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Çocuklarda COVID-19'a İkincil Gelişen Multisistemik İnflamatuar Sendrom Tanılı Hastaların COVID-19 Aşısına Karşı Tutumları

The Attitudes of the Patients with the Multisystem Inflammatory Syndrome in Children Secondary to SARS-CoV-2 Regarding COVID-19 Vaccines

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ÖZ

Amaç: Çocuklarda multisistemik inflamatuar sendrom (MIS-C); SARS-CoV-2 ile enfekte olduktan sonra ortaya çıkan anormal bir bağışıklık yanıtıdır. Bu hastalarda BNT162b2 mRNA aşısının etkinliğini ve güvenliğini ortaya koyan bir çalışma yoktur. Bu çalışmada MIS-C tanısı almış 12 yaşın üzerindeki hastalarımızın COVID-19 aşısına karşı tutumları ve eğer aşılandılarsa gelişen yan etkileri sunmayı amaçladık.

Materyal ve Metot: Çalışmada Mayıs 2020-Ocak 2022 tarihleri arasında MIS-C tanısı ile takip edilen 12 yaş ve üzeri olguların dosyaları geriye dönük olarak taranarak hasta ve ailesine ait aşılanma bilgileri edinildi.

Bulgular: Çalışmaya 36 hasta (12 kız, 24 erkek) dahil edildi. Ortanca yaşları 13,5 (12-17) yıldı. Sekiz hasta (% 22,2) MIS-C tanısından ortanca üç (üç-altı) ay sonra aşı olmuştu. Aşı sonrası herhangi bir yan etki saptanmadı ve hiçbir çocukta hastalık reaktivasyonu olmadı. Hastaların aşı olmayı reddetmelerinin en sık nedenleri; hastalığı geçirmiş olmaları ve hastalığın tekrarlayabileceği korkusuydu.

Sonuç: MIS-C tanılı olguların SARS-CoV-2 aşılarına karşı tutumunu değerlendiren bu çalışmada; çoğu hasta ve ebeveynlerinin COVID-19 aşısı olmaya karşı olduğu, aşı olan grupta ise aşının güvenli olduğu gösterildi.

Anahtar Kelimler: Aşı güvenliği, BNT162b2 mRNA aşısı, çocuklarda multisistemik inflamatuar sendrom

ABSTRACT

Objective: Multisystem inflammatory syndrome (MIS-C) in children is an abnormal immune response that occurs after exposure to SARS-CoV-2. To our knowledge, there is no study demonstrating the efficacy and safety of the BNT162b2 mRNA vaccine in children who were diagnosed with MIS-C previously. In this study, we aimed to present the attitudes of MIS-C patients over the age of 12 years towards the COVID-19 vaccine, and the side effects of the vaccine in vaccinated patients.

Materials and Methods: The files of patients who were followed up with the diagnosis of MIS-C between May 2020 and January 2022 aged 12 years and over were reviewed retrospectively.

Results: Thirty-six patients (12 girls, 24 boys) were included in the study. The median age was 13.5 (12-17) years. Eight of the 36 patients (22.2%) were vaccinated at a median of 3 (3-6) months after the diagnosis of MIS-C. No side effects or disease reactivation was observed following vaccination. The most common reasons for patients' refusal to be vaccinated were having had the disease and being concerned about a recurrence.

Conclusion: This study showed that COVID-19 vaccination was safe in children who were diagnosed with MIS-C, although most of our patients were against it.

