CASE REPORT

Protocol-defined Systemic Steroid Dose-induced Bradycardia in Multisystem Inflammatory Syndrome in Children: A Case Report

Manaf S. Kadori, Ahmed M. Galbat, Imadeldin M. Mahgoub, Osamah M. Al-Qassab

Department of Pediatric, Riyadh Care Hospital, Riyadh, KSA

ABSTRACT

High dose of corticosteroid can induce several cardiac adverse reactions including bradycardia. However, bradycardia is not a known adverse effect of a normal therapeutic dose of administered steroids. We reported a case of bradycