Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine

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Background: Vaccines are paramount in the effort to end the coronavirus disease 2019 global epidemic. BNT162b2 is approved for the vaccination of adolescents over 16 years of age. Systemic adverse events were scarce though the pretested cohort of this age group was relatively small. The aim of the current study is to raise awareness for potential adverse reactions.

Methods: This is a case series of patients diagnosed with perimyocarditis following vaccination. Patients were compiled from 3 pediatric medical centers in Israel through a network of pediatricians and data regarding those cases was collected. In addition, incidence of perimyocarditis during the vaccination period was compared with previous years.

Results: All patients were males 16–18 years old, of Jewish descent, who presented with chest pain that began 1–3 days following vaccination (mean, 2.1 days). In 6 of the 7 patients, symptoms began following the 2nd dose and in 1 patient following the 1st dose. All cases were mild and none required cardiovascular or respiratory support. The incidence of perimyocarditis during the vaccination period was elevated in comparison to previous years.

Conclusions: This case series describes a time association between coronavirus disease 2019 vaccine and perimyocarditis in adolescents. All cases were mild, although only long-term follow-up can reveal the true impact of this cardiac injury. While it seems that the incidence of perimyocarditis during the vaccination campaign period is increased, a more comprehensive data collection on a wider scale should be done. We hope this report will serve as a reminder to report events and allow for analysis of potential adverse reactions.

Key Words: coronavirus disease 2019, vaccination, children, myocarditis, pericarditis

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Since the first detection of coronavirus disease 2019 (COVID-19) in 2019, over 160 million cases have been reported worldwide.[1] While major mortality and morbidity has been mainly reported in the elderly and in those with risk factors,[2] newer virus variants may manifest more severely in young adults and children. Combined with the post COVID-19 effects such as multisystem inflammatory syndrome in children (MIS-C), the burden of the disease may increase in the pediatric population.[3] The substantial consequences of the disease and its epidemic proportions has raised the need to promptly develop a vaccine against the virus.[4,5] At the end of 2020, 2 vaccines based on a mRNA platform received emergency use authorization from the American Food and Drug Administration.[6] One of these products is the BNT162b2 vaccine that is currently employed worldwide and has been administered to nearly 130 million patients in the United States alone.[7]

Following Food and Drug Administration approval, Israel launched a wide scale vaccination campaign using the BNT162b2 mRNA COVID-19 Vaccine.[8] With the Israeli four health maintenance organizations exclusively and effectively conducting the inoculation, over 3.2 million patients (approximately 34% of the country's population) have been vaccinated with 2 consecutive doses by the end of February 2021. Initially summoning individuals 60 years of age or older, the campaign gradually expanded to include all pretested age groups with adolescents older than 16 years being the final group to begin inoculation at the end of January 2021. Nearly 200,000 teenagers above 16 years of age have received at least 1 dose and approximately 65,000 received 2 doses of the vaccine by the end of February 2021.[9]

The BNT162b2 phase 3 study, which was performed in people over 16 years old, showed a favorable safety profile.[4,5] Local effects included pain at injection site and injection site erythema or swelling, while reported systemic reactions included mainly fatigue, headache, fever and chills. Participants reporting severe or serious adverse events were scarce. Younger recipients (16–55 years of age) reported systemic events more frequently than older recipients, although no specific mention was made in relation to the 16–18-year-old participants. While only 138 adolescents 16–18 years of age were enrolled in the vaccine group, comprehensive safety data regarding this age group is lacking.[10]

In this study, we describe a series of young adolescents 16–18 years of age who developed perimyocarditis soon after inoculation with COVID-19 BNT162b2 vaccine. Our objective is to discuss the time association and the differential diagnosis of these cases.

METHODS

Cases of perimyocarditis in adolescents 16–18 years of age following the BNT162b2 vaccine from 3 medical centers in Israel were collected. Patients were compiled using a network of pediatricians and details were collected from patients' medical files. Cases were excluded solely due to insufficient information. For the purpose of this series, perimyocarditis was defined as suitable clinical presentation and one of the following: elevated cardiac biomarkers, electrocardiogram (ECG) findings or abnormalities on echocardiogram.[11] Data regarding the incidence of perimyocarditis was collected from records of the medical centers participating in the current study. For this study, we gathered all children 16–18 years of age diagnosed with acute pericarditis or acute myocarditis using the International Classification of Diseases, 9th revision

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(codes 420 and 422). A comparison of pericarditis and myocarditis incidence between the vaccination campaign (January 1, 2021, to February 28, 2021) and the same time period in previous years was performed.

Due to the case report nature of this data collection, a waiver was granted from the institutional Helsinki committee.

RESULTS

During the vaccination campaign in January 2021 and February 2021, 7 cases of perimyocarditis following COVID-19 vaccination in children 16–18 years of age were found in 3 pediatric centers in Israel.

Here, we describe a single representative case from Schneider medical center, following a table summarizing information of all cases: A 16-year-old male presented to the emergency room with exertional chest pain and cough that started on the day of admission, 2 days following inoculation with a second dose of the BNT162b2 vaccine. Due to the protocol implemented in the educational institution he was attending, he underwent routine sequential COVID-19 polymerase chain reaction (PCR) tests in the weeks before his admission, all were negative. Upon arrival to the emergency room, vital signs and physical examination were normal. Chest radiograph did not demonstrate any pathologic findings. ECG revealed normal sinus rhythm, right ventricular conduction delay, ST-segment elevation in leads I, II, augmented vector foot and in V4–V6 and ST depression in leads V1 and augmented vector right (Fig. 1). Laboratory testing revealed 8900 white blood cells/microliter, hemoglobin level of 13.2 g/dL, platelet level of 120,000 cells/microliter, C-reactive protein level of 3.3 mg/dL, maximal troponin level of 3130 nanogram/L (normal range<14 ng/dL), N-terminal pro-brain natriuretic peptide of 631 picograms/mL (normal range <125 pg/mL), fibrinogen level of 571 mg/dL (normal range, 200–530 mg/dL) and D-dimer of 855 nanogram/mL (normal range <500 ng/mL). Biochemistry and coagulation studies were within the normal limits. Echocardiography demonstrated normal right ventricular and pulmonary artery pressures, near-normal ventricular function (left ventricular fractional shortening of 28%), no pericardial effusion. The patient was admitted to the pediatric intensive care unit with a presumed diagnosis of myocarditis and was treated with ibuprofen. An extensive laboratory investigation was performed including cultures and serologies for prevalent pathogens (ie, viruses, typical and atypical bacteria associated with perimyocarditis) as well as a rheumatologic panel, although no specific etiology was found. Throughout his hospitalization, he was hemodynamically stable and did not require inotropic support. During his 6 days of hospitalization, he gradually began to show clinical, laboratory and echocardiographic improvement. Subsequent echocardiography was found normal with fractional shortening of 38%. Troponin level upon discharge plummeted to 53 nanogram/L. Three weeks post discharge, he was asymptomatic and had a normal ECG and echocardiogram.

During the study period, additional cases were found with the following similar features and are summarized in Table 1: All patients were males and 16–18 years of age, of Jewish descent, that presented with chest pain beginning 1–3 days following vaccination (mean 2.1 days). In 6 of the 7 patients, symptoms began after the 2nd dose and in 1 patient after the 1st dose. Notable abnormal findings in these cases include elevated troponin levels averaged 3538 nanogram/L (range 252–13,720 nanogram/L), ECG changes consistent with pericarditis or myocarditis (6/7 cases) and abnormal findings in echocardiography predominantly pericardial effusion (3/7 cases). Prior potential exposure to individuals infected with COVID-19 was found in 2 patients, however, they tested negative in repeated PCR examinations. All patients underwent COVID-19 PCR test on the day of admission as part of a routine screening to all hospitalized patients. Four patients were admitted to the pediatric intensive care unit for observation, none required cardiovascular or respiratory support. Five children were treated with Ibuprofen, 1 was treated with aspirin and 1 did not receive any pharmacologic treatment.

Myocarditis and pericarditis incidence during the inoculation campaign compared with previous years: Data collected from all 3 medical centers during the time period between January 1,

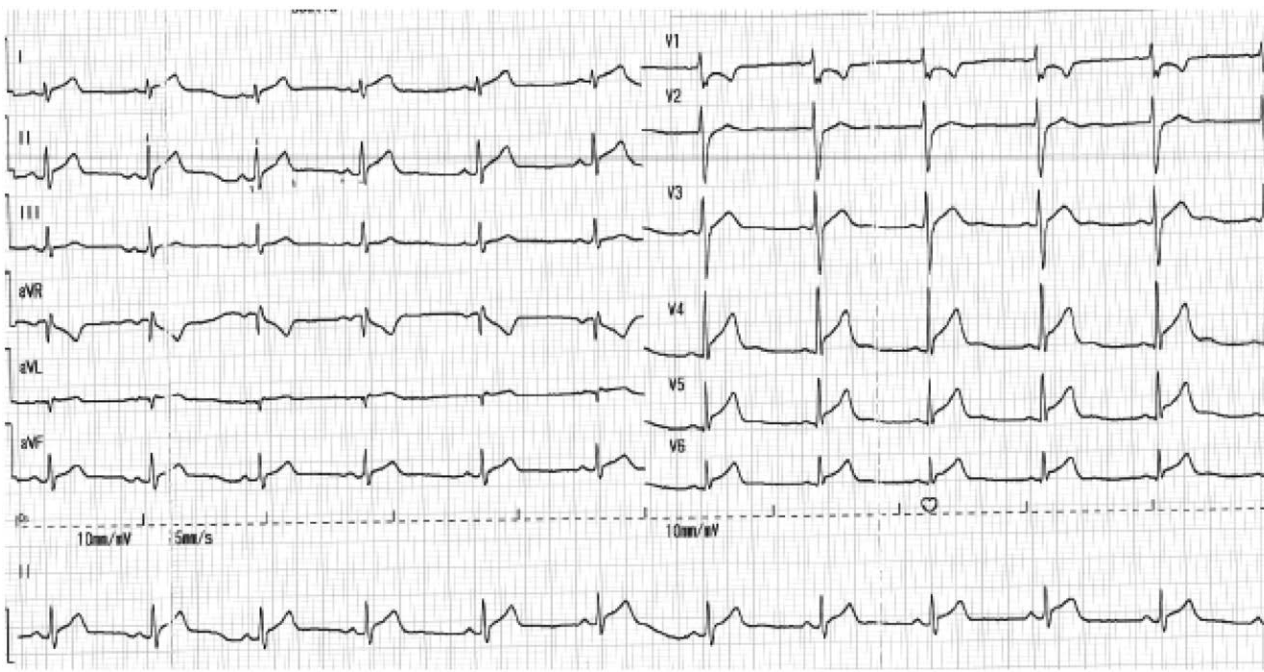

FIGURE 1. Electrocardiography of a 16-year-old male consistent with perimyocarditis. aVF indicates augmented vector foot; aVL, augmented vector left; aVR, augmented vector right.

TABLE 1. Characteristics of the Described Cases

Case	Age	Gender	Symptoms After 1st/2nd Vaccination	Days From Vaccination to Symptoms	Symptoms	Maximum CRP Level (mg/dL)	Maximum Troponin Level (ng/dL)	NT-pro-BNP (pg/mL)	COVID-19 Serology	ECG Finding	Echocardiography Finding	Length of Hospitalization (d)
1	17.1	Male	2nd	3	Chest pain	2	1332	238	NA	Mild ST elevation, RBBB	Normal	4
2	16.2	Male	2nd	1	Chest pain	4.6	2205	726	Positive anti-S	Diffuse ST elevations	Normal function, mild pericardial effusion	6
3	16.8	male	2nd	2	Chest pain cough	3.3	3130	631	NA	ST elevation in leads I, II, AVF, V4–V6, ST depression in leads V1, AVR. ICRBB	Borderline function FS 28%	6
4	16.3	Male	2nd	3	Chest pain nausea	5.6	1649	571	Positive anti-S	ST elevations in leads V2–V6, PR depression on lead II	Normal function, minimal AI, mild PI, mild pericardial effusion	4
5	17.5	Male	2nd	1	Chest pain headache	9.2	13,720	NA	Positive anti-S negative anti-N	ST elevations on V3–V6	Normal, FS 33%	5
6	16.6	Male	1st	2	Chest pain dyspnea diarrhea fever	3.6	2482	NA	Positive anti-S negative anti-N	ST elevations on leads II, III, V5	Normal	5
7	17.6	Male	2nd	3	Chest pain dyspnea	3.6	252	NA	Positive anti-S	Normal	Normal function, small pericardial effusion	3

AI indicates aortic insufficiency; AVF, augmented vector foot; AVR, augmented vector right; CRP, C-reactive protein; FS, fractional shortening; ICRBBB, incomplete right bundle branch block; NA, data not available; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PI, pulmonary valve insufficiency; PR, P wave to R wave interval; RBBB, right bundle branch block.

2021, and February 28, 2021, revealed a total of 10 children 16–18 years of age diagnosed with pericarditis and myocarditis, 8 of them following the COVID-19 vaccination (7 are described above and a single case was excluded due to inadequate documentation). During the same time period in previous years, a lower incidence of perimyocarditis was reported in this age group, with only 2 cases in 2018 and 2020 and 4 cases in 2019.

During January–December 2020, only eleven children were diagnosed with perimyocarditis in all 3 medical centers.

DISCUSSION

Vaccines are arguably one of the greatest inventions of the 20th century allowing to eradicate or to contain various diseases. Vaccine development and implementation are paramount to resolution and return to normalcy in the recent COVID-19 pandemic and the beginning of the vaccination campaign was widely anticipated by the public in Israel.

Although vaccines have been proven safe, possible side effects continue to be widely studied. National monitoring mechanisms of adverse events have been long established in developed countries including the US Vaccine Adverse Event Reporting System and EudraVigilance—the European database of suspected adverse drug reaction reports. When the analysis of these event reports leads to a suspicion of causality between the vaccine and the reaction, a change in its usage policy may be in order or to prioritize a different vaccine with a better safety profile. Such was the case of the Rotashield - Rotavirus vaccine that was found to be associated with an increased risk of intussusception leading to its withdrawal and a change in recommendations regarding the age of vaccination.[12,13]

In this study, we describe 7 cases of perimyocarditis in adolescent males occurring 1–3 days after inoculation with BNT162b2 vaccine. Although these patients underwent thorough clinical and laboratory investigation, a specific etiology to the development of perimyocarditis was not identified.

Considering the differential diagnosis and possible pathogenesis of the above cases, COVID-19 itself may still be suspected. COVID-19–related myocardial involvement in adults has been described in both acute disease and in a cardiac magnetic resonance imaging performed in convalescing adults (ie, after an isolation period and at least 72 symptoms-free hours).[14–16] In children and adolescents, perimyocarditis associated with COVID-19 is mainly described as part of MIS-C (which is estimated to occur in 0.2%–0.6% of cases), although myocarditis can also appear as the initial presentation of the infection in rare instances.[17] Even so, in most of our cases, no fitting exposure to an infected individual took place and none of our patients tested positive for COVID-19 in PCR investigation. Additionally, the described patients did not show clinical and laboratory findings consistent with MIS-C; no fever, rash, conjunctivitis or hemodynamic changes were noticed and inflammatory markers were not significantly elevated.

Perimyocarditis as an adverse event was studied along the years as published literature includes numerous case reports following inoculation with various vaccines in both adults and children.[18–20] No specific risk factors were suggested in those case reports, nor was a clear mechanism suggested. Historically, smallpox vaccines were reported to be associated with a significant number of cases of perimyocarditis in both first-time vaccines and after recurrent doses.[21] However, a more recent population-based study of more than 400,000 adults who were inoculated with one or more live viral vaccines (other than smallpox) did not show increased risk of perimyocarditis in the time period of 42 days following the vaccination.[22] Perimyocarditis was studied through Vaccine Adverse Event Reporting System as well and

was found to be most frequently associated with human papillomavirus meningococcus, hepatitis A and Influenza vaccine in patients under 18 years of age.[23] However, when analyzing reports of adverse events following immunization, the data was not sufficient to determine or to eliminate causality.

To our knowledge, this is the first description of transient cardiac injury in children following the BNT162b2 vaccine and no such cases were described in the studies performed throughout its developmental process. Although adolescents were in fact included in the phase 3 testing performed by Pfizer, the trial included only 138 subjects 16–18 years of age and this small cohort is likely not to portray the full spectrum of potential adverse reactions following the vaccine. Israel was the first country to vaccinate all pretested age group on mass, thus enabling to describe a temporal association between the vaccine and potential complications.

This study entails a few limitations including its retrospective nature and the small number of cases. Moreover, the identification and collection of these cases was not systematically done and other potential cases in other medical centers may have been missed. As any adverse event after vaccination is mandatorily reported to the Israeli Ministry of Health, we hope a more comprehensive report on a national wide scale will follow. Seeing that comprehensive reports of adverse events in adolescents are not yet published, this rapid communication is intended to raise awareness of the time association between the vaccine and these cases.

In conclusion, this case series describes a time association between COVID-19 vaccine and perimyocarditis in adolescents 16–18 years of age. All cases were mild, and none required hemodynamic or respiratory support, although only long-term follow-up will reveal the true impact of this cardiac injury. While it seems that the incidence of perimyocarditis during the vaccination campaign period is increased, a more comprehensive data collection on a wider scale should be done. We hope this report will raise awareness to the subject and will serve as a reminder to report events as part of the post-marketing investigations and allow for a thorough adverse events following immunization analysis.

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