



The Effect of Measles, Rubella, Mumps, Hepatitis A and Hepatitis B IgG Seropositivity on The Clinical Course of COVID-19 Disease in Children

Kızamık, Kızamıkçık, Kabakulak, Hepatit A ve Hepatit B IgG Seropozitifliğinin Çocuklarda COVID-19 Hastalığının Klinik Seyrine Etkisi

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Cite this article as: Şahin A, Kara Aksay A, Ekemen Keleş Y, Üstündağ G, Demirçelik Y, Bayram A, et al. The effect of measles, rubella, mumps, hepatitis A and hepatitis B IgG seropositivity on the clinical course of COVID-19 disease in children. J Pediatr Inf 2021;15(4):e217-e222.

Abstract

Objective: Many hypotheses have been proposed and researched regarding why coronavirus disease 2019 (COVID-19) disease is clinically milder and has better outcomes in pediatric patients. These include immune differences, inflammatory response level, T-lymphocyte profile, ACE 2 expression level, melatonin secretion level, less exposure to environmental contaminants, less chronic diseases, and cross-immunity to other viruses.

Material and Methods: In this study, it was aimed to examine the relationship between measles, rubella, mumps, hepatitis A and B vaccine serological responses and the asymptomatic or symptomatic course of COVID-19 infection in children diagnosed with COVID-19. Between March and June 2020, we compared the symptomatic status of children with COVID-19 who were vaccinated for these factors and who did not have a history of measles, rubella, mumps, hepatitis A and hepatitis B infection among the SARS-CoV-2 PCR positive cases.

Results: Seventy-two patients were included in the study. Half of the patients were males. The median age of the cases was 167 months (min: 18 months, max: 213 months). Thirty-seven (51.3%) of all cases were asymptomatic and 35 (48.6%) were symptomatic. There was no statistically significant difference between measles, rubella, mumps, hepatitis A and hepatitis B serological vaccine responses and clinical classification.

Öz

Giriş: Pediatrik hastalarda koronavirüs hastalığı 2019 (COVID-19) hastalığının neden klinik olarak daha hafif geçirildiği ve sonuçlarının daha iyi olduğuna yönelik birçok hipotez öne sürülmüş ve araştırılmıştır. Bunlar arasında bağışıklık farklılıkları, inflamatuvar yanıtın düzeyi, T-lenfosit profili, ACE 2 ekspresyonu düzeyi, melatonin salgılanma düzeyi, çevresel kirlenmelere daha az maruz kalma, kronik hastalıkların daha az görülmesi ve diğer virüslere karşı gelişen çapraz bağışıklık yer almaktadır.

Gereç ve Yöntemler: Bu çalışmada, COVID-19 tanılı çocuklarda kızamık, kızamıkçık, kabakulak, hepatit A ve B aşı serolojik yanıtları ile bu yanıtlarla COVID-19 enfeksiyonunun asemptomatik ya da semptomatik seyri arasındaki ilişkinin incelenmesi amaçlanmıştır. Mart-Haziran 2020 tarihleri arasında hastanemizde SARS-CoV-2 PCR pozitif saptanan olgulardan kızamık, kızamıkçık, kabakulak, hepatit A ve hepatit B enfeksiyonunu geçirme öyküsü olmayan ve bu etkenlere yönelik aşılanmış olan COVID-19 tanılı çocuk olguların, semptomatik olup olmama durumları karşılaştırıldı.

Bulgular: Çalışmaya 72 hasta dahil edildi. Hastaların yarısı erkekti. Olguların median yaş değeri 167 aydı (min: 18 ay, maks: 213 ay). Tüm olguların 37 (%51.3)'si asemptomatik, 35 (%48.6)'i ise semptomatik idi. Kızamık, kızamıkçık, kabakulak, hepatit A ve hepatit B serolojik aşı yanıtları ile klinik sınıflama arasında istatistiksel olarak anlamlı fark saptanmadı.

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Received: 22.10.2020

Accepted: 19.04.2021

Available Online Date: 29.12.2021

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Available online at www.cocukenfeksiyon.org

Conclusion: As a result, in our study, no significant association was found between measles, rubella, mumps, hepatitis A and hepatitis B serological vaccine responses and symptom development status in COVID-19. Further studies are needed to investigate the reasons for the better clinical course of the disease in pediatric cases compared to adults.

