Vaccine: X 14 (2023) 100350

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Myocarditis following COVID-19 mRNA vaccinations: Twin and sibling case series

P. Shenton [a,b], D.R. Cheng [a,b,c,d,*], P. Simm [b,c], B. Jones [b,c], N.W. Crawford [a,b,c]

[a] SAEFVIC, Murdoch Children's Research Institute, Parkville, VIC, Australia
[b] The Royal Children's Hospital Melbourne, Parkville, VIC, Australia
[c] Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
[d] Centre for Health Analytics, Melbourne Children's Campus, Parkville, VIC, Australia

ARTICLE INFO

Keywords:
Myocarditis
COVID-19 vaccination
Adverse Events of Special Interest
Vaccine safety

ABSTRACT

Importance

Myocarditis and myopericarditis are well described adverse events of special interest (AESI) following COVID-19 vaccinations. Whilst the aetiology is still being investigated; there is evidence that genetic predisposition may be a risk factor for the development of myocarditis. Furthermore, hormones are thought to contribute to sex-specific differences in myocarditis, skewed toward a larger risk in adolescent males.

Objective: This unique sibling case series may help highlight potential mechanisms and prognostic factors in the development of myocarditis following COVID-19 vaccination in adolescent males. In this context, twin and familial studies provide a unique epidemiological perspective to investigate the interplay between genetic predisposition and other factors.

Participants: Observational case series of all siblings reported to SAEFVIC[1] with chest pain following COVID-19 vaccinations in Victoria, Australia.

Exposure: mRNA vaccination (Comirnaty BNT162b2 COVID-19 (Pfizer-BioNTech) and Spikevax mRNA-1273 (Moderna).

Findings: Our case series comprises 6 young males; two sets of monozygotic twins and one set of fraternal brothers following reports of chest pain associated with COVID-19 mRNA vaccination. Five patients were diagnosed with myocarditis as per Brighton Collaboration Criteria (Level 2). The remaining sibling, who did not have myocarditis, was subsequently diagnosed with pubertal delay.

Conclusions: Understanding the genetic and hormonal risk factors and aetiology for myocarditis associated with COVID-19 vaccines is paramount. Further evaluation of specific genetic targets or biomarkers is required to understand the implications of population vaccine policy, particularly for adolescent and young adult males at highest risk for this AESI.

Background

The overall benefit for COVID-19 vaccination has been demonstrated in its instrumental effect in the response to the SARS-COV-2 pandemic [1]. However, myocarditis and myopericarditis are described adverse events of special interest (AESI) following COVID-19 vaccinations. Although rare [1], the risk is significantly increased following the second dose of mRNA COVID-19 vaccination in young males, with peak incidence in 16–17-year-old males [1,2].

Myocarditis is also a known complication of SARS-CoV-2 and other viral infections such as coxsackievirus, parvovirus B-19 and HHV6 [3]. Understanding the reasons and risk factors for susceptibility and differences in prognosis remains limited, noting there is a higher background rate in adolescent and young adult males from all causes [3–5]. This background rate is more than double in young males aged 18–34 years (37 per 100,000 person years) compared to females (16 per 100,000 person years) [5].

There is emerging evidence that genetic predisposition may contribute to diagnosis of myocarditis [4,6,7]. Sex hormones are also thought to contribute to sex-specific differences in rates and outcomes of

* Corresponding author at: The Royal Children's Hospital, 50 Flemington Rd, Parkville, VIC 3052, Australia.
E-mail address: daryl.cheng@rch.org.au (D.R. Cheng).

[1] SAEFVIC: Surveillance of Adverse Events Following Vaccination in the Community.

https://doi.org/10.1016/j.jvacx.2023.100350
Received 2 March 2023; Received in revised form 23 May 2023; Accepted 6 July 2023
Available online 7 July 2023

all-cause myocarditis [8–10]. Thus, twin studies may assist in providing unique epidemiological perspectives to investigate the interplay between genetic predisposition and other factors such as these.

Methods

SAEFVIC is the vaccine safety surveillance service for Victoria, Australia. This series presents three sets of twin and sibling chest pain AESI reports, with five of the six patients described having confirmed myocarditis as per Brighton Collaboration criteria (BCC) [11] following COVID-19 mRNA vaccinations (Cominarty or SpikeVax), as per Australian COVID-19 recommendations for this age group. BCC criteria were applied based on data available at initial presentation and investigation of suspected myocarditis.

