

Change in the Frequency of Autoimmune Diseases in Children During the COVID-19 Pandemic and Lock-Down Period Compared to the Pre-Pandemic Period

COVID-19 Pandemisi ve Karantina Döneminde Çocuklarda Otoimmün Hastalıkların Sıklığının Pandemi Öncesi Döneme Göre Değişimi

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Abstract

We aimed to determine the frequencies of new-onset disease/attacks of autoimmune diseases (AD) during the COVID-19 pandemic and lock-down period compared to the pre-pandemic period. The patients (n=171) (aged between 0-18 yrs.) who were applied with AD to our hospital during the one year period before and first year of the COVID-19 pandemic and lock-down were included in this study. The frequencies of hospital applications with new-onset disease/attacks of AD were investigated retrospectively and compared between the two periods. The number of new-onset disease/attacks in the pre-pandemic and pandemic periods were determined as follows, 111 and 65 respectively (p<0.001). The proportions of applications to hospital in patients with post-streptococcal disease and Henoch-Schönlein purpura have decreased during the pandemic, while a significant increase in frequency of new-onset type 1 diabetes mellitus has been observed. The frequency of applications for minimal change disease, systemic lupus erythematosus and Guillain Barre syndrome and multiple sclerosis did not alter substantially between the two periods. None of the patients were diagnosed with COVID-19. During the COVID-19 pandemic and lockdown period, the frequencies of AD diseases such as Henoch-Schönlein purpura and post-streptococcal disease have decreased considerably indicating indirectly that infectious agents related with the etiology/course of AD and thus highlights the importance of isolation and hygiene measures. Increased frequency of type diabetes mellitus during this period suggests that factors other than infections may be effective in the etiopathogenesis of disease, or that protective agents or their effects might have decreased or changed.

Keywords: COVID-19 pandemic and lock-down, Autoimmune diseases, Children.

Özet

COVID-19 pandemi ve kapanma döneminde pandemik öncesi döneme kıyasla yeni başlangıçlı hastalık/otoimmün hastalıkların ataklarının sıklığını belirlemeyi amaçladık. Bu çalışmaya COVID-19 pandemisi ve kapanma döneminin bir yıl öncesi ve ilk yılı boyunca hastanemizde otoimmün hastalık tanısı ile izlenen hastalar (n = 171) (0-18 yaş arası) dahil edildi. Yeni tanı alan hasta sayısı ve otoimmün hastalığın atak sayılarının sıklıkları geriye dönük olarak araştırıldı ve iki dönem arasında sıklıklar karşılaştırıldı. Pandemi öncesi ve pandemik dönemde yeni başlangıçlı hastalık/atakların sayısı sırasıyla 111 ve 65 olarak belirlendi (p <0.001). Post-streptokokal hastalık ve Henoch-Schönlein purpurası hastalarında hastaneye başvuru oranları pandemi sırasında azalırken, yeni tanı tip 1 diabetes mellitus sıklığında önemli bir artış gözlemlendi. Minimal lezyon hastalığı, sistemik lupus eritematozus, Guillain Barre sendromu (GBS) ve multipl skleroz için başvuru sıklığı iki dönem arasında anlamlı bir farklılık göstermedi. Hastaların hiçbirine COVID-19 teşhisi konmadı. COVID-19 pandemisi ve kapanma dönemi boyunca, Henoch-Schönlein purpurası ve post-streptokokal hastalık gibi otoimmün hastalıkların sıklıkları, otoimmün hastalık etiyolojisi ve seyrinde enfeksiyöz ajanların rol oynadığını destekleyecek şekilde önemli ölçüde azalmıştır. Bu durum izolasyon ve hijyen ölçümlerinin önemini vurgulamaktadır. Bu dönemde tip 1 diabetes mellitus sıklığının artmış sıklığı, enfeksiyonlar dışındaki faktörlerin hastalığın etiopatogenezinde etkili olabileceğini veya koruyucu ajanların veya etkilerinin azalmış olabileceğini veya değişebileceğini düşündürmektedir.

Anahtar Kelimeler: COVID-19 pandemi ve kapanma dönemi, Otoimmün hastalıklar, Çocukluk çağı

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1. Introduction

On February 11, 2020 by World Health Organization (WHO); the disease by this infection was defined as COVID-19 and as a pandemic on March 11, 2020. The first case of COVID-19 in Turkey was officially announced on March 11, 2020. It continues to spread rapidly all over the world and cause a large number of deaths.