Keywords: COVID-19, vaccine, child

Introduction

COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to affect the whole world. As of October 2020, over 40 million people in 216 countries have contracted the COVID-19 disease, and over one million deaths have occurred (1). According to the preliminary report by the Chinese Disease Control and Prevention Center, most of the patients affected were aged between 30-79, and there were few patients aged under 19 (2). Again, in a large-sized case series, it has been reported that children and young adults typically have a mild form of the disease, but older patients, especially with comorbidities, have a severe form of the disease and a higher mortality rate (3). It has been demonstrated in a meta-analysis of studies on children that pediatric patients have a mild course of the disease when compared to adult patients (4,5). Since most of the studies are centered around adult patients, the reason why children have a mild course of the disease is still vague. The less severe course of the disease in children has been associated with lower exposure to the virus and with factors related to the host. Immunity differences, level of inflammatory response, T-lymphocyte profile, the expression level of angiotensin converting enzyme 2 (ACE 2), the level of melatonin secretion, less exposure to environmental pollutants, less presence of chronic diseases, and cross immunity developed to other viruses have been indicated among the possible reasons debated on the subject in relevant articles (6-8). Moreover, it has been argued that non-specific effect of attenuated live vaccines such as Bacillus-Calmette-Guerin (BCG) and Measles, Mumps, Rubella (MMR) might have a mitigating effect on COVID-19 clinical findings (9). Similarly, due to the structural likeness of the spike (S) protein of coronaviruses and the fusion proteins of measles and mumps, it is considered that children previously immunized with the MMR vaccine may develop cross reactive antibodies against coronavirus (10).

In this study, it was aimed to investigate the relation between the serologic responses of MMR, hepatitis A and B vaccines in children diagnosed with COVID-19 and the asymptomatic or symptomatic course of the COVID-19 infection through these responses.

Materials and Methods

The study included cases whose reverse transcriptase-polymerase chain reaction (RT-PCR) detected positive

Sonuç: Sonuç olarak çalışmamızda; kızamık, kızamıkçık, kabakulak, hepatit A ve hepatit B serolojik aşı yanıtları ile COVID-19 hastalığında semptom gelişme ve gelişme durumu arasında anlamlı bir ilişki bulunmamıştır. Pediatrik olgularda hastalığın erişkinlere göre daha iyi klinik seyrinin nedenlerine yönelik ileri araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, aşı, çocuk

for SARS-CoV-2 virus with the Bio-speedy SARS CoV-2 double gene RT-qPCR kit (Bioeksan-Turkey) on combined oropharyngeal-nasopharyngeal swab sample in our hospital between March 2020 and June 2020. Inclusion criteria were as follows: SARS-CoV-2 PCR positivity, not having caught any of the measles, mumps, rubella, hepatitis A and hepatitis B diseases, being immunized against measles, mumps, rubella, hepatitis A and hepatitis B, and at least one month should have passed from the immunization against the specified agents. Exclusion criterion was determined as the presence of conditions decreasing serologic response to vaccines (immunodeficiency or history of dialysis, receiving steroid treatment, having received intravenous immunoglobulin). Vaccination status of the patients was obtained from the vaccination cards of the Ministry of Health. It was seen from the vaccination cards that all patients had received BCG immunization and all had BCG scars. The patients were divided into two clinical classes as asymptomatic and symptomatic:

1. Asymptomatic; no clinical signs and symptoms and no abnormal finding on pulmonary imaging
2. Symptomatic; presence of the symptoms that fit to the case definition of COVID-19, including fever, fatigue, muscle pain, cough, and diarrhea.

In addition to the routine blood samples taken during hospital presentation, HbsAg, AntiHbs, AntiHbc IgM, AntiHbc IgG, measles IgG, rubella IgG, mumps IgG, and AntiHAV IgG levels were studied. Serum samples taken from patients were studied on ALEGRIA (Orgentec Diagnostika GmbH, Mainz, Germany) ELISA with the kits belonging to the same device in the Medical Microbiology Laboratory of our hospital, and the results were evaluated in line with the manufacturer's recommendations. Furthermore, in serum samples, HBsAg, AntiHbs, AntiHbc IgM, AntiHbc IgG, and AntiHAV IgG tests were studied with the Chemiflex method on the ARCHITECT i2000SR device (Abbott- Germany), and the results were evaluated in line with the manufacturer's recommendations. For the study, approval was obtained from the Ethics Board of our hospital and from the Scientific Research Board of the Ministry of Health (Ethics Board No: 2020/7-24). Additionally, informed consent was received from the parents of the children participating in the study.