Follow-up of each case was undertaken as part of public health AESI management. SAEFVIC data is part of a clinical quality registry with standing ethics approval that forms part of Victoria's vaccine safety surveillance program. Consent to report the symptoms and for SAEFVIC to contact the patient's guardians was obtained by the initial reporting clinician. Patient's families were then contacted by the SAEFVIC clinical team and medical records were obtained from their respective treating health services. They were reviewed directly as part of the Victorian Specialist Immunisation Service (VicSIS) Clinic at the Royal Children's hospital, Melbourne. Finally, patient and/or family consent was obtained for inclusion in this case series.

Results

A total of 208 cases of myocarditis were recorded in the SAEFVIC database as meeting case definition criteria for myocarditis following COVID-19 vaccination in Victoria between 22nd February 2021 and 30 September 2022. The following cases are siblings identified from this cohort. Cases are described below with key demographics, symptoms and investigation results in Table 1.

Table 1
Key findings in each case.

Case	Dose # / Vaccine Platform	Time to onset (days)	Presenting Symptoms	Troponin Peak (Normal range (NR))	Electrocardiogram Findings	Echocardiogram Findings	Cardiac MRI Findings (5.5 to 8 months post diagnosis)	Diagnosis (Brighton Level)	Self-Rated Tanner Stage
A1	Dose 2/ Comirnaty	2	- Central pleuritic chest pain (worse lying flat) - Palpitations - Shortness of breath	12062 ng/L (NR <72)	Initial ECG: mild lateral ST elevation in V4-6 Subsequent: anteroinferior T wave inversion with biphasic T waves	Normal systolic ventricular function, mild TR**, and no pericardial effusion or regional wall motion abnormalities.	LGE* present in the mid to apical anterolateral wall with subpericardial distributon and in the basal inferolateral mid wall. Probable subtle mid wall septal LGE.	2	5
A2	Dose 2/ Comirnaty	2	- Pleuritic chest pain – B/L upper chest (worse on side) - Associated neck pain - Urge to cough - Palpitations - Nausea	20996 ng/L (NR <72)	Initial: mild lateral V4-6 ST elevation of 1mm with biphasic T wave inversion. Subsequent: anteroinferolateral T wave inversion.	Normal left ventricular systolic function. Trivial TR, no pericardial effusion or regional wall motion abnormalities.	Extensive patchy LGE of the myocardium in the subepicardial and mid wall distribution involving the inferolateral and anterolateral walls and apical septum. Some minor linear mid wall septal enhancement.	2	5
B1	Dose 2/ Comirnaty	3	- Shoulder -> central chest pain - Palpitations	2200 ng/L (NR < 11)	Postural sinus tachycardia, improving by discharge, nil other concerning features.	Structurally normal heart with good function and no pericardial effusion.	Structurally normal heart, normal biventricular systolic function. No evidence of myocardial infarction, fibrosis or infiltration.	2	5
B2	Dose 2/ Comirnaty	10	- Two distinct episodes of left sided focal brief chest pain - Intermittent palpitations	<2 ng/L (NR<11)	Sinus tachycardia, improved with reassurance.	POCUS# – unremarkable.	N/A	5 (does **not** meet criteria for diagnosis)	2
C1	Dose 2/ Spikevax	3	- Central chest pains	2444 ng/L (< 21)	Evolution of T wave inversion in lead III	Unremarkable with no effusion or wall motion abnormality detected	Structurally normal heart, normal biventricular systolic function. No evidence of myocardial infarction, fibrosis or infiltration.	2	5
C2	Dose 2/ Spikevax	10	- Syncope - Mild central chest discomfort	439 ng/L (<21)	Initial: PR depression and ST elevation in V2	Unremarkable (2 month follow up)	Unavailable at time of publication	2	5

For ease of description and maintenance of confidentiality each sibling set is ascribed a letter (A-C) and each sibling within the pair is assigned a number (1 or 2).
Patients were investigated in Emergency Departments as per PREDICT (Paediatric Research in Emergency Departments International Collaborative) *mRNA Chest Pain* guidelines[1].
*LGE = Late Gadolinium Enhancement, **TR = tricuspid regurgitation # POCUS = Point of care Ultrasound.

A Twins

These 17-year-old identical twin males had a remarkably similar onset and duration of symptoms as well as investigation findings. Their clinical courses followed previously described trajectories for this AESI, with onset of symptoms including chest pain 2 days after dose 2 of a COVID-19 mRNA vaccination.

