkiyi belirlemektir.

Yöntemler: Çalışmamıza Mart 2018 ile Mart 2022 tarihleri arasında çeşitli kliniklerden, otoimmün hastalık ön tanısı olan hastalardan Tıbbi Mikrobiyoloji Laboratuvarı'na gönderilen serum örnekleri dâhil edildi. Bu dönemde laboratuvarımızda çalışılan indirekt immünofloresan antikor test sonuçları hastanemiz otomasyon sisteminden elde edilerek retrospektif olarak değerlendirildi.

Bulgular: Coronavirus Disease 2019 (COVİD 19) pandemisinden önceki iki yılda ve pandemi dönemindeki iki yılda indirect immunofluorescence assay (IIAF) değerlendirmesi yapılan 8325 hastanın 2256'sında anti-nükleer antikor (ANA) pozitifliği saptandı [2038 hastada tekli patern (1363'ü benekli), 218 hastada çoklu patern]. Otoantikor pozitifliğinin zaman içindeki değişimi incelendiğinde, pandeminin ilk iki yıllık döneminde önceki iki yıla göre ANA, anti-double-stranded DNA antibody (anti-dsDNA), antigliadin,anti-islet cell antibody (anti -ICA) ve anti-Gliadin otoantikorlarının pozitiflik oranlarında istatistiksel olarak anlamlı bir artış olduğu tespit edildi. anti-mitochondrial antibody (AMA),, anti-smooth muscle antibody (ASMA), anti-Endomysium, anti-neutrophil cytoplasmic antibody (ANCA), otoantikorlarının ise pozitiflik oranlarında COVID-19 pandemi döneminde ve öncesinde farklılık gözlenmedi.

Sonuç: Pandemi döneminde ANA, anti-dsDNA, anti-ICA, anti-Gliadin otoantikorlarının pozitiflik oranlarının artması, COVID-19 sürecinin bazı otoimmün hastalıkları etkileyebileceğini düşündürdü.

Anahtar Sözcükler: İndirek immunfloresan ölçüm; otoantikorlar; otoimmün hastalıklar; SARS-CoV-2

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Received/*Geliş* : 27.05.2024
Accepted/*Kabul*: 17.07.2024

DOI: 10.21673/anadoluklin.1490524

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INTRODUCTION

Autoimmune diseases (AD) are caused by the development of immune responses against the organism own tissues and cells and autoantibodies are of great importance in the diagnosis of these diseases (1). Autoantibodies called anti-nuclear antibodies (ANA), which develop against nuclear structures in the cell nucleus and/or cytoplasm, are important diagnostic criteria in connective tissue diseases. Currently, there are many methods developed for the detection of ANA positivity (2). The gold standard method for ANA detection is the indirect immunofluorescence assay (IIFA) using Hep2 cells (1).

Many ADs are multifactorial, related to both genetic and environmental factors such as viral infections. Viruses are known to be among the most common exogenous factors that trigger the development of autoimmunity in genetically susceptible individuals (3). Specific virus types can promote the production of autoantibodies and cytokines by causing widespread non-specific B and T activation. For example, the presence of Epstein-Barr virus and Parvovirus B19 is associated with Hashimoto's thyroiditis, Human T-lymphotropic virus-1 with Graves disease and autoimmune encephalitis after infection with Herpes simplex virüs (4).

On 7 January 2020, the World Health Organization (WHO) announced that this agent was a new coronavirus that causes infection in humans. There is increasing evidence that SARS-CoV-2 infection is associated with the development of autoimmunity phenomena. The clinical spectrum of autoimmunity-related symptoms in COVID-19 patients ranges from organ-specific autoimmune diseases to systemic autoimmune and inflammatory diseases (5).

In this study, in order to investigate the effect of the COVID-19 pandemic period on the autoantibodies' positivity rates, it was aimed to examine the autoantibody test results evaluated by the IIFA method in the pre-pandemic period and during the pandemic period.

MATERIAL AND METHODS

In this study, serum samples sent to Düzce University, Medical Microbiology Laboratory between March 2018 and March 2022 with suspicion of ADs from patients in various clinics were included. IIFA parameters results of the samples were examined in our laboratory during this period were obtained from the automation system of our hospital and evaluated retrospectively.

Among the autoimmune test parameters; ANA, anti-double-stranded DNA antibody (anti-dsDNA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-endomysium, anti-gliadin, anti-islet cell antibody (anti-ICA), perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) tests were included in the study. For these tests, IIFA method was used according to the recommendations of the manufacturer (Euroimmun AG, Germany). EuroimmunEurostar (Euroimmun AG, Germany) fluorescence microscope was used.

This study was approved by the Düzce University Faculty Of Medicine Non-invasive Health Practices Ethics Committee (date: 10.17.2022, decision no: 2022/162.

Statistical analyses

Statistical Package for the Social Sciences software for Windows, version 22.0, was used for the statistical analysis (SPSS, Chicago, IL, USA). Appropriate descriptive statistics were calculated according to the type of data. The relationships between categorical variables were analysed by Chi-square, Fisher Freeman-Halton (post-hoc Bonferroni test) and Fisher's Exact tests. $p<0.05$ was considered statistically significant.

RESULTS

The study included 2448 patients who were found to be positive for any autoantibody among 8325 patients whose serum samples were sent to the microbiology laboratory for IIFA testing with suspicion of autoimmune disease in the two years before the COVID-19 pandemic and two years during the pandemic period.

Of the patients who were positive for IIFA, 1684 (68.80%) were female and 764 (31.20%) were male with a mean age of 41±19.44 years. The positivity rates of ANA, AMA, Anti-ICA tests were higher in women than in men. The evaluation of the positive tests of the patients according to gender is showmemran in Table 1.

Table 1. Evaluation of positive tests according to gender

	Female		Male		*p*
	n	%	*n*	%	
ANA	**1563/5076**	**30,80**	693/2600	26,66	***<0,001***
Anti-dsDNA	8/3139	0,25	0/1665	-	0,057
AMA	**17/601**	**2,82**	4/482	*0,82*	***0,024***
ASMA	12/673	1,78	12/535	2,24	0,569
ANCA	**34/988**	**3,44**	19/875	2,17	0,100
Anti-ICA	**7/205**	**3,41**	5/482	1,03	***0,030***
Anti- Endomisyum/Gliadin	43/1042	4,12	31/682	4,54	0,675
Total	**1684/5505**	**30,59**	764/2825	27,04	***0,001***

ANA: anti-nuclear antibodies, anti-dsDNA: anti-double-stranded DNA antibody, AMA: anti-mitochondrial antibody, ANCA: anti-cytoplasmic antibody, Anti-ICA: anti-islet cell antibody, n:number, %:percentage

Table 2. Distribution of ANA positivity according to time intervals [number (%)]

ANA positivity	**Time intervals**								
	Before COVID-19				**COVID-19 pandemic period**				
Six-month rates	April 2018 - September 2018	October 2018 - March 2019	April 2019 - September 2019	October 2019 - March 2020	April 2020 - September 2020	**October 2020 - March 2021**	April 2021 - September 2021	October 2021 - March 2022	*p*
	248/1159 (21,4)	412/1344 **(30,6)**	249/1014 (24,5)	259/1181 (21,9)	163/486 (33,5)	**281/639 (44,0)**	311/815 (38,2)	333/1050 (31,7)	**<0,001**
Annual rates	April 2018-March 2019		April 2019-March 2020		**April 2020-March 2021**		April 2021- March 2022		
	660/2503 (26,4)		508/2195 (23,1)		**444/1125 (39,5)**		644/1865 (34,5)		**<0,001**
Two-yearly rates	April 2018-March 2020				**April 2020-March 2022**				
	1168/4698 (24,9)				**1088/2990 (36,3)**				**<0,001**

ANA: anti-nuclear antibodies

ANA positivity was detected in a total of 2256 patients, of which 2038 had single pattern and 218 had multiple patterns (Fifure 1, Figure 2).

The period with the highest rate of ANA positivity was determined as the second six-month period in the COVID-19 pandemic. The second highest rates were detected in the first and third six months during the COVID-19 pandemic period and there was no difference between them (p=0.094) (Table 2).

When we examined the change in anti-dsDNA positivity rates over time, it was observed that the positivity rate was statistically significantly higher in the first year of the COVID-19 pandemic compared to other years (p=0.038) (Table 3).

When we examined the change in anti-ICA positivity rates over time, it was observed that the positivity rates were statistically significantly higher in the COVID-19 pandemic period with a rate of 7.3% compared to the pre-pandemic period (p=0.034).

There was no difference between anti-endomysium positivity rates before and during the COVID-19 pandemic (p=0.968).

Anti-Gliadin positivity was significantly higher in the second year of the COVID-19 pandemic period with a rate of 6.6% compared to other years (p=0.010). When the six-month rates were analyzed, the highest positivity was found in the third six-month period after COVID-19 (p=0.038).

The rate of ANCA positivity was 0.6% in the fourth six-month period before COVID-19 (April 2018-September 2018), which was lower than the other periods (p=0.023). No significant difference was found

Table 3. Distribution of anti-dsDNA positivity according to time intervals [number (%)]

Anti-dsDNA positivity	Time intervals								
	Before COVID-19				COVID-19 pandemic period				
Six-month rates	April 2018 - Sep. 2018	October 2018 - March 2019	April 2019 - Sep. 2019	October 2019 - March 2020	April 2020 - Sep. 2020	October 2020 - March 2021	April 2021 - Sep. 2021	October 2021 - March 2022	*p*
	1/953 (0,1)	0/954 (0,0)	0/446 (0,0)	1/425 (0,2)	1/288 (0,3)	**3/374 (0,8)**	2/516 (0,4)	0/650 (0,0)	***0,022***
Annual rates	April 2018-March 2019		April 2019-March 2020		April 2020-March 2021		April 2021- March 2022		
	1/1907 (0,1)		1/871 (0,1)		**4/662 (0,6)**		2/1166 (0,2)		***0,038***
Two-yearly rates	April 2018-March 2020				April 2020-March 2022				
	2/1778 (0,1)				**6/1828 (0,3)**				0,289

anti-dsDNA: anti-double-stranded DNA antibody, Sep.: September

between the other periods (p=0.221, p=0.275, respectively).

In addition, during the study period, 41 patients whose COVID-19 test was positive were later found to have a positive ANA test [speckled (74%), dense fine speckled (15%), homogeneous (7%), nuclear membrane (2%) and nuclear with few spots (2%) patterns].

DISCUSSION AND CONCLUSION

Autoimmune disorders are more common in females due to hormonal differences. In a study conducted by Sung et al. in patients with rheumatoid arthritis, the rate of females was reported as 81.9% and the rate of males as 18.1% (6). In a study conducted by Çelikbilek et al. with the sera of patients with ANA positivity, the rate of females was 77% and the rate of males was 23% (7). In our study, 68.8% of the patients with autoantibodies positivity were women and all autoimmune parameters were found more frequently in females. The positivity rates of ANA, AMA, and anti-ICA tests were statistically higher in females than in males. We thought females were more susceptible to autoimmune diseases than males.

Autoimmune diseases can occur at any age, but different diseases have their own characteristic age of onset (8). Barut et al. evaluated 309 patients with positive ANA test by IIFA method and found the mean age to be 42.50±14.66 years (9). In our study, the mean age of patients with autoantibody positivity was found to be 41±19.44 years, which was similar to the studies in our country.

In the study conducted by Yanik et al., in which ANA patterns of 843 samples were evaluated by IIFA, it was found that the most common pattern was speckled (75.0%), the second most common pattern was nucleolar (10.4%), followed by homogenous (6.8%) (10). In a study conducted by Mariz et al. in 918 healthy and 153 individuals with OIH in Brazil, it was shown that the most common ANA pattern in both groups was the dense fine speckled pattern with a rate of 45.8% in healthy individuals and 42% in individuals with ADs. The second most common ANA pattern was shown to be a coarse speckled pattern in individuals with OIH (26.1%) and a dense fine spotted pattern in healthy individuals (33.1%) (11). In our study, 2038 and 218 of 2256 patients with ANA positivity had single and multiple patterns, respectively. When the distribution of single patterns was analyzed, the most common pattern was speckled pattern with 1363, followed by 340 dense fine speckled, 152 homogeneous, 92 nucleolar, 38 nuclear membrane, 32 centromere, 13 few nuclear dots and 8 multiple nuclear dots patterns, respectively. Similar to the single patterns, the most common pattern was specled pattern in the multiple patterns. It has been observed that the most common pattern worldwide is the speckled pattern.

In a study from Izmir, 50 serum samples from acute COVID-19 patients and 50 control serum samples collected before the outbreak were evaluated for ANA positivity by IIFA method. A higher rate of ANA positivity was found in COVID-19 patients (18%)

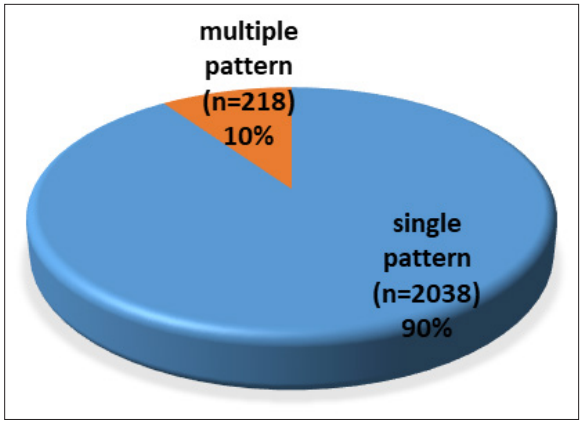

Figure 1. Single and multiple pattern distribution of ANA positivity

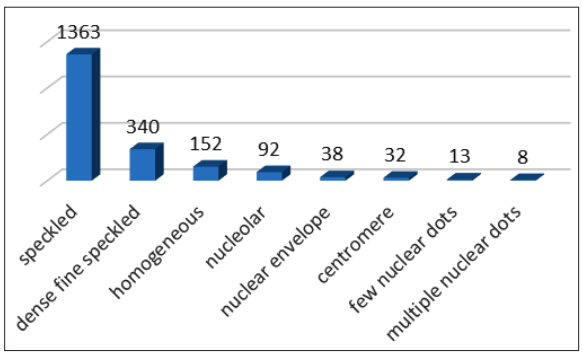

Figure 2. Distribution of single pattern

compared to the control group (2%), but the difference was not statistically significant (12). Pascolini et al. examined the presence of ANA by IIFA method in 31 patients with COVID-19-related pneumonia and 25 patients with pneumonia with etiology other than COVID-19. ANA positivity in patients with COVID-19 (33.3%) was found to be significantly higher than in patients with other non-COVID-19 pneumonia (0.08%) (13). In our study, ANA positivity evaluated by the IIFA method was detected at a higher rate in the post-pandemic period compared to the pre-pandemic period. These results suggested that COVID-19 disease, drugs, or vaccines may activate the autoimmune system.