SPSS 24.0 program was used for data analysis. Mean \pm standard deviation was used when continuous data showed

conformity to normal distribution, median (minimum-maximum) was used when continuous data did not show conformity to normal distribution, and number (n) and percentages (%) were used for categorical variables. Chi-square test was used in the comparisons for categorical variables. Statistical significance in the study was accepted as $p < 0.05$.

Results

Seventy-two patients were included into the study. Thirty-six (50%) of the patients were boys, 36 (50%) were girls, and their median age was 167 months (min: 18 months, max: 213 months). When evaluated as per clinical classification, 37 (51.3%) of all cases were asymptomatic and 35 (48.6%) were symptomatic. When clinical classification was compared according to sex, a statistically significant difference was not found ($p = 0.908$) (Table 1). The cases were divided into 5 groups as regards age range. Ten of the cases (13.8%) were in the 1-5 years age group, 9 (12.5%) were in the 5-10 years age group, 30 (41.6%) were in the 10-15 years age group, and

23 (31.9%) were aged 15 years and over. When clinical classification was compared according to age groups, a statistically significant difference was not observed ($p = 0.106$) (Table 1).

When vaccine serologic responses were reviewed as regards clinical classification, AntiHbs response of 70 cases was evaluated. While AntiHbs response was detected positive in 16 (45.7%) of the 35 asymptomatic cases, it was negative in 19 (54.3%). While 14 (40%) of the 35 symptomatic cases were positive, 21 (60%) were negative for AntiHbs response. When statistically evaluated, a significant difference was not determined between hepatitis B serologic response and clinical classification ($p = 0.629$) (Table 2). Seventy-two cases were evaluated for measles serology. While measles IgG response was positive in 21 (58.3%) of the 36 asymptomatic cases, it was negative in 15 (41.7%). Of the 36 symptomatic cases, 23 (63.9%) were positive and 13 (36.1%) were negative for measles serology. When statistically evaluated, a significant difference was not determined between measles serology

Table 1. Demographics and clinical characteristics of the patients

| | Asymptomatic | Symptomatic | Total | p |
|-------------|--------------|-------------|-------------------|-------|
| Sex | | | | |
| Female | 18 (50%) | 18 (50%) | 36 (50%) | 0.908 |
| Male | 19 (52.7%) | 17 (48.6%) | 36 (50%) | |
| Age range | | | | |
| 1-5 years | 5 (50%) | 5 (50%) | 10 (13.8%) | 0.106 |
| 5-10 years | 6 (66.7%) | 3 (33.3%) | 9 (12.5%) | |
| 10-15 years | 19 (63.3%) | 11 (36.7%) | 30 (41.6%) | |
| >15 years | 7 (30.4%) | 16 (69.6%) | 23 (31.9%) | |

Table 2. Comparison of vaccine serologic responses and clinical responses

| | Asymptomatic | Symptomatic | p |
|--------------------|--------------|-------------|-------|
| Hepatitis B IgG | | | |
| Positive | 16 (45.7%) | 14 (40%) | 0.629 |
| Negative | 19 (54.3%) | 21 (60%) | |
| Total n= 70 | 35 | 35 | |
| Measles IgG | | | |
| Positive | 21 (58.3%) | 23 (63.9%) | 0.629 |
| Negative | 15 (41.7%) | 13 (36.1%) | |
| Total n= 72 | 36 | 36 | |
| Rubella IgG | | | |
| Positive | 20 (83.3%) | 19 (86.4%) | 0.775 |
| Negative | 4 (16.7%) | 3 (13.6%) | |
| Total n= 46 | 24 | 22 | |
| Mumps IgG | | | |
| Positive | 19 (76%) | 12 (54.5%) | 0.121 |
| Negative | 6 (24%) | 10 (45.5%) | |
| Total n= 47 | 25 | 22 | |
| Hepatitis A IgG | | | |
| Positive | 8 (38.1%) | 8 (42.1%) | 0.769 |
| Negative | 13 (61.9%) | 11 (57.9%) | |
| Total n= 40 | 21 | 19 | |

and clinical classification ($p=0.629$) (Table 2). Rubella serology was evaluated in 46 cases. Of the 24 asymptomatic cases, rubella serology was positive in 20 (83.3%) and negative in 4 (16.7%). Of the 22 symptomatic cases, rubella IgG response was positive in 19 (86.4%) and negative in 3 (13.6%). When statistically evaluated, a significant difference was not determined between rubella serology and clinical classification ($p=0.775$) (Table 2). Forty-seven cases were evaluated in terms of mumps serology. Of the 25 asymptomatic cases, mumps serology was positive in 19 (76%) and negative in 6 (24%). Out of the 22 symptomatic cases, mumps serology was positive in 12 patients (54.5%) and negative in 10 (45.5%). When the results were evaluated statistically, a significant difference was not detected between mumps serology and clinical classification ($p=0.121$) (Table 2). Forty cases were evaluated for Hepatitis A serology. Of the 21 symptomatic cases, it was positive in 8 (38.1%) and negative in 13 (61.9%) patients. Of the 19 symptomatic cases, it was positive in 8 (42.1%) and negative in 11 (57.9%) patients. However, a significant difference was not found between hepatitis A serology and clinical classification ($p=0.769$) (Table 2).

Discussion

Severe acute respiratory syndrome coronavirus 2 causes acute respiratory infections in varying degrees in different age groups, and children have a relatively mild course of the disease when compared to adults (3,5). According to a report from Centers for Disease Control and Prevention (CDC), the number of cases aged under 18 years make up of 8.8% of total cases in the United States of America (11). Mortality rate is less than 0.1% of total deaths (11). Similar to other data, it has been reported in epidemiological studies from our country that children have a mild course of COVID-19 (12,13). One of the possible reasons for this is that the cells in the immune system of children and adults show differences in function and content. With advancing age, adaptive immune system is dysregulated, T cells are decreased, and immune memory gained by vaccines is diminished (14). This effect is not only seen in adaptive immune response but also in innate immune response, and an increase is observed in proinflammatory cytokine production (15). In terms of SARS-CoV-2, while an evident decrease is in lymphopenia, CD4+ and CD8+ T cell, auxiliary T cell and storage T cell numbers, lymphopenia has been less reported in children (16,17). Dhochak et al. (18) have also commented that children's adaptive immune response against SARS-CoV-2 is better. It is considered that this condition is due to the fact that children's immune system is secondarily more active and "trained" thanks to live vaccines and frequent viral infections, and thus the infection is controlled at an early stage (6,18). Trained immunity is defined as the reactivation of innate immune cells through re-programming by metabolic and epigenetic changes that develop secondary to vaccines or previous infection (19).

Observational or experimental studies have shown that some attenuated live vaccines administered during childhood have non-specific effects that provide a decrease in infection-related mortality and hospitalization rates (20-22). In a cohort study from Denmark, having had the MMR vaccine decreased hospitalization rate due to any infection (23). Similarly, there have been data suggesting that vaccination with MMR diminishes hospital presentation due to respiratory syncytial virus (24). The non-specific effect of the vaccines is considered to be associated with the fact that vaccines "train" the leucocyte precursors in the bone marrow against infectious agents and provide a more effective function and with T cell-mediated cross reactivity (25,26).

Studies conducted so far have demonstrated that natural killer cells (NK) and interferons (IFN), which are a part of innate immune system, have an important role against viral infections (27,28). It has been put forth that viral vaccines, even in the clinical absence of an infection, stimulates NK cell reproduction and that this response has a longer lifespan, and therefore, viral vaccines can be a potentially therapeutic option in preventing severe viral infections (29).

In an experimental immunological study, it has been asserted that BCG vaccine induces epigenetic modulations of human monocytes, leading to an increase in the production of proinflammatory cytokine and thus provides a protective effect against another infection (30). In another randomized study with placebo controls, it has been demonstrated that BCG vaccine sustains epigenetic re-programming in monocytes in vivo and is protective against an experimental infection caused by yellow fever virus vaccine strain (31). As a result of all studies investigating the non-specific effects of BCG vaccine, BCG vaccine has been shown to provide decrease in acute upper respiratory tract infections (32). BCG vaccine was also administered in our patients. These data have given rise to the hypothesis that BCG vaccine might have protective effect against COVID-19, and clinical studies have been commenced on BCG vaccination (33-36).