From the beginning of the pandemic, in order to prevent the spread and transmission of the infection, isolation measures have been taken by both individuals and governments all around the world as in our country, which also lead to severe socio-economic bad consequences. Measures and interventions to prevent the transmission and spread of this virus have been a part of our lives and our lifestyle has changed and people's mobility and contact decreased. Although intermittently, a nationwide curfew was imposed, which still continue on weekends and for children and people over the age of 65 until March 2021. Schools were closed and online education started(1). There have been limitations in workplaces and flexible working order has been introduced. All social activities, religious activities, all kinds of sports and travel activities were stopped. Eating and drinking outside the home were restricted. Many individuals provide for their needs through online shopping. Restrictions for the shopping and public transport capacity, obligation to wear a mask, social isolation and the obligation to leave physical distance, personal and social hygiene measures and many other obligatory interventions for prevention of spread of the virus has been applied. Thus, the contact of people with each other has been minimized. Due to all these isolation and hygiene measures, it is thought that other infections via airborne and faecal-oral transmission have been decreased and therefore the frequency of morbidity associated with infections has also decreased as well as COVID-19. It has been observed that admissions/visits to hospitals have decreased due to the fear of contamination of the virüs(2-6).

Autoimmune diseases are characterized by persistent inflammatory reactions and the

presence of autoantibodies due to loss of immune tolerance leading to various organ damage and dysfunction(7). Viral and bacterial infections are one of the environmental factors that trigger autoimmunity(8). During infections caused by these microorganisms, autoimmune reaction starts with mechanisms such as molecular mimicry, bystander activation, epitope spreading and presentation cryptic antigens(9). Virus-induced AD can be counted as systemic lupus erythematosus (SLE), type-1 diabetes mellitus (DM), multiple sclerosis (MS), Gullian Barre syndrome (GBS), encephalitis and autoimmune myocarditis(10).

SLE, which is the prototype of autoimmune disorders, begins with periods of exacerbation and remission in childhood in about 20% of cases, causing irreversible tissue damage and even premature death(11). The exact etiology of SLE is still unknown. However, infections play a role as an environmental factor inducing or promoting the onset and exacerbations of SLE in genetically susceptible individuals(12). MS is a chronic, immune-mediated, neurodegenerative disorder of the central nervous system. At about 3 to 10% of all MS patients initiates first clinical symptoms in childhood or adolescence(13, 14). Viral pathogens may play a role in MS pathogenesis and relapses(15). GBS is a typical post-infectious disease which progresses rapidly shortly after an infection caused by viruses and bacteria, usually without recurrence(16). It has been reported that viral infections have both a triggering and protective role in the development of type-1 DM(17).

Idiopathic nephrotic syndrome (INS), is the most frequent glomerular disease in childhood. In children >1 year of age, minimal change disease (MCD) is the most common cause of nephrotic syndrome, accounting for 70%–90% of patients(18). In some cases with INS, an upper respiratory tract infection, an allergic reaction, vaccines, malignancies or another factor may precede the development or relapses of the disease(19).

The etiology of HSP is not well known. Approximately one and a half of the cases of

HSP are preceded by an upper respiratory tract infection(20). It can also be triggered by viral infections, vaccinations, and insect bites. Another AD in which bacterial infections play a role in its etiology is post-streptococcal disorder (PSD). PSD occurs within 3-4 weeks after group A beta-hemolytic streptococcal tonsillopharyngitis. The poor treatment of this infection is the main cause of PSD(21).

In this study, we aimed to determine that if there was a change in the frequencies of AD in the one year period before COVID-19 pandemic and in the first one-year period of the COVID-19 pandemic, where strict hygiene and isolation measures were applied on a personal and social basis.

2. Materials and Methods

Study population

The patients aged between 0 and 18 years applied to the pediatric departments of our hospital in the one-year periods before the COVID-19 pandemic (from March 11, 2019 to March 11, 2020) and during the first year period of the pandemic and strict lock-down (from March 11, 2020 to March 11, 2021). The frequency of applications with a new-onset disease or attacks/relapses of AD and the clinical characteristics of the patients were retrospectively obtained from the hospital records. COVID-19 PCR test was negative in all patients whose data were included in the study during the pandemic period. Data of patients with positive COVID-19 PCR test were not included in the study. In order to exclude AD due to COVID 19, the data of patients with a history of contact or known to have had COVID 19 before were excluded from the study.