Chang et al. in a study involving 47 patients hospitalized with COVID-19-induced infection in Korea, ANA positivity rate was found to be 21.3% (10/47). In the same study, the most common patterns were found to be 50% (5/10) nucleolar and 30% (3/10) speckled patterns (14). Peker et al. evaluated ANA by IIFA method in serum samples of 50 patients with acute COVID-19 infection and found that ANA test was positive in 9 patients and nucleolar pattern was the most common pattern (12). In our study, in 41 patients with positive COVID-19 test and positive ANA test, the speckled pattern was the most common pattern in 30 (74%) patients. Dense fine speckled (15%), homogeneous (7%), nuclear membrane (2%), and nuclear with few dots (2%) patterns followed in order of frequency. In our study, the most common pattern in ANA positivity was speckled, which was not found to be consistent with other studies when compared with the literature. In addition, dense fine speckled pattern was not found in patients with COVID-19 infection in other studies and it was the second most common pattern in our study. This suggested that the COVID-19 pandemic may have an effect on systemic autoimmune diseases.

In the study by Peker et al. in which anti-dsDNA antibodies were examined by IIFA method in acute COVID-19 patients and healthy control group, anti-dsDNA antibodies were not detected in both group (12). In our study, when the pre-COVID-19 pandemic period and the COVID-19 pandemic period were compared, a statistically significant increase in the positivity rate of anti-dsDNA antibodies was observed during the COVID-19 pandemic period. These results show that there may be an increase in systemic autoimmune diseases, especially Systemic lupus erythematosus.

In the study by Singh et al., liver enzymes of a COVID-19-positive patient were found to be elevated, and the patient was diagnosed with autoimmune hepatitis-primary biliary cholangitis triggered by COVID-19 infection after AMA, ASMA, anti-ds DNA antibodies were found to be positive in further investigations (15). In our study, although there was no statistically significant difference between the pre-COVID-19 pandemic period and the COVID-19 pandemic period, an increase in the positivity rates of AMA and ASMA antibodies indicating autoimmune liver diseases was observed during the COVID-19 pandemic period.

In a case published by Hollstein et al., a 19-year-old female patient who presented with diabetic ketoacidosis was found to have COVID-19 infection 5-7 weeks prior to admission. In this case, although the relationship between COVID-19 and the development

of diabetes was not fully demonstrated, it was thought that COVID-19 may adversely affect pancreatic function with its direct cytolytic effect on pancreatic β-cells (16). When we examined the change in anti-ICA positivity rates over time in our study, a statistically significant increase was found in the annual rates of the COVID-19 pandemic compared to the annual rates before the pandemic. The findings in our study contribute to the literature by showing the relationship between the COVID-19 pandemic and the incidence of autoantibody-mediated type 1 diabetes.

In the study by Çakır et al. comparing patients diagnosed with celiac disease before and during the COVID-19 pandemic, an increase in the frequency of celiac disease was observed in the paediatric age group during the pandemic period (17). In our study, COVID-19 pandemic had no effect on anti-endomysium antibodies, which is not compatible with the literature.

In the study by Duran et al., vasculitis-associated glomerulonephritis was diagnosed and positive ANCA tests were detected in two patients with recent COVID-19 positivity upon the development of acute kidney injury (18). In a study conducted by Gelzo et al. on 124 COVID-19-positive patients (16 asymptomatic and 108 hospitalised) and 48 control groups to define the frequency of ANCA-related autoimmunity in patients with COVID-19 infection, it was observed that patients with COVID-19 infection had significantly higher serum ANCA levels than the control group (19). In our study, ANCA positivity was found to be higher in the COVID-19 pandemic period (3.3%) compared to the COVID-19 pre-pandemic period (2.4%), although not statistically significant.

There are some limitations in our study due to the retrospective nature of our data. The full spectrum of autoimmune phenomena that may occur in patients during or after COVID-19 is still unclear. However, the findings of our study may help to show the relationship between COVID-19 and new-onset autoimmune diseases.

In our study, it was observed that there was an increase in some autoantibody positivity during the pandemic period. Long-term studies are needed to examine the relationship between COVID-19 disease and new-onset systemic and organ-specific autoimmune diseases.

Conflict-of-Interest And Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study

Acknowledgments

This study was produced from the first author's Medical Microbiology specialization thesis.

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