Both twins were initially investigated with blood tests and an electrocardiogram (ECG). Their significantly elevated troponins and abnormal ECG results (Table 1) were diagnostic for myocarditis and they were admitted for cardiac monitoring and further investigation including serial troponins, telemetry and echocardiograms as well as extensive work up for alternative causes.

Twin A1 reported his symptoms as largely resolved by 2 days post onset, whereas twin A2 reported most symptoms resolved by 5 days post onset.

Both twins had wide ranging investigations for other causes of myocarditis which were negative. These included screens for several viral and bacterial infections as well as autoimmune causes.

Importantly, both SARS-CoV-2 PCR and respiratory virus PCR tests were negative in both twins, indicating that their myocarditis was highly unlikely to be related to a wild-type COVID-19 infection.

As expected the brothers appeared phenotypically similar and both appeared pubertally appropriately developed during follow up appointments. A self-rated Tanner stage was completed to assist in pubertal assessment (Table 1) in the context of the subsequent monozygotic twin presentations described below.

B Twins

The B Twins were 16-year-old monozygotic twin brothers with significantly different presentations.

B1 presented with chest pains after his second dose of COVID-19 mRNA vaccination. He was diagnosed with myocarditis based on symptoms and significant troponin elevation findings and admitted for observation and telemetry monitoring. He was noted to have postural tachycardia on standing but had a normal echocardiogram. His symptoms largely settled by 3 days.

Although B2 was 16-years-old, he had been previously investigated at 14 years of age for pubertal delay in the context of growth discrepancy compared to his monozygotic twin brother. He developed intermittent palpitations and brief atypical episodes of chest pain 10 days after dose 2 COVID-19 mRNA vaccination.

Given the concern about his symptoms as well as his brother's recent diagnosis, he was investigated with troponin, ECG and cardiac point of care ultrasound (POCUS). His ECG demonstrated sinus tachycardia and POCUS was unremarkable. It was noted that his tachycardia improved once he was reassured of his normal troponin result.

During the clinical follow up process, the significant growth discrepancy between the brothers was again noted, with twin B2 appearing remarkably less mature than B1. Twin B2′s investigations revealed a slightly low testosterone (3.5 nmol/L, normal range: 9–35 nmol/L) and luteinizing hormone level for age (1.9 nmol/L, normal range: 3–10 nmol/L) and a slightly delayed bone age in keeping with delayed pubertal onset. At the time, B2 had a self-rated Tanner stage of 2 and was referred for endocrinological assessment and management andhe subsequently commenced treatment for delayed puberty with testosterone injections.

C siblings

The C siblings were also both diagnosed with myocarditis. C1 was 16 years old and developed chest pains 3 days after his dose 2 COVID-19 mRNA vaccine. His investigations included a peak troponin similar to that of the A twins and B1.

C2 was a 13-year-old male with an atypical presentation; he experienced a syncopal episode at home overnight, approximately 10 days after COVID-19 mRNA immunisation. This was followed by mild central chest discomfort and he was found to have moderately elevated troponin and minor ECG abnormalities. His pain resolved and he was discharged the following day.

None of the patients required readmission to hospital during follow up to 6 months post diagnosis.

Discussion

Five of the six reported cases fit the clinical and demographic phenotype as well as diagnostic criteria of COVID-19 vaccine related myocarditis. The unique epidemiological perspectives of twin and sibling evaluations in this study prove invaluable in contributing to the body of evidence around potential risk factors and etiology for this AESI.

The remarkable similarities in the cases of the A twins highlight that there may be genetic factors associated with the onset and prognosis of myocarditis. This includes incredibly similar follow up cardiac MRI results, performed almost 8 months after symptoms onset. This may take the form of specific cardiac gene mutations rather than recessive genetic predispositions. Novel gene targets such as desmoplakin have been identified in a recent case series of twins with non-COVID-19 vaccine related myocarditis [6]. Furthermore, similar cardiac MRI findings have been found in other twin studies with underlying desmoplakin (DSP) gene variants [6] and pathogenic filamin C variants [8] and these findings are typical of those found in heritable arrhythmogenic cardiomyopathy phenotypes [12]. Evaluations of specific cardiac biomarkers such as IL-1RA antibodies, which have been proposed as a potential marker following COVID-19 mRNA vaccine related myocarditis [13], may hold the key to understanding this further.

When comparing the cases of A and B monozygotic twins, a correlation between genetic predisposition and hormonal influence in pubertal development may be a plausible explanation for the predisposition toward myocarditis following COVID-19 vaccines in certain subgroups.. In particular, the influence of testosterone has been hypothesized as an explanation for the demographic distribution of all cause myocarditis, which peaks in adolescent and young adult males and further is thought to be linked to differences in prognosis between sexes [8,9]. Given B2′s pubertal delay and low testosterone levels, one might hypothesize that this could have been a protective factor in this scenario, regardless of any pre-existing cardiac related gene mutation. The remaining cases also completed self-rated Tanner staging (as a validated non-invasive method of pubertal developmental comparison [14]) with results indicating advanced puberty – suggestive of higher testosterone levels. One might hypothesise that genetic predisposition in the context of hormonal influence is the most significant risk factor. Another recent case study of fraternal brothers (with remarkably similar growth parameters) who both developed myocarditis following COVID-19 vaccination [15] also potentially supports evidence of genetic predisposition to this AESI.

These cases aid in identifying hypotheses and future investigation pathways to understand the causative pathophysiology behind myocarditis, including those associated with COVID-19 vaccination as well as potential mRNA therapeutics. Although the authors acknowledge that with such small numbers in this limited case series no definitive causes can be implied, twin studies provide unique epidemiological tools with which to investigate such theories. With the advances and expansion in mRNA technology, understanding these factors will become increasingly important and may help to weigh up the benefits against potential side effects and risks of future mRNA treatments.

Conclusion

Whilst this twin study presents hypotheses related to COVID-19 vaccine associated myocarditis, further research is needed to evaluate, test and understand these concepts. Long term follow-up of clinical

outcomes and involvement in international biobanking and cardiac biomarker collaboration studies will aid in a more comprehensive understanding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

References

[1] Australian Technical Advisory Group on Immunisation (ATAGI). Guidance on Myocarditis and pericarditis after mRNA COVID-19 vaccines. Australian Government Department of Health and Aged Care; 2021. https://www.health.gov.au/resources/publications/covid-19-vaccination-guidance-on-myocarditis-and-pericarditis-after-mrna-covid-19-vaccines.

[2] Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA 2022;327(4):331.

[3] Kang M, An J. Viral Myocarditis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 26, 2022.

[4] Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol 2022;19(2):75–7.

[5] Li X, Ostropolets A, Makadia R, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ 2021;373.

[6] Kissopoulou A, Fernlund E, Holmgren C, Isaksson E, Karlsson J-E, Green H, et al. Monozygotic twins with myocarditis and a novel likely pathogenic desmoplakin gene variant. ESC Heart Fail 2020;7(3):1210–6.

[7] Arbustini E, Narula N, Giuliani L, Di Toro A. Genetic Basis of Myocarditis: Myth or Reality? Myocarditis 2020 Mar;7:45–89.

[8] Schubert J, Tariq M, Geddes G, Kindel S, Miller EM, Ware SM. Novel pathogenic variants in filamin C identified in pediatric restrictive cardiomyopathy. Hum Mutat 2018;39(12):2083–96.

[9] Diaconu R, Donoiu I, Mirea O, Bălşeanu TudorAdrian. Testosterone, cardiomyopathies, and heart failure: a narrative review. Asian J Androl 2021;23(4):348.

[10] Heymans S, Eriksson U, Lehtonen J, Cooper Jr LT. The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy. J Am Coll Cardiol 2016;68(21):2348–64.

[11] Sexson Tejtel SK, Munoz FM, Al-Ammouri I, Savorgnan F, Guggilla RK, Khuri-Bulos N, et al. Myocarditis and pericarditis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2022;40(10):1499–511.

[12] Corrado D, Zorzi A, Cipriani A, Bauce B, Bariani R, Beffagna G, et al. Evolving Diagnostic Criteria for Arrhythmogenic Cardiomyopathy. J Am Heart Assoc 2021;10(18):e021987.

[13] Thurner L, Kessel C, Fadle N, et al. IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination . 2022 Sept *N* Engl J Med. 2022;10.1056/NEJMc2205667.

[14] Chavarro JE, Watkins DJ, Afeiche MC, Zhang Z, Sánchez BN, Cantonwine D, et al. Validity of Self-Assessed Sexual Maturation Against Physician Assessments and Hormone Levels. J Pediatr 2017;186:172–178.e3.

[15] Moosmann J, Gentles T, Occleshaw C, Mitchelson B. COVID Vaccine-Associated Myocarditis in Adolescent Siblings: Does It Run in the Family? Vaccines (Basel) 2022 Apr 14;10(4):611. https://doi.org/10.3390/vaccines10040611.