Keywords: BNT162b2 mRNA vaccine, multisystem inflammatory syndrome in children, vaccine safety

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory state that emerges four to five weeks after SARS-CoV-2 infection.[1] Although the disease is characterized mostly by fever and rash, it can affect multiple systems and even result in multiple organ failure. The incidence rate is 2 cases per 100,000.[2] The United States Centers for Disease Control and Prevention (CDC) defines the characteristics of MIS-C as; being younger than 21 years old, fever (≥38.0 °C) lasting longer than 24 hours, and severe disease causing hospitalization, inflammation demonstrated by laboratory, evidence of a previous SARS-CoV-2 infection with multiple organ involvement including at least two systems (positive SARS-CoV-2 polymerase chain reaction [PCR] or positive antibody test, or contact with a suspected or confirmed COVID-19 patient in the past four weeks).[3]

An abnormal immune response following SARS-CoV2 infection is assumed to be responsible for the development of MIS-C. Therefore, avoiding SARS-CoV-2 contact can prevent the development of MIS-C. Undoubtedly, one of the most effective ways against contagious diseases is vaccination. Many vaccine studies on COVID-19 had been conducted, and finally, the BNT162b2 mRNA vaccine has been approved. BNT162b2 mRNA vaccine received Emergency Use Authorization (EUA) for children firstly above 16 years old on December 11, 2020, and afterward, the vaccination age has been expanded to 12 years old and above on May 10, 2021.[4]

However, there is no data in the literature on vaccination of children who have recovered from MIS-C. In this study, we aimed to present the attitudes of children who were diagnosed with MIS-C, toward the COVID-19 vaccine, and also to report, if any, side effects in vaccinated children.

MATERIALS AND METHODS

Ethics Committee Approval: All procedures performed involving human participants were in accordance with the ethical standards of the local ethics committee and with the 1964 Helsinki Declaration and its lat-er amendments. The study was approved by the ethics com-mittee of Kocaeli University (Date: 24.03.2022, decision no: GOKAEK-2022/06.14).

We conducted the study between May 2020 and January 2020 at Kocaeli University Department of Pediatric Cardiology. Children aged 12 and up who had previously been diagnosed with MIS-C were included in our study population. The diagnosis of MIS-C was established through the criteria determined by the CDC.[3] We reviewed retrospectively the files of patients and examined whether the patients had received a COVID-19 vaccine. We reported, if any, the side effect of the vaccine or reactivation of the disease in vaccinated children. If not vaccinated, we noted what the reason for refusing COVID-19 vaccine was. In addition, demographic (age, gender, age at diagnosis), clinical, intensive care admission, and treatment characteristics of the patients were recorded.

Statistical Analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (SPSS, Chicago, IL, USA). The study variables were investigated using visual (histogram and probability plots) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk's tests) to determine the normality of their distribution. Numeric variables were presented with median (minimum-maximum). Descriptive analyses are presented as median and range.

RESULTS

A total of 36 children with MIS-C were included in the study. Of them, 12 (33.3%) were female and 24 were males (66.7%). The median age was 13.5 years (range 12 to17). All of the patients had fever on admission. In addition to the fever, gastrointestinal involvement was present in 27 patients, cardiac involvement in 22, rash in 17, conjunctivitis in 11, strawberry tongue in 6, edema in distal extremities in 6, cervical lymphadenopathy in 3, and renal involvement in 2 patients. The median duration of hospitalization was 8 days (range 3-20). Seven patients (19.4 %) required admission to the pediatric intensive care unit (PICU). All patients received intravenous immunoglobulin (IVIg) at a dose of 2gr/kg. Only one patient received a second dose of IVIg. 21 patients were treated with steroid together with IVIg. All patients were given subcutaneous enoxaparin during hospitalization and discharged on acetylsalicylic acid alone at a dose of 5mg/kg/ day (Table 1). There was no cardiac sequel in any patient on follow-up.

None of the patients had been vaccinated before being hospitalized with the diagnosis of MIS-C. Eight patients (22.2%) had been vaccinated with BNT162b2 mRNA vaccine at a median of 3 months (range 3-6) after the diagnosis of MIS-C. Seven patients had received the second dose and one patient had received a single dose. Any adverse effects other than local side effects were not seen following vaccination. The remaining 28 patients had not been vaccinated (Table 2).

When they were asked what the reason for refusing COVID-19 vaccination was, having already had the disease was the most frequent reason. Other reasons are shown in Figure 1.

