//Follow-up and comparison of children and adolescents with COVID-19 vaccine-associated myocarditis against non-vaccine-associated myocarditis in the MYKKE registry//

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A few months after the start of the COVID-19 vaccination campaign, it had already become apparent that there is a connection between the use of COVID-19 mRNA vaccines and the very rare occurrence of myocarditis or pericarditis, predominantly in young men under the age of 30. Risk warnings have been included in the Summary of Product Characteristics and the Standing Committee on Vaccination (Ständige Impfkommission, STIKO) has taken this side effect into account in its risk-benefit assessment and vaccination recommendations. In cooperation with the Registry for Children and Adolescents with Suspected Myocarditis (Register für Kinder und Jugendliche mit Verdacht auf Myokarditis, MYKKE Registry), the Paul-Ehrlich-Institut collected data for a prospective study of suspected heart muscle inflammation cases in children and adolescents after COVID-19 vaccination and recently published the results.[1] The study and results are summarised below.

BACKGROUND

A few months after the start of the COVID-19 vaccination campaign, there was already evidence showing that COVID-19 mRNA vaccines are associated with an increased risk of myocarditis, especially in males aged 16 to 39 years.[2] Since then, numerous case studies have shown a connection between myocarditis and mRNA COVID-19 vaccines.[3–5] It has been apparent for some time that myocarditis occurring after COVID-19 vaccination is associated with a better clinical outcome than conventional myocarditis and myocarditis resulting from SARS-CoV-2 infection.[6] Data on paediatric COVID-19 vaccine-associated myocarditis (vaccine-associated myocarditis, VA myocarditis) is rare. Although the course of this type of myocarditis appears to be mild, little is currently known about the long-term effects on patients.[7]

Therefore, the aim of this study was to compare the course of VA myocarditis in children and adolescents with the course of non-VA myocarditis in this age group. The first step of the comparison was to characterise the clinical course of myocarditis after COVID-19 vaccination, including the follow-up data collected within the framework of the multicentre Registry for Children and Adolescents with Suspected Myocarditis – MYKKE (www.mykke.de). These patients were then compared with a paediatric non-vaccine-associated myocarditis cohort (non-vaccine-associated myocarditis, NVA myocarditis) from the MYKKE registry to determine any differences in disease progression.

A total of 279 cases of suspected myocarditis in children and adolescents (aged 12 to 17 years) after COVID-19 mRNA vaccination were reported to the Paul-Ehrlich-Institut by or on 31 October, 2023. In only a few cases were additional details on diagnostics and/or therapy or disease progression obtained after being requested.

MYKKE Registry

MYKKE is a multicentre, prospective long-term registry that comprises patients with suspected paediatric myocarditis. In addition to making a record of diagnostic and therapeutic procedures as well as the long-term course of paediatric myocarditis, MYKKE provides a research platform for further clinical studies.[8] The National Register for Congenital Heart Defects provides administrative and technical support for the MYKKE registry (www.mykke.de). Since 2013, 29 medical centres in Germany, Switzerland, and Austria have joined, providing information on 750 patients and their follow-up examinations.

METHOD

Patients aged five to 17 years with suspected myocarditis occurring within 21 days of COVID-19 vaccination were enrolled in the PedMYCVAC cohort of the MYKKE registry, subject to parental consent. The data was collected retrospectively and prospectively from 1 July, 2021, until 1 December, 2022. Baseline clinical data and data from three-month and nine-month follow-ups were collected and compared with those of paediatric patients with confirmed cases of NVA myocarditis, taking into account various baseline characteristics. Only male patients over the age of nine were included in the comparative analysis for improved comparability.

Based on the US Centers for Disease Control and Prevention (CDC)[9] case definition for probable cases of COVID-19 VA myocarditis, myocarditis is suspected in patients with the following symptoms:

- one or more new clinical symptoms: chest pain or pressure, shortness of breath/breathlessness, palpitations, fatigue

AND

- one or more new diagnostic findings: increased levels of troponin or pro-BNP (brain natriuretic peptide)/N-terminal BNP prohormone (NT-proBNP); abnormalities in the electrocardiogram (ECG) or newly occurring arrhythmias; abnormalities in the echocardiogram or cardiac magnetic resonance imaging (cMRI) that are compatible with myocarditis; or myocarditis detected by biopsy.[10]

The clinical data was entered into the study's online database by the attending physicians. The data included vaccination data, the patient's medical history with symptoms, and results from diagnostics, therapy, and follow-up examinations. All diagnostic procedures were performed for the purpose of clinical indication.

RESULTS

There were 56 patients with COVID-19 VA myocarditis (mean age 16.3 years, 91% male) in the data reported from 15 centres between July 2021 and December 2022. Eleven patients (20%) had a slightly reduced left ventricular ejection fraction (LVEF; 45-54%). No cases of severe heart failure, no cases requiring a heart transplant, and no deaths were observed. 14 of 49 patients (29%) had residual symptoms at the three-month follow-up (median [IQR] 94 days; 63–118 days). The most common symptoms were atypical intermittent chest pain and fatigue. Diagnostic abnormalities were still present

in 23 of the 49 patients (47%), primarily residual changes in the cardiac MRI. None of the 21 patients examined at a nine-month follow-up still had symptoms (median 259 days; 218-319 days) and nine patients continued to have residual MRI changes, all of which were already declining.

Comparison between COVID-19 vaccine-associated myocarditis (VA myocarditis) and non-vaccine-associated myocarditis (NVA myocarditis)

The following differences were found when comparing the clinical features and diagnostic findings between predominantly male paediatric patients with COVID-19 VA myocarditis (n=50) and NVA myocarditis (n=108) at their first examination: While patients with COVID-19 VA myocarditis were more likely to experience chest pain (p=0.013), patients with NVA myocarditis were more likely to have symptoms of heart failure (p=0.003). Accordingly, patients with NVA myocarditis had a lower LVEF on the echocardiogram (p<0.001) and were more likely to have a left ventricular enlargement (p=0.045). Cardiac arrhythmias were also more frequent in the NVA myocarditis group (p=0.031). There were no other significant differences in symptoms and clinical diagnosis between the two cohorts. In NVA myocarditis patients, the need for mechanical circulatory support (n=5.5%), the need for a heart transplant (n=4.4%), and events such as cardiorespiratory resuscitation (n=4.4%) and death (n=2.2%) were more likely. No such serious events occurred in patients with COVID-19 VA myocarditis.

The parameters recorded and the comparison of the symptoms between NVA myocarditis and COVID-19 VA myocarditis are described in detail in the original publication, which is available free of charge.[1]

DISCUSSION

At the three-month follow-up examination in the COVID-19 VA myocarditis cohort, 29 percent of patients had residual symptoms, most commonly atypical intermittent chest pain and fatigue. Similar symptoms were described at a one-month follow-up in 50 percent of adolescent patients (aged 12 to 17 years) with probable or definitive COVID-19 VA myocarditis.[11] In the study presented here, a quarter of patients were prescribed medication for heart failure or cardiac arrhythmias. These results are consistent with another study in young adults and adolescents with COVID-19 VA myocarditis with a follow-up examination 90 days after onset of first myocarditis symptoms.[12]

At the follow-up examination nine months after the occurrence of the first myocarditis symptoms, nine patients were found to have additional diagnostic abnormalities, including three cases of slightly reduced left ventricular function appearing in the echocardiogram or the cardiac magnetic resonance imaging. It is important to note that at the time the publication was submitted, there was no data regarding the nine-month follow-up for more than 50 percent of the original cohort. Even if the diagnostics were completely unremarkable in all remaining subjects, the proportion of subjects showing diagnostic abnormalities would lie at 16 percent.

However, most of the limited data published so far on the course of COVID-19 VA myocarditis shows that the left ventricular functional impairment was completely reversed in all paediatric patients by the time of the short-term or medium-term follow-up exam.[13–15]

Consistent with previously published studies, the clinical course of COVID-19 VA myocarditis has been mild, and no cases of severe heart failure or death have been observed.[13] In contrast, NVA myocarditis is reported to be more likely to result in severe disease progression in paediatric patients, especially in young children.[16]

CONCLUSION

The study described here presents a deeply phenotyped paediatric cohort of COVID-19 vaccine-associated myocarditis compared to non-vaccine-associated myocarditis. It is the first study to show detailed differences in clinical and diagnostic findings between these two entities at the initial examination and during follow-up.

The course of COVID-19 vaccine-associated myocarditis in paediatric patients appears to be mild and differs from non-vaccine-associated myocarditis in paediatric patients. Due to a number of residual symptoms and diagnostic abnormalities at the follow-up examinations, further studies are needed in order to make assertions about the long-term effects.

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