MEDDOCS Open Access Publisher

ISSN: 2639-4391

Annals of Epidemiology & Public Health

Open Access | Case Report

COVID-19 Vaccination-Induced Rhabdomyolysis and Hyponatremia Complicated with Acute Kidney Injury

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Received: Aug 06, 2022

Accepted: Sep 01, 2022

Published Online: Sep 05, 2022

Journal: Annals of Epidemiology and Public health

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Rhabdomyolysis; Hyponatremia; Astrazeneca Vaccine; Covid-19 Vaccine.

Abstract

COVID-19 vaccine-induced rhabdomyolysis is rare. The concurrent presentation of rhabdomyolysis and hyponatremia secondary to COVID-19 vaccine has never been reported. A 54-year-old gentleman had developed rhabdomyolysis two days after receiving his first dose of the AstraZeneca (ChAdOx1 nCoV-19) vaccine. His initial Creatine Kinase (CK) and sodium level were 12,588 U/L and 113mmol/L, respectively. He was treated with two-steps fluid management strategy. Initially, he received hypertonic saline, fluid restriction, and Desmopressin injection to slowly correct the plasma sodium. Subsequently, he received aggressive isotonic crystalloids. He sustained acute kidney injury despite treatment, and was advised against receiving a second dose of the AstraZeneca vaccine. The exact mechanisms of COVID-19 vaccination-induced rhabdomyolysis are unknown. The management for simultaneous rhabdomyolysis and hyponatremia requires different approaches to fluid management.

Physicians should be vigilant about the risk of rhabdomyolysis and hyponatremia following COVID-19 immunization, and the treatment paradox in the context of fluid administration.

Introduction

Vaccine development against COVID-19 has expanded at an unprecedented rate. As more research on the efficacy of the COVID-19 vaccines are published, there is a growing concern regarding the vaccine's safety and adverse effects. Adverse reactions to immunisation are often mild to moderate in severity and dissipate within 48 to 72 hours [1]. COVID-19 vaccine-induced rhabdomyolysis is rarely reported in literature. To date, there are three published cases of rhabdomyolysis linked to COVID-19 vaccination [1-3]. Rhabdomyolysis is a syndrome of acute muscle injury manifested by muscle weakness, muscle swelling and release of myofibre intracellular contents into systemic circulation. The biochemical features of rhabdomyolysis are raised Creatine Kinase (CK) and urine myoglobin (pigmenturia) [1-3]. Rhabdomyolysis caused by hyponatremia is excep-

Cite this article: Kamil MKM, Zambri A, Med MEM, Jeng TG. COVID-19 Vaccination-Induced Rhabdomyolysis and Hyponatremia Complicated with Acute Kidney Injury. AEpidemiol Public Health. 2022; 5(2): 1085.

tionally rare and has been reported in patients with intense exercise [4], psychogenic polydipsia [5], and using thiazide diuretics [6]. Hyponatremia or rhabdomyolysis have also been observed in COVID-19 patients, albeit the mechanisms remain controversial [7,8,11].

The concurrent presentation of rhabdomyolysis and hyponatremia have never been reported as an adverse effects of post-COVID 19 vaccination. Not only are the mechanisms unknown, but this also poses a medical conundrum and a treatment paradox in the context of fluid resuscitation. Herein, we present a case of rhabdomyolysis and severe hyponatremia in a patient who received the first dose of the AstraZeneca (ChAdOx1 nCoV-19) vaccine.

Case report

Patient is a 54-year-old gentleman with a background history of hypertension on Tablet Amlodipine/Valsartan (Exforge) 10mg/160mg presented to the emergency department for altered mental state. He reported to receive his first AstraZeneca vaccine injection two days prior to presentation. He complained of severe generalized body ache following the vaccination and a low grade fever (37.5 °C) which was relieved by paracetamol. The next day, patient was less responsive, lethargic, and unable to walk. He had no history of recent vigorous exercise, heavy lifting, trauma, excessive alcohol consumption or recreational drugs consumption. He had no close contact with any COVID-19 patients prior.

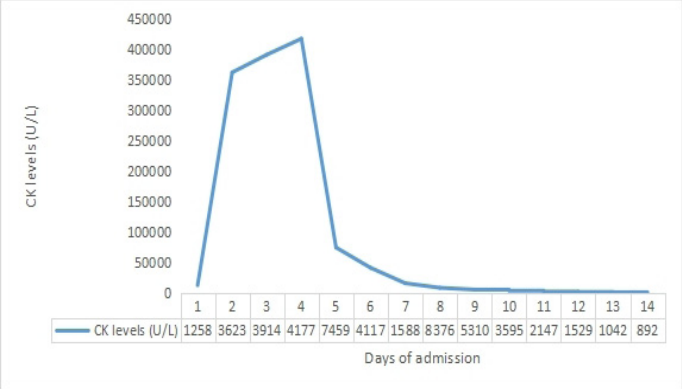
On examination, he appeared drowsy with GCS 10/15 (E3, V2, M5). His pupils were 3 mm bilaterally and reactive. His blood pressure was 180/100 mmHg, heart rate 89 beats/min, temperature 37.6 C, and saturation of 100% under room air. His cardiovascular and respiratory examinations were unremarkable. Abdominal examination showed palpable bladder. Neurological signs demonstrated a normal tone of both limbs, power of at least 4/5 and symmetrical, normoreflexia with negative Babinski. No signs of meningism demonstrated. A urinary catheter inserted and 800 ml of brownish tea-coloured urine was drained.

