

Peer Review File

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Reviewer A

This is a well written case report including key clinical data and a balanced discussion which does not overstate the findings or potential association with vaccination. Whilst there are now a handful of case reports in adults ranging from age 19-80 (see review Hannah et al, Clin exp rheum 2022), this appears to be the first paediatric case and given the extension of vaccination programmes into children anything impacting the risk-benefit balance of vaccination is worthy of discussion. The authors correctly identify that causality is not proven and clear benefits of vaccination outweigh potential extremely rare risks.

Reviewer B

Nice case report, I don't have any special comment except for the conclusion: You mention the clear benefit of vaccination in reducing deaths and hospitalizations, this statement is clearly true for adult population, but should be balanced for children as COVID19 infection is usually less severe with few complications in this population.

Reply 1: Thank you for your comment. I believe that you are referring to the statement outlined below from line 130-131. Though the risk of morbidity and mortality associated with COVID 19 infection is higher in adults as compared to children, with this statement of goal is to affirm that generally, the benefits of vaccination outweigh the risk of adverse events. We have chosen to remain general and leave statement as is, although we agree there is more data documenting efficacy in reducing morbidity/ mortality in adults but there is still data showing vaccine efficacy in adolescents e.g. in reducing rare complications such as MIS-C in the adolescent age group (91% reduction. Shown by Zambrano LD, Newhams MM, Olson SM, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12–18 Years — United States, July–December 2021. MMWR Morb Mortal Wkly Rep 2022;71:52–58. DOI: <http://dx.doi.org/10.15585/mmwr.mm7102e1>..

Line 130-131: "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."

Changes in the text: None.

Reviewer C

This manuscript described a rare case of "Severe Rhabdomyolysis Temporally Associated with SARS-CoV-2 Vaccine in an Adolescent: A Case Report".

The case is interesting and has a clinical importance. However, there are some things which should be verified for improvement of the paper.

The following should be answered to be considered for publication.

Comment 1: In Case presentation, "red urine" was described. Is that true? Isn't it brown or dark?

Reply 1: Thank you for your comment. To more accurately reflect the colour, we will change the description.

Changes in the text: We have changed the description to "...dark red, tea-colored urine..." on page 3, line 44.

Comment 2: In Case presentation, the patient received only a hydration. Were there any other treatments?

Reply 2: Thank you for your question. In this particular case, hyperhydration was the only treatment administered.

Changes in the text: None.

Comment 3: In Diagnostic Assessment, "Urine dipstick was positive for blood, but there were no erythrocytes on microscopy." Please explain clearly why this is so.

Reply 3: Thank you for noting this opportunity for further explanation.

Changes in the text:

- See page 4; line 68-70:
 - Previous version: "Urine dipstick was positive for blood, but there were no erythrocytes on microscopy."
 - Updated version: "Urine dipstick was positive for blood, but there were no erythrocytes on microscopy, **indicating myoglobin was the likely cause of the finding on dipstick.**"

Comment 4: In Diagnostic Assessment, "Anti-SARS-CoV-2 total assay (nucleocapsid) was negative but positive for both IgG and IgA." Is this a result of the vaccine?

Reply 4: Thank you for your question. This patient's negative PCR test for SARSCoV2 excludes a recent SARS-Co-V2 infection and sero-negativity to the viral nucleocapsid also further supports that the Ig G and IgA humoral response to spike protein was not triggered by a natural infection but by the spike protein is used in the BNT162b2_V vaccine. I would highlight the brackets following "IgG and IgA," clarifying that these antibodies were related to the spike protein which is found in the vaccine this patient received, as opposed to the viral nucleocapsid.

Changes in the text: None.

Comment 5: Are there imaging tests including MR on the muscles with lesions?

Reply 5: Thank you for your question. At the time no MR was completed.

Changes in the text: None.

Comment 6: Did you perform a muscle biopsy? Post-vaccination, inflammatory activity has increased and there is a possibility of developing direct myotoxicity, immunologically induced inflammatory myopathy, macrophagic myofasciitis, or inflammatory myopathy with abundant macrophages. Can you rule out these myositis by inflammatory cells?

Reply 6: Thank you for your inquiry. During this patient's admission, muscle biopsy was not pursued given clinical improvement with hydration. Without a biopsy, we are unable to confirm the underlying histopathology. If findings had not continued to improve at follow-up a biopsy would have been necessary.

Changes in the text: None

Reviewer D

Overall, a good case report that is well-written and easy to understand. There have been many case reports in adults already published establishing the temporal relation between COVID-19 mRNA vaccines and rhabdomyolysis. Certainly, there are no tests currently available to prove a causal relationship between them.

-I have a couple of feedback points for the authors.