The diagnosis and management of MCD was done according to KDIGO guideline(22). EULAR/PRINTO/PRES criteria were used in the diagnosis of HSP(23). The Systemic Lupus International Collaborating Clinics

(SLICC) criteria were used in the diagnosis of SLE(24). Multiple sclerosis was diagnosed according to McDonald criteria(25). Global International Diabetes Federation (IDF) / International Society for Pediatric and Adolescent Diabetes (ISPAD) 2011 Guideline was used for type 1 DM diagnosis(26).

Ethical Approval

This study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki (Number: 8, Date: 26.01.2021).

Statistical Analysis

Data analysis was performed with IBM SPSS v21. Qualitative variables were given as count and percentages in the tables. Normality of quantitative variables were evaluated with Shapiro Wilk test. For the normally distributed groups, comparisons were performed with independent samples t test, while Mann-Whitney U test was used for non-normal distributed group comparisons. The relationship between the types of diseases and the time of the patient admission to hospital was evaluated with Pearson Chi-square analysis. For significant Chi-square test results, in each row column proportions were compared using z test with a Bonferroni correction. Significant differences between the column proportions denoted with different letters in each row. P values less than 0.05 were considered significant.

3. Results

The data of 171 patients were included in the study. The total number of patients admitted during the pre-pandemic and pandemic periods were 108 and 63, respectively ($p<0.001$). The number of applications of the patients in the pre-pandemic and pandemic period was 111 and 65, respectively. The distribution of the number of the patients and applications according to AD is shown in Table 1.

Table 1. The number of applications and patients according to the autoimmun diseases

Disease	Pre-pandemic Period					Pandemic Period				
	Total Admission n (%)	Sex (F/M)	Previously diagnosed		New Onset Disease (n)	Total Admission* n (%)	Sex (F/M)	Total Patient (n)	Attack /Relapse (n)	New Onset Disease (n)
			Total Patient (n)	Attack /Relapse (n)						
Type 1 diabetes mellitus	25 (22.5) ^a	11/14	25		25	34 (52.3) ^b	20/14	34		34
Post Streptococcal Disorders	20 (18) ^a	12/8	20		20	1 (1.5) ^b	1/0	1		1
Minimal change disease	15 (13.5) ^a	13/2	15	7	8	10 (15.4) ^a	7/3	10	6	4
Henoch Sheinlein purpura	29 (26.1) ^a	15/14	29		29	6 (9.2) ^b	4/2	6		6
Systemic lupus erythromatosus	7 (6.3) ^a	6/1	7		7	5 (7.7) ^a	5/0	5		5
Multiple sclerosis	13 (11.7) ^a	19/1	8	11	2	8 (12.3) ^a	6/0	6	8	
Guillain Barre syndrome	2 (1.8) ^a	0/2	2		2	1 (1.5) ^a	0/1	1		1
Total	111	108				65		63		

*Having same letter in a row denotes that column proportions of application time period categories do not differ significantly at the 0.05 level.

While the number of patients and applications for other AD decreased during the pandemic period, it was observed that the number of patients with newly diagnosed DM increased by 36%. The total number of patients and applications who applied with other AD other than DM were 83/29 and 86/31 during the pre-pandemic and pandemic periods, respectively, and the number of patients and the number of hospital visits decreased by 65% and 64%, respectively, during the pandemic period.

A 93 of these patients who applied during the pre-pandemic period and 51 of the patients who applied during the pandemic period were diagnosed with a new-onset disease. During the pandemic period, the number of patients diagnosed with a new-onset disease decreased by 18%. While the number of patients applied with attack/relapse in the pre-pandemic period was 15 and the total number of attacks was 18. In pandemic period, the number of patients and the total number of attacks were 12 and 14, respectively.

The number of patients with DM were 25 (aged 4-17.5 years) and 34 (2-18 years) during the pre-pandemic and pandemic periods,

respectively. All diabetic patients were hospitalized, and PCR tests were negative for COVID-19 in all. There was 36% increase in the frequency of new-onset diabetes during the pandemic period. The number of admissions with ketoacidosis of these patients were 12 and 18, respectively in the two periods. Difference in terms of age, HbA1c levels (12,2% and 11,95% in the pre-pandemic and pandemic periods, respectively) and the frequency of ketoacidosis was not found between the two periods (p>0.05).