On admission, his biochemical results showed a raised CK of 12,588 U/L and sodium of 113 mmol/L. Other results demonstrated potassium 3.2 mmol/L, calcium 2.09 mmol/L, phosphate 0.9 mmol/L, creatinine of 54 umol/L and blood sugar of 6.8 mmol/L **(Table 1)**. Urine microscopy revealed microscopic haematuria with 10 erythrocytes/uL and mild proteinuria. The serum osmolality was low (258 mmol/kg), but the urine osmolality and urine sodium levels were within normal range. Urine myoglobin was unavailable. His chest x-ray was unremarkable. Both Computed Tomography (CT) of the brain and CT venogram revealed no significant abnormalities. Hepatitis B, Hepatitis C, HIV, Syphilis, Leptospira, and the SARS-CoV-2 antigen were all negative. His thyroid function and serum cortisol levels were within normal range. These results led to the diagnosis of rhabdomyolysis and severe euvolaemia hypoosmolar hyponatremia. Possible differentials include syndrome inappropriate antidiuretic hormone (SIADH) and salt wasting syndrome owing to urine osmolality > 100 mmol/kg. However, the absence of natriuresis made these differentials less likely.

Table 1: Summary of biochemical results.

	Admission	Ward (Day 4)	Upon discharge	Reference ranges
Hemoglobin (g/L)	121	130		130.0 - 170.0
Red Blood Cell (10^12/L)	5.7	6.27		4.50 - 5.50
White Blood Cell (10^9/L)	12.9	9.8		4.0 - 10.0
Platelet (10^9/L)	292	308		150 - 400
Sodium (mmol/L)	113	139	141	136 - 145
Chloride (mmol/L)	85	112	104	99 - 109
Calcium (mmol/L)	2.09			2.20 - 2.60
Magnesium (mmol/L)	0.8			0.53 - 1.11
Phosphate (mmol/L)	0.9			0.78 - 1.65
Urea (mmol/L)	3.7	8.1	7.4	3.2 - 8.2
Creatinine (umol/L)	54	231	220	> 90
Alanine transaminase (U/L)	38	328	63	10 - 49
Aspartate aminotransferase (U/L)	105	2174	44	< 34
Creatine Kinase (U/L)	12588	417700	892	46 - 171
Serum Osmolality (mmol/kg)	258			275 - 295
Urine Osmolality (mmol/kg)	111			50 - 1200
Urine Sodium Random (mmol/L)	11			
Urine Potassium Random (mmol/L)	5.8			25.0 - 125.0

The initial treatment was focused on sodium correction. He was treated with bolus of hypertonic saline (3%) with restrictive fluid strategy and intravenous Desmopressin. Over the course of several days, his sodium level gradually improved and he regained full consciousness. He complained of pain and fatigue in his lower limbs and the back. His CK levels skyrocketed, peaking at 417,700 U/L on day four. He developed acute kidney injury with a creatinine level of 234 umol/L and deranged liver enzymes with alanine transaminase (ALT) of 328 U/l and aspartate aminotransferase (AST) of 2174 U/L. Once his sodium level was normalized, he was given a substantial volume of intravenous normal saline. The patient's CK level was closely monitored and displayed a downward trend, noting that patient responded well to fluid resuscitation **(Figure 1)**. Urine output was maintained between 200 and 300 ml/hour. He was discharged on day 14 of his admission after his CK level dropped below 1,000 U/L. Despite treatment, he had acute kidney injury, necessitating nephrology follow-up. He was cautioned against receiving a second dose of the AstraZeneca vaccine.



Discussion

This case demonstrated the simultaneous presentation of rhabdomyolysis and hyponatremia following AstraZeneca vaccination. Three case reports have been published pertaining to COVID-19 vaccination-induced rhabdomyolysis. Mack *et al* found mRNA vaccination-induced rhabdomyolysis with a CK level of 6,546 U/L in patients who had previously been infected with COVID-19. The author concluded that previous exposure to the COVID-19 virus may enhance the mRNA vaccine's immunological response [2]. Nassar *et al* made similar observations after Pfizer/ BioNTech vaccination in a young patient with underlying asthma and social marijuana abuse. The author speculated there was a chronological association between vaccine and rhabdomyolysis, despite the fact that the patient had been using marijuana daily [1]. Another example described a myopathic flare in a patient with carnitine palmitoyltransferase II deficiency, resulting in a CK level of 102,560 U/L. Tan *et al* hypothesized biopharmaceutical products such as Triton X-100, which was used in the AstraZeneca vaccine, impaired fatty acid oxidation and increased fatty acid deposition in the muscle [3]. Although it is uncommon, influenza vaccination has been reported to cause rhabdomyolysis. Raman *et al* reported rhabdomyolysis in a renal transplant patient after a week of receiving the influenza vaccine. Interestingly, the patient was also taking statins for dyslipidaemia [9]. Plotkin *et al* had reported a similar case that was treated with cerivastatin and bezafibrate [10]. The authors concluded that influenza vaccination may have triggered immunologically mediated response in patients receiving concurrent myotoxic drugs [9,10]. Many reports included confounding factors such as statin or fibrate use, metabolic deficiency, past COVID-19 infection, and illicit drug use. However, our patient had none of these recognized risk factors.

Rhabdomyolysis has been linked to COVID-19 infection in several case reports, though the exact pathophysiology is unknown. Several postulations have been proposed including viral cell invasion and cytokine-mediated direct muscle injury [11]. These notions were initially debated as post-mortem and immunohistochemical samplings of these patients exhibited positive staining over type II pneumocytes in the lungs, but negative staining in other organs such as kidney, liver, lymph node, spleen, and skeletal muscles [12]. Nevertheless, recent evidence from renal histopathological of 26 post-mortem findings in COVID-19 patients revealed positive staining of SARS-CoV-2 in renal tubules [13]. More research is needed to understand the pathogenesis of COVID-19 infection and vaccination-induced rhabdomyolysis.

Rhabdomyolysis and hyponatremia have been linked in multiple cases that involve patients who had intense exercise [4], psychogenic polydipsia[5], and were using thiazide diuretics [6]. Changes in intracellular potassium and calcium concentrations, as well as hypotonic cell swelling, were postulated as processes, both of which contribute to cellular membrane instability or lysis [4]. Additionally, complications from COVID-19 pneumonia may result in hyponatremia and syndrome inappropriate antidiuresis (SIADH). Ravioli *et al* revealed two cases of COVID-19 pneumonia-related SIADH. Both patients demonstrated bilateral ground-glass opacities on CT of the chest and biochemical results showed hypoosmolar hyponatraemia, normal urine osmolality, and natriuresis suggesting diagnosis of SIADH. Another study by Yousaf *et al* reported three cases of SIADH-related COVID-19 patients who had severe hyponatremia. It is postulated that interleukin-6 released by monocytes and macrophages contributes to non-osmotic release of ADH. Other factors such as intravascular volume depletion, emotions, stress, and pain had been postulated to trigger the hypothalamic-pituitary axis, stimulating ADH secretion [14]. However, it is uncertain whether SIADH is prevalent among COVID-19 patients.

The management for concurrent rhabdomyolysis and hyponatremia are on the opposing perspectives of the fluid management continuum. The cornerstone of rhabdomyolysis management is vigorous isotonic fluid hydration to avoid accumulation of myoglobin in the kidney and prevent acute kidney injury [4,5]. A combination of intravenous crystalloids and a bicarbonate infusion has been advocated to prevent acute kidney injury from occurring [5]. In contrast, the appropriate treatment for hyponatremia depends on aetiology, severity of symptoms, onset of presentation, and clinical volume of patient [4,5]. Overcorrection of chronic hyponatremia can develop osmotic demyelination syndrome [5]. Often, correction between 8-12 mmol/L/day is recommended [5,15]. In our patient who demonstrated euvolemic hypoosmolar hyponatremia with altered mental state, initial bolus of hypertonic saline was administered to reverse acute neurological impairment. Patient was then put on fluid restriction and intravenous Desmopressin. Desmopressin acetate administration can be an effective method for preventing unintentional hyponatremia overcorrection [15]. He was then treated for rhabdomyolysis with aggressive fluid hydration. Although he showed improvements clinically, he required nephrology follow-up upon discharge due to the acute kidney injury.

COVID-19 vaccinations are generally safe for the population with only a small percentage of risk towards adverse events such as anaphylaxis, rhabdomyolysis and hyponatremia. Physicians should be aware of the risk of rhabdomyolysis follow-

ing COVID-19 immunization, as early recognition and prompt treatment are crucial to prevent acute kidney injury. Continued surveillance of the vaccine adverse reactions is needed to determine the incidence of vaccine-induced rhabdomyolysis and hyponatremia.

Disclosures

Acknowledgements

We would like to express our appreciation to the Director General of Ministry of Health (MOH), Malaysia for the publication of this journal.

CRediT authorship contribution statement

All authors made substantial contributions. Aliyah Z.: Writing- editing & reviewing. Tan GJ: Conceptualization and supervision.

Source of support and funding: None.

Availability of data and materials

The anonymised data are available from the corresponding author.

Conflict of iinterest: None declared.

Informed consent: Written consent and permission was obtained from the patient.

Ethical approval: None.

Human rights: None declared.

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