Comment 1: Line 132: "Although our case had a good outcome, severe rhabdomyolysis can be associated with unfavorable outcomes." This statement needs appropriate citation. The authors should read the following case report where the patient could not survive due to rhabdomyolysis post-vaccination.

-Ajmera KM. Fatal Case of Rhabdomyolysis Post-COVID-19 Vaccine. *Infect Drug Resist.* 2021;14:3929-3935. <https://doi.org/10.2147/IDR.S331362>

Reply 1: After a thorough review we have noted some significant concerns which have led us to the conclusion that we are not comfortable including it as a reference.

The following are our concerns:

- 1. Lack of balanced discussion of all the patient's presentation and demise.** We note in particular this lack of reference to this patient's polypharmacy (no drug levels noted) or the influence of infection, particularly in her death (right sided pneumonia with elevated CRP noted). Death followed cardiac death with suspected hypoxic/anoxic brain injury. Further, there is no clear statement clarifying that this temporal association with possible drug triggers not eliminated. We would like to highlight the following drug associations, not noted in the paper. These drugs/drug classes known on their own to cause rhabdomyolysis and potentially renal failure
 - a) Metoprolol: beta blockers have been associated muscles symptoms inclusive of rhabdomyolysis.
 - b) Rosuvastatin: rhabdomyolysis is a known side-effect of statin therapy and combined therapy (combination increases the susceptibility to this complication. Rosuvostatin in presence of platelet inhibitors have been implicated in several reports of rhabdomyolysis and renal failure)
 - c) Platelet inhibitors (PI): When given with statins are well known to induce ARF and rhabdomyolysis.
 - Please refer to the following paper - (*Am J Med Case Rep.* 2019 ; 7(12): 337–341. doi:10.12691/ajmcr-7-12-9) Drugs in this class include Clopidogrel and Ticagrelor. Experts recommend dose adjustment when these drugs are combined. Of note, this patient was not reported to have dose adjustments
 - d) Angiotensin blockers: Angiotensin receptor blockers (ARBs) are another class of routinely used drugs known to cause myotoxicity. According to the prescribing information on the various ARBs, myalgia with elevated CPK has been reported as a common adverse event ($\geq 1/100$, $< 1/10$) with telmisartan as compared to other angiotensin blockers ie this drug is the

- member of its class most likely to cause muscle damage on its own.
- Valiyil R, Christopher-Stine L. Drug-related myopathies of which the clinician should be aware. *Curr Rheumatol Rep* 2010; 12: 213–20.
 - Telmisartan. [amended 2013 Apr 29]. In: Boehringer-Ingelheim, [Internet]. [Burlington, Ontario]: Available at http://www.boehringer-ingelheim.ca/content/dam/internet/opu/ca_EN/documents/humanhealth/product_monograph/MicardisPlusPMEN.pdf (last accessed 31 October 2014).)
- e) Antidepressants (serotonin antagonists): Trazadone is a well-recognized to cause rhabdomyolysis especially in females over 60 with 90% occurring within a month of starting. Trazadone overdose has been associated with fatalities and given that this is an elderly woman with recent strokes who on polypharmacy could have had accidental overdose, it would have been helpful to document drug levels to address potential overdose contributing to fatality.
- f) Antidepressant and statin interactions: Pharmacotherapy for depression and hypercholesterolemia may result in potentially fatal drug-drug interactions involving the cytochrome P-450 (CYP-450) system. Hepatic hydroxymethyl glutaryl coenzyme (HMG-CoA) reductase inhibitors (statins) are metabolized by the 3A4 isoenzyme, while drugs like trazadone, nefazodone, inhibit. This can result in higher levels of statins and potentially higher chance of adverse events from statins including potentially statin induced rhabdomyolysis if statin doses are not adjusted after initiating drugs that inhibit the enzymes responsible for metabolizing statins
- 2. Alternative viral cause, given elevated CRP:** Alternative viral causes of myositis were not discussed, even in the context of the high CRP of 74 on admission which raises question around infection/inflammation. There was no respiratory viral panel testing to assess for well-established causes of myositis such as influenza and COVID-19. Further, pneumonias are well-described complications post-viral infection and her chest imaging was concerning for right sided pneumonia. Lastly, at her age sepsis could easily be in mix.

Comment 2: In the conclusion section, the authors should write a few sentences on what preventative measures individuals should take post-vaccination (i.e. staying hydrated) and when they should seek immediate medical attention as a take-home message.

Changes in the text: We have modified our text as advised (see Page 3, line 44)"

- Line 134 – 136
 - Original: 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.
 - Updated: 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, Individuals

receiving the vaccine should be educated to seek medical attention if they note dark red, tea coloured urine, or experience severe muscle pain or weakness following vaccination.