Severe rhabdomyolysis temporally associated with SARS-CoV-2 vaccine in an adolescent: a case report

Talia Baird[1], Amrit Kirpalani[2,3], Michael Knauer[4], Brett Plouffe[2], Farah Abdulsatar[2,3]

[1]Schulich School of Medicine and Denistry, University of Western Ontario, London, ON, Canada; [2]Department of Pediatrics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada; [3]Children's Health Research Institute, Lawson Health Research Institute, University of Western Ontario, London, ON, Canada; [4]Departments of Medicine Pathology and Laboratory Medicine, University of Western Ontario, London, ON, Canada

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Correspondence to: Farah Abdulsatar. Department of Pediatrics, Schulich School of Medicine and Dentistry, 800 Commissioners Road East, London, Ontario N6A 5W9, Canada. Email: farah.abdulsatar@lhsc.on.ca.

Background: Rhabdomyolysis has been reported following common vaccines such as influenza vaccines. It has now more recently been temporally associated with SARS-CoV-2 vaccine administration in adults. To our knowledge, there are no published reports of severe rhabdomyolysis temporally associated with SARS-CoV-2 vaccine administration in children.

Case Description: We report a case of severe rhabdomyolysis occurring in a 16-year-old previously healthy female, following receipt of the second dose of the Pfizer/BioNTech SARS-CoV-2 vaccine without any other identifiable triggers on history, physical examination, and laboratory investigations. This patient's creatinine kinase (CK) peaked at 246,900 U/L, at about 90 hours post-vaccination. The patient was hospitalized and treated successfully with intravenous hyperhydration over a 3-day hospital admission with subsequent complete recovery.

Conclusions: This is the first pediatric report of rhabdomyolysis temporally associated with administration of the SARS-CoV-2 vaccine. This patient's full recovery followed a brief hospitalization for hyperhydration. While causality cannot be assigned to this single event, reporting of such adverse events following SARS-CoV-2 vaccination in the pediatric populations is important to create awareness, and to ensure continued post-licensure surveillance of COVID-19 vaccines. The benefits of these vaccines in reducing hospitalizations and deaths, however, continue to outweigh any potential risk of rare adverse events.

Keywords: COVID-19; adverse event; mRNA vaccine; myoglobinuria; case report

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Introduction

Rhabdomyolysis is a known complication of SARS-CoV-2 infection (1) and has been reported following SARS-CoV-2 vaccination in adults (2-5). In North America, vaccination of adults and adolescents 16 years and older began in December 2020 (6). In May 2021, the Pfizer/BioNTech vaccine (BNT162b2_V) was approved for use in adolescents 12–15 years old. Since its roll-out, concern has been raised about reports of myocarditis following the vaccine in the adolescent population (6). To our knowledge, there are no published reports of myositis or severe rhabdomyolysis following BNT162b2_V in the pediatric population. We present this rare and potentially serious event following

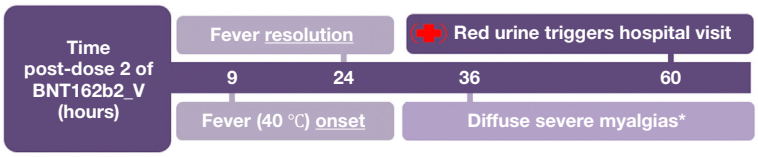

Figure 1 Symptom development timeline. *, proximal greater than distal.

receipt of BNT162b2_V in accordance with the CARE reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-18/rc).

Case presentation

A previously healthy 16-year-old female developed fevers peaking at 40 ℃ and fatigue within 9 hours of receiving the second dose of the BNT162b2_V (*Figure 1*), timed 28 days after an event-free first dose. Fevers settled within 24 hours and were followed at 36 hours post-BNT162b2_V by the onset of diffuse myalgia severe enough to limit motor activity disproportionately in proximal more than the distal limb muscles. Soreness along with nonpruritic erythematous macular rash were noted on the arm that BNT162b2_V was administered. Sixty hours post-vaccine, dark red, tea-colored urine was noted which triggered initial emergency room visit. There were no associated cardio-respiratory symptoms and no known past SARS-CoV2 infection. She had not travelled or had sick contacts and had no medications beyond Clindamycin-Tretinoin topical gel, herbal supplements, precipitating trauma, rigorous exercise, or recreational drug ingestion.

At admission to our hospital (5 days post-vaccination), a detailed assessment revealed that the injection site was warm and mildly tender without any palpable nodules, induration or fluctuance. There was ipsilateral reactive axillary lymphadenopathy. Neck muscles and proximal limb muscles were mildly tender causing pain at full range of proximal muscle activity, limiting proximal strength assessment symmetrically to grade 4 at initial assessment.

Resolution of macroscopic myoglobinuria and myalgias occurred within 36 hours of admission for hyperhydration, which was well-tolerated per the patient, with adherence monitored via urine output. Over the 3-day hospital stay, renal function was preserved and by discharge there was an 85% reduction from admission peak. At follow-up, twelve days post vaccination there was continued improvement in biochemical markers (*Table 1*) and proximal muscle strength gradually returned to baseline.

Complete blood count, estimated glomerular filtration rate, and electrolytes were normal. C-reactive protein was 11.0 mg/L (normal ≤5 mg/L). Creatine kinase (CK) was 165,197 U/L and peaked at 90 hours post-vaccination at 246,900 U/L (normal ≤170 U/L). Aspartate transaminase (AST) peaked 112 hours post-vaccination at 6,605 U/L (normal ≤32 U/L). Alanine transaminase (ALT) fluctuated throughout admission between 935 and 1,060 U/L (normal ≤33 U/L) without abnormal hepatic markers (*Table 1*). Urine dipstick was positive for blood, but there were no erythrocytes on microscopy, indicating myoglobin was the likely cause of the finding on dipstick. Serology for Hepatitis A and B, Parvovirus, Epstein Barr Virus and Cytomegalovirus was negative as was polymerase chain reaction testing for influenza A and B, Parainfluenza,

Highlight box

Key findings

- Rhabdomyolysis has been reported to be temporally associated with SARS-CoV-2 vaccines in adults.
- We describe a case of severe rhabdomyolysis temporally associated with SARS-CoV-2 vaccine in an adolescent.

What is known and what is new?

- This previously well 16-year-old female developed myalgia at 36 hours post-BNT162b2_V vaccine and by 60 hours post-vaccine developed dark tea-colored urine triggering presentation to our emergency room.
- The patient had a brief hospitalization for intravenous hyperhydration.
- At follow-up, this patient's strength continued to improve and returned to baseline.

What is the implication, and what should change now?

- While causality cannot be assigned to such single event, reporting of adverse events following SARS-CoV-2 vaccination is important to ensure continued post-licensure surveillance of COVID-19 vaccines.
- The benefits of SARS-CoV-2 vaccines in reducing hospitalizations and death, however, continue to outweigh any potential risk of rare adverse events.

Table 1 Laboratory findings throughout the course of illness

Laboratory findings	Initial value[1]	Peak value [time post-vaccine in hours]	Convalescent 12 days post-BNT162b2_V	Reference range
CK (U/L)	165,197	246,900 [90]	643	≤170
ALT (U/L)	510	1,060 [160]	306	≤33
AST (U/L)	Not documented	6,605 [112]	1,187	≤32
GGT (U/L)	11	11 [60]	10	≤40
ALP (U/L)	63	63 [60]	Not repeated	50–117
CRP (mg/L)	11	11 [60]	0.6	≤5
Creatinine (μmol/L)	54	54 [60]	53	55–100
Urea (μmol/L)	3.4	3.4 [60]	5.3	≤8.3

[1], documented on first presentation to the emergency department 60 hours post-vaccination. CK, creatinine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein.

Enterovirus, Adenovirus, Rhinovirus, Metapneumovirus, Bocavirus, Coronavirus Respiratory Syncytial Virus and SARS-CoV-2. Anti-SARS-CoV-2 total assay (nucleocapsid) was negative but positive for both IgG and IgA (Spike; S1). C3 and C4, Thyroid Stimulating Hormone, ferritin and ceruloplasmin were within normal limits. IgA, IgG and IgM levels were normal. Antinuclear antibody was negative. Abdominal ultrasound and echocardiogram were both normal.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The investigations done on this patient were part of the standard of care provided. Written informed consent was obtained from the patient herself as she was deemed by the medical team to be competent to provide consent. The patient's parents were agreeable to this case report as well. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Rhabdomyolysis has previously been linked to SARS-CoV-2 infection and more recently it has been temporally associated with SARS-CoV-2 vaccination in adults, though no clear established mechanism explains a potential link (5). While myositis is well-described in infection, and myalgias have been reported in 32% of participants following the second dose, published data does not indicate that there was any episode of clinically significant myositis or that CK levels were evaluated in BNT162b2_V clinical trials (6,7). To our knowledge there are no published pediatric case reports of myositis or rhabdomyolysis in the pre-licensure trials and none since emergency use approval was granted (2-5).

This 16-year-old female presented with severe rhabdomyolysis, without renal impairment, following receipt of the second dose of the BNT162b2_V and was successfully solely managed with hyperhydration, without acute adverse outcome. However, recovery of muscle strength following muscle break down may lag behind biochemical recovery and therefore may impact daily function for several weeks (8). In the absence of another identifiable trigger, event onset, in close proximity to vaccine administration, raises questions around whether the vaccine could have played a role.

A search of the Vaccine Adverse Event Reporting System (VAERS) database identified 591 unverified events involving rhabdomyolysis temporally linked to SARS-CoV-2 vaccination, as of April 22nd, 2022 (9). Of these, 396, 148 and 33 cases followed administration of the Pfizer/BioNTech, Moderna and Janssen vaccines respectively (two of unknown manufacturer). All but seven cases, following Pfizer/BioNTech administration, and two following Moderna administration, occurred without concurrent myocarditis. However, only nineteen of these events occurred in adolescents (*Table 2*), all of whom received the Pfizer/BioNTech vaccine. These events were more commonly reported after repeat vaccine doses and occurred within a week of administration, affecting both males and females

Table 2 Pediatric cases of rhabdomyolysis post-Pfizer/BioNTech SARS-CoV-2 (including cases reported in VAERS as of January 14, 2021)

Report date	Age (years)	Sex	Doses of vaccine received	Onset of myalgia (days)	Other triggers	Peak CK (U/L)	Course and outcome
2021/05/27	17	M	2	5	Drug overdose	Not reported	Hospitalized for overdose**
2021/06/21	14	M	1	2	Unknown	1,628	Hydration at home
2021/06/23	12	F	2	1	Exercise[a]	11,400	Hospitalized for 2 days
Our case	16	F	2	1.5	None	246,900	Hospitalized for 3 days
2021/07/05	16	M	2	2	Unknown	>500	Hospitalized for unknown period**
2021/07/17	17	M	1	14	Exercise[b]	20,167	Hospitalized for 3 days
2021/07/23	12	M	1	19	Exercise[c]	21,980*	Hospitalized for unknown period
2021/07/23	12	M	2	3 days prior to vaccination	Unknown	74,111	Not hospitalized
2021/07/27	12	F	2	2	Predisposed by VLCAD diagnosis	9,032	Hospitalized for 11 days
2021/08/04	15	M	Unknown	53	Unknown	2,925	Hospitalized for 4 days
2021/08/26	15	M	1	1	Unknown	7,016	Hospitalized for unknown period
2021/09/24	14	F	2	0	Unknown	Unavailable	Not hospitalized
2021/09/29	12	M	2	15	Exercise[d]	Unavailable	Hospitalized for 2 days
2021/09/29	15	F	2	0	Unknown	Unavailable	Not hospitalized
2021/09/29	16	M	2	Unknown	Unknown	Unavailable	Not hospitalized
2021/11/08	12	F	2	1	Unknown[e]	Unavailable	Not hospitalized
2021/11/09	14	M	2	1	Increased tic severity	Unavailable	Not hospitalized
2021/11/16	15	F	1	0	Unknown	6,777	Hospitalized for 2 days
2021/12/13	17	F	1	18	Exercise[f]	9,776	Hospitalized for unknown period
2022/04/12	7	F	3	1	Unknown	>3,300	Not hospitalized

[a], black belt training; [b], active athlete playing basketball and weightlifting; [c], three hours playing basketball following period of inactivity; [d], small weight lifting the previous day with recent fracture in the same limb; [e], COVID-19 test pending at the time of report; [f], possible effect of exercise; *, not designated as peak; **, co-presentation with myocarditis. VAERS, Vaccine Adverse Event Reporting System; M, male; F, female; VLCAD, very long chain acyl carnitine dehydrogenase deficiency; CK, creatinine kinase.

across the adolescent age spectrum. Almost half of cases had an identifiable trigger, other than SARS-CoV-2 vaccination, and except for our case, CK elevations were mild.

In the adult population, there are published case reports of rhabdomyolysis following both adenoviral vector vaccines as well as messenger ribonucleic acid (mRNA) vaccines (3,4). Given that these reports have not been verified to be vaccine-linked and are still extremely rare relative to the millions of SARS-CoV-2 vaccine doses administered worldwide, it would be difficult at this time to assign more than a temporal association, especially as there are several other recognized triggers for the rapid breakdown of skeletal muscle (8). Each year, 26,000 cases of rhabdomyolysis are reported in the United States (10). Common causes of rhabdomyolysis include excessive muscular activity, crush injuries and toxins and infections (8). Respiratory viruses such as influenza and enteroviruses, but as well herpes group viruses are well-established causes of myositis and rhabdomyolysis (8,11). More recently, SARS-CoV-2 infection has been recognized as a cause (12). Proposed mechanisms include direct viral invasion into muscle, cytokine-induced injury or exaggerated immune response.

Vaccines have been associated with inflammatory myopathies and rhabdomyolysis (12,13). Aberrant autoimmune response to adjuvants in vaccines, as seen in the autoimmune inflammatory syndrome induced by adjuvants (ASIA), may result in post-vaccination rhabdomyolysis which has been reported following hepatitis B and human papillomavirus vaccines, among others (13). However, adjuvants like aluminium are not present in BNT162b2_V. Post-vaccination autoimmune phenomena other than ASIA have been documented in connection to a variety of vaccinations with report of rhabdomyolysis secondary to H1N1 influenza vaccination (14); molecular mimicry has been suggested as a potential explanation (15). Of note, genetic similarity has been established between the SARS-CoV-2 spike glycoprotein, a core element of the BNT162b2_V, and several human proteins (16). As of-yet, no clear peptide sharing between the SARS-CoV-2 spike protein and skeletal muscle-related proteins has been identified, reactions to vaccines resulting in eosinophilic myocarditis have been reported following hepatitis, meningococcal and some combination vaccines however (17). As such reactions may occur without peripheral eosinophilia, tissue biopsy demonstrating eosinophilic infiltrates is confirmatory. Although a hypersensitivity response was considered, eosinophilia and urticaria were absent. We are not aware of any cases of eosinophilic myositis following vaccines.

Lastly, there is a potential that recipients who were previously infected with SARS-CoV2 before vaccination may have a pronounced immune response, which was the case in one of the published reports in an adult (2). However, given the absence of SARS-CoV-2 antibodies to the nucleocapsid, we were unable to demonstrate evidence that our patient had had a preceding SARS-CoV-2 infection. However, we cannot exclude a distant infection more than 3 months prior, given natural immunity may wane after 3 months (18). Even in the absence of a past infection, an immune-mediated adverse event would be more likely to occur after the expected boosting from the second dose and may explain why most of cases (*Table 2*) occurred after the second dose. Although, we were able to demonstrate an immune response to BNT162b2_V in our patient given she had both IgG and IgA to spike protein, her nonspecific antibody assay (IgG, IgA and IgM) showed no evidence of a non-specific hyperimmune response.

Although the temporal proximity to the vaccine raises the possibility of a link, we cannot assign causality. With over 3.85 million adolescents and children in Canada and over 27.7 million adolescents and children in the United States already receiving at least one dose of the vaccine (19,20), even if this were causal, it would be extremely rare. As such the clear benefits of mRNA vaccines in reducing deaths and hospitalizations due to COVID-19 infections far outweigh potential risk of rare adverse events.

Conclusions

Our report is unique in that it represents the first pediatric case of severe rhabdomyolysis with more than 1,000-fold increase in CK levels following BNT162b2_V with no other identifiable potential triggers. Although our case had a good outcome, severe rhabdomyolysis can be associated with unfavorable outcomes. As more healthy adolescents with robust immune systems become vaccinated, it will be important for clinicians to monitor for rhabdomyolysis among other adverse events post-SARS-CoV-2 vaccination in pediatric patients. However, robust, vaccine safety monitoring systems are in place in North America to rapidly detect potential safety signals. Such systems ensure that as pediatric vaccination rates increase, very rare potential adverse events are identified, and follow-up studies are conducted.

Patient perspective

Our patient shared the following with us:
"This experience was very unexpected and scary- especially because I was trying to do something to keep from getting sick. All of my muscles hurt so badly that everyday activities like lifting my arms, getting out of bed, walking, and eating were extremely painful and took a lot of effort. Once out of the hospital, it took about a month for me to feel like I was back to my usual strength. I am very happy to be fully recovered and so thankful for all of the care I was given."

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-22-18/rc

Peer Review File: Available at https://pm.amegroups.com/article/view/10.21037/pm-22-18/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-22-18/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report as the patient was deemed by the treating medical team to be competent to provide consent. The patient's parents were agreeable to this case report as well. A copy of the written consent is available for review by the editorial office of this journal.

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