The possible protective effects of viral vaccines have become a current issue since proinflammatory cytokines, IFN production, and NK cell response are at the forefront in COVID-19 pathogenesis (37,38). The similarity found between the mode of transmission of measles, mumps, rubella viruses and SARS-CoV-2 and between their primary replication characteristics in the upper respiratory tract has made us consider that the innate immune response stimulated by MMR vaccination might have a cross protective effect against SARS-CoV-2. Similarly, the mild course of the COVID-19 disease seen in 955 sailors of the U.S.S Roosevelt of the U.S Navy has been interpreted as the possible protective effect of BCG vaccine administered to the sailors when they joined the Navy (39). Franklin et al. (40) have carried out an amino acid sequencing analysis

based on the similarity between the glycoproteins of measles, mumps and coronaviruses and have found a 29% amino acid sequencing similarity between rubella and SARS-CoV-2. In animal studies where attenuated live recombinant measles vaccine has been used as a vector, the antibodies formed had neutralizing effect on SARS-CoV and induced antibody production (41,42). In a prospective observational study carried out in Mexico by Larenas-Linnemann et al. (43), the possible protective and mitigating effect of MMR vaccine on COVID-19 clinic has been researched. This study included 255 adults and children vaccinated by MMR due to the fact that an increase was seen in measles cases during the time when COVID-19 pandemic started in their country and a program for re-immunization against MMR was initiated by their Ministry of Health. These 255 cases were followed for COVID-19 infection and SARS-CoV-2 RT-PCR test and/or antibodies specific to SARS-CoV-2 were studied. Of the 255 cases vaccinated for MMR, COVID-19 did not develop during the notification period in 219 cases, Definite COVID-19 infection was seen in 24 patients, and highly-probable COVID-19 infection was observed in 12 patients. In 13 of these 36 cases, of whom 6 were children, COVID-19 disease had a mild course despite the risk factor, which was associated with the non-specific effect of MMR vaccine (43). In line with these data, we also aimed at investigating the effect of the antibody response of the hepatitis A and B and MMR vaccines administered in the childhood on the asymptomatic course of COVID-19 in children. A significant difference was not found between the seropositivity rate related to hepatitis A, B and MMR vaccines in asymptomatic children and the symptomatic group. AntiHbs seropositivity and AntiHAV IgG seropositivity in cases included into the study were found respectively as 42.8% and 40%. Again, measles IgG, rubella IgG, and mumps IgG seropositivity rates were detected respectively as 61.1%, 84.7%, and 73.8%. In comparison with the literature, seropositivity rates of measles, rubella, mumps, and hepatitis A and B were found low (44-46). However, seropositivity rate that develops after vaccination is known to be related to intrinsic (age, genetics, and etc.) and extrinsic (vaccine type, way of administration, and etc.) factors (47). We are of the opinion that these reasons might have caused the low seropositivity rates found in our study. The presence of intrinsic factors affecting age response between the groups and low number of patients are limitations to our study.

To conclude, children have a milder course of SARS-CoV-2 infections when compared to adults, and a better recovery and prognosis is seen in children. The reasons for this condition are still vague. In our study, a significant relation was not found between the asymptomatic and symptomatic presentation of COVID-19 and the children's serologic response to measles, rubella, mumps, and hepatitis A and B vaccines in children diagnosed with COVID-19. Further studies in terms of the possible effects of immunization are needed to better

understand the reasons of good clinical course and outcomes seen in children when compared to adults.

Ethics Committee Approval: Approval for the study was obtained from the İzmir Tepecik Training and Research Hospital Ethics Committee and the Scientific Research Committee of the Ministry of Health (Decision no: 2020/7-24).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- YCD, SA; Design- KAA, SA; Supervision- KAA, YCD; Resource- SA, BA; Data Collection and/or Processing- SA, EKY; Analysis and/or Interpretation- SA, KAA; Literature Search- SA, UG; Writing- SA, KAA; Critical Review- KAA, BA, YCD, DY.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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