During the pandemic period, the applications with PSD were decreased significantly compared to the pre-pandemic period (Table 1). In the pre-pandemic period, 20 new applications of PSD were observed (15 with new-onset acute rheumatic fever, 4 with rheumatic heart disease, 1 with poststreptococcal reactive arthritis). The patients' ages ranged from 5 to 18 years. The major criterias were carditis in 8 patients, carditis with polyarthralgia in 4 patients, carditis with chorea in 5 patients, polyarthritits in 2 patients and monoarthritits in 1 patient. During the pandemic period, there was no admission with the reactivation and only one new patient (13-years-old boy) was applied

with polyarthritis with elevated acute phase reactants and diagnosed with acute rheumatic fever. The PCR test for COVID-19 of him was negative.

The number of patients followed-up with a diagnosis of new-onset HSP were 29 (aged 2.8-15.9 years) and 6 (aged 3.5-16.1 years) respectively in the pre-pandemic and pandemic periods. All of these patients were newly diagnosed HSP cases. Compared to the pre-pandemic period, the number of patients presenting with newly diagnosed HSP was 80% less during the pandemic period (Table 2). 12 patients in the pre-pandemic period and 2 patients in the post-pandemic period were hospitalized and treated.

In the pre-pandemic period, 15 patients (aged 2.3-15.3 years) were followed-up with MCD (8 new-onset MCD, 7 relapsed). Nine patients were treated by hospitalization. Ten patients (aged 4.5-16.5 years) were admitted with MCD syndrome (4 new-onset, 6 relapsed) during the pandemic period.

In these both periods, 7 (aged 10.2-15.8 years) and 5 patients (aged 12.5-19 years), respectively were diagnosed with new-onset SLE. There was no patient presenting with SLE attack in both periods.

During the pre-pandemic period, a total of 10 patients were followed-up with MS. Two patients (aged 6.3-17 years) diagnosed with new-onset disease of MS. Eight patients (aged 14.1-17 years) which were previously being followed-up with MS presented with a total of 11 attacks in the pre pandemic period. One patient also had Sjögren's syndrome and another patient had type 1 DM. All these patients were treated by hospitalization. During the pandemic period, a total of 6 MS cases (aged 16-17.5 years) which were previously diagnosed with MS, were admitted with total of 8 attacks. One patient also had type-1 DM.

The number of patients diagnosed with GBS were 2 (9.4- and 10.8-years old) and 1 (3.3-year old) respectively in the pre-pandemic and pandemic periods. There was not statistically significant difference in the frequencies of

SLE, MCD, MS and GBS between the two periods (Table 1).

4. Discussion and Conclusion

We investigated the changes in the frequencies of AD diseases in which infections play a role in the etiology and/or clinical course in one-year periods before and during the COVID-19 pandemic and lock-down. Our results showed that there was significant decreases in the frequencies of the PSD, HSP and an increase in the frequency of new-onset diabetes during the pandemic.

It has been reported that the number of applications to the emergency services and/or hospital visits related to all kinds of health problems from all over the world has decreased considerably. In the early stages of the pandemic, some people even postponed their visits to the hospital for serious problems due to the fear of transmission of SARS-CoV-2 (2-6). We also experience this situation in our routine practice in our hospital.

It is obvious that the transmission and frequency of other infectious diseases beside COVID-19 infection decrease during the lock-down period when strict hygiene and isolation measures were taken on a personal and social basis. In a study conducted in France, COVID-19 lock-down were associated with a significant reduction in pediatric infectious disease spread by airborne transmission⁶. Therefore, we investigated whether there was a change in some AD in which an infection played a role in the etiopathogenesis and clinical course during the pandemic and lock-down period compared to pre-pandemic period. The symptoms/diseases investigated in this study such as diabetes, ketoacidosis, convulsion, respiratory distress, fever, rash, arthritis and eudema etc. require urgent treatment and can't be handled at home. So, in the presence of these symptoms or conditions, it is not possible to postpone hospital admissions due to the risk/fear of transmission of COVID-19.