Table 1. Demographic and clinical findings of patients at the diagnosis of MIS-C.

Sex (M/F)		24/12
Age (year)		13.5 (12-17)
Fever n (%)		36 (100 %)
Gastrointestinal Involvement n (%)		27 (75 %)
Cardiac Involvement n (%)		22 (61 %)
Rash n (%)		17 (47 %)
Conjunctivitis n (%)		11 (30 %)
Strawberry Tongue n(%)		6 (21 %)
Edema in Distal Extremities n(%)		6 (21 %)
Cervical Lymphadenopathy n(%)		3 (8.3 %)
Renal Involvement n(%)		2 (5.5 %)
Median Duration of Hospitalization (day)		8 (3-20)
Intensive Care Unit n (%)		7 (19%)
Treatment n (%)	IVIg	36 (100%)
	Steroid	21 (58.3%)
	Enoxaparin	36 (100%)

Table 2. BNT162b2 mRNA vaccination status of patients.

Patients receiving two-doses BNT162b2 mRNA Vaccine n (%)	7 (19.4 %)
Patients receiving single-dose BNT162b2 mRNA Vaccine n (%)	1 (2.8 %)
Patients not receiving BNT162b2 mRNA Vaccine n (%)	28 (77.8)

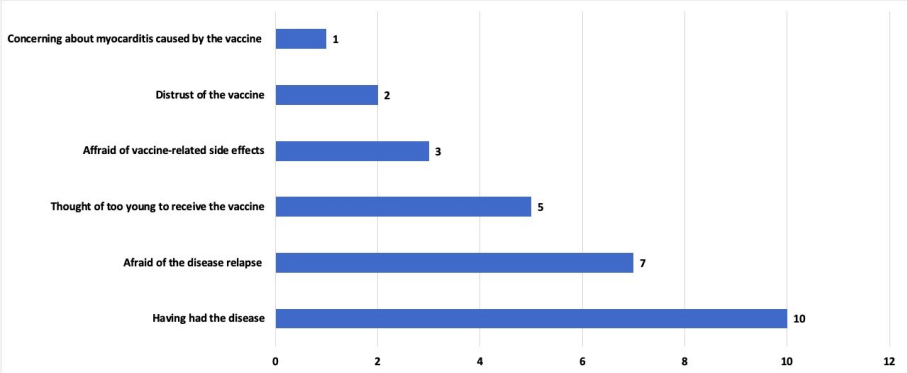

Figure 1. The reasons for refusing COVID-19 vaccination.

DISCUSSION AND CONCLUSION

In this study, the attitudes of patients diagnosed with MIS-C towards BNT162b2 mRNA COVID-19 vaccine were evaluated. None of our cases had been vaccinated before the diagnosis of MIS-C. Eight (22.2%) patients had been vaccinated after discharge. None of them had reported COVID-19 vaccine-related adverse events or experienced disease relapse. Having had the disease and the possibility of disease relapse were the most common causes for refusing vaccination. None of the patients who had needed PICU admission had been vaccinated after discharge, due to the possibility of adverse effects and their mistrust of COVID-19 vaccine. This attitude toward the COVID-19 vaccine shows that medical professionals should take approaches that eliminate hesitations against the COVID-19 vaccine.

Yousef et al.[5] conducted a surveillance study evaluating the incidence of MIS-C following the COIVD-19 vaccine among young people aged 12-20 years between December 2020 and August 2021. They reported 21 cases with a median age of 16 years. Of them, 12 (57%) cases needed PICU admission. More importantly, 15 of the 21 cases diagnosed with MIS-C had laboratory evidence of past COVID-19 infection. They reported that 21.335.331 doses of the COVID-19 vaccine had been administered to individuals aged 12-20 years and to young adults in the USA between December 2020 and August 2021. MIS-C associated with COVID-19 vaccine was one case per million. When the fifteen cases with evidence of past COVID-19 infection were excluded, the ratio of MIS-C associated with the COVID-19 vaccine was reduced to 0.3 per million.[5]

In a study from France, it has been reported that the incidence of MIS-C was less in vaccinated children

than in unvaccinated ones.[6] Zambrano et al.[7] reported that two doses of BNT162b2 mRNA vaccine had prevented (up to 91 %) significantly the occurrence of MIS-C. Besides these publications, the number of cases of MIS-C following COVID-19 vaccination has continued to increase. These cases have recently been referred to as Vaccine-related Multisystem Inflammatory Syndrome (MIS-V).[8] Therefore, worrying about whether the COVID-19 vaccine may give rise to a recurrence of MIS-C should not be ignored. In our study, 22.2 % of 36 children aged 12 years and up had been vaccinated with a median of 3 months (range 3-6) after hospital discharge. None of our cases experienced a recurrence of MIS-C.

Although the most frequent adverse effects following BNT162b2 mRNA vaccine are local side effects, cardiac adverse events following COVID-19 vaccination have been reported. Chin et al.[9] evaluated cardiac complications occurring after COVID-19, MIS-C, or BNT162b2 mRNA vaccine. They reported that there were cases of myopericarditis or myocarditis presenting with chest pain after one to five days of the second dose of the vaccine. According to data published on November 21, 2021, by Vaccine Adverse Event Reporting System (VERS) in the United States, there exists 1959 cases diagnosed with myopericarditis or myocarditis following mRNA vaccination.[10] In our study, 22 of the 36 children had cardiac involvement during hospitalization for MIS-C, all of the vaccinated children (eight cases) had left ventricular systolic dysfunction at the time of diagnosis of MIS-C, and none of them had myopericarditis, myocarditis, or MIS-V following mRNA vaccination.

The exact pathogenesis of MIS-Chas not yet been clarified. Some studies have demonstrated increased antibody responses to receptor-binding protein (RBD) of SARS-CoV-2 in children results in MIS-C.[11,12] Both SARS-CoV-2 and BNT162b2 mRNA vaccine may induce abnormal antibody responses and cause MIS-C in susceptible individuals.[13]

Despite the fact that our study was conducted with a small number of cases at a single center, it is unique in regard to containing information about vaccination of children who had had MIS-C. According to the data from the Turkish Health Ministry, the number of persons who received 2 doses of the COVID-19 vaccine is 52.945.667, which correspond to 62.8 % of Turkey's population.[14] Young persons in Turkey between 10-19 years of age constitute 15 % of the entire population of the country.[15] However, data on what percentage of this age group are vaccinated are lacking. Therefore, we could not compare the vaccination rates of our study group with healthy counterparts. This was also one of the limitations of our study. Because vaccine response may be influenced by ethnic origins, a single-center study cannot be applied to all ethnicities. Furthermore, the response to the vaccine was not evaluated in our vaccinated patients. Inflammatory conditions may influence the humoral response toward the vaccines. However, recently, Akgün et al.[16] showed markedly elevated antibody titers in patients with rheumatic disease after the second dose of the COVID-19 vaccine.

In conclusion, the study demonstrated that BNT162b2 mRNA vaccine was safe in children who had had MIS-C, although most of our patients and their parents refused COVID-19 vaccination for various reasons. There is no doubt that a larger case series need to be examined before drawing definitive conclusions.

Ethics Committee Approval: All procedures performed involving human participants were in accordance with the ethical standards of the local ethics committee and with the 1964 Helsinki Declaration and its lat-er amendments. The study was approved by the ethics com-mittee of Kocaeli University (Date: 24.03.2022, decision no: GOKAEK-2022/06.14). Written informed consent forms were obtained from the parents and/or relatives of all the patients in the study.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – EZB, HES; Supervision – KB, EZB; Materials – HES, DA; Data Collection and/or Processing – HES, EZB, DA; Analysis and/ or Interpretation – HES, EZB; Writing –KB, EZB, KB.

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