In our study, during the pandemic period, the frequencies of applications for infection related morbidities/diseases except new-onset

DM have decreased by 65%. This result indirectly demonstrates the relation of infections with the etiology/clinical course of the AD.

In our study, it has been determined that the frequencies of some AD such as PSD and HSP, have decreased significantly during the pandemic period. It is known that group A Streptococcus infections play a crucial role in the disease's pathogenesis of HSP as well as viral infections and other factors(27). Although its role in HSP development is not as direct as PSD development, our finding indicates that hygiene measures and isolation during the pandemic is highly effective in preventing the transmission of group A beta-hemolytic streptococcus infection as well as development of PSD and HSP.

It was determined that the frequencies of these AD diseases such as MS and SLE, MCD, MS and GBS in both pre-pandemic and pandemic periods were quite low and there was no statistical difference between these two periods. On the other hand, from France, Harambat et al. reported that the relapse rate of nephrotic syndrome during the pandemic period was not different than the period before the pandemic as in our study(28).

Viruses are suggested to be one of the environmental agents that play a role in the emergence and progression of autoimmunity that plays a role in the etiopathogenesis of DM. However, it has been reported that viral infections have a protective role for DM(17). The hygiene hypothesis suggests that increased hygiene habits in early childhood and western hygiene lifestyle, leads to less frequent microbial infections that play a role in the emergence of allergic and AD diseases in advanced ages. According to this hypothesis, DM and other AD occur more frequently in the countries where the industry is developed and fewer infectious diseases were observed(29). We found that the frequency of new-onset diabetes in the pandemic period has increased considerably when the severe and widespread isolation and hygiene measures are taken. This result indicates that other factors may be more effective than infectious factors in the etiopathogenesis of diabetes or that protective agents may have decreased or changed during

this period. It comes to mind that one of these factors may be increased level of psychological stress. In addition, this finding may be explained by the hygiene hypothesis. However, it can be said that duration of the current pandemic period is too short for a comment to be made related with the hygiene hypothesis in the pathogenesis of DM.

Our hospital is a regional reference hospital and there has been no change in the diabetic patient referral conditions to our hospital in terms of change in socio-demographic status and presence of pediatric endocrinologists in our region during the time of this study. Therefore, it cannot be said that diabetic patient referrals to our hospital have decreased or increased with that reason.

In addition, could the increase in diabetes frequency that we detected during the pandemic period be related to SARS-CoV-2 infection question comes to mind. In a multicenter study conducted in United Kingdom, it was reported that the prevalence of new onset type-1 diabetes increased by 80% between March and June 2020 in two centers compared to previous years. SARS-CoV-2 PCR positivity was found in five of these patients. They suggested that the increased frequency of this disease may be related to the exposure to SARS-CoV-2(30). We think that the increase in DM prevalence is related to the change in environmental factors. SARS-CoV-2 PCR test in our patients with DM were negative and none of patients with DM in our study had a history and symptoms of SARS-CoV-2 infection. On the other hand, in a study conducted in Germany, the frequency of type-1 DM in children during the pandemic and lock-down period covering 13 March to 13 May 2020 was not different from the frequency observed during the same periods of the previous years(31). In our study, the frequency of admissions with ketoacidosis of new-onset DM were not different between the pre-pandemic and pandemic periods. Kamrath et al. reported that the frequency of ketoacidosis especially severe ketoacidosis in type-1 diabetic children increased in Germany during the pandemic period(32).

There are several limitations in our study. Firstly, this study is retrospective study.

Secondly, this study have small patient number. Thirdly, not all children were tested for the SARS-CoV-2 antibody.

In conclusion, the frequency of applications of morbidities/diseases associated with infections have decreased considerably with the isolation and hygiene measures applied during the period of COVID-19 pandemic and lock-down compared to pre-pandemic period. This decrease was observed to be more pronounced in the diseases in which bacterial infections as well as viral infections play a directly or indirect role in the

ethiopathogenesis or attacks/relapses such as PSD, HSP. No difference was observed in the frequency of diseases associated with mainly with viral infections such as INS, SLE, MS have been found. Our results indirectly indicate that infections may have a role in the emergence of AD diseases and prevention of infections is important. On the other hand, increase in the frequency of DM during this period suggests that factors other than infections are also effective in the etiopathogenesis of this disease, or that protective agents or its effects may have decreased or changed during this period.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Number: 8, Date: 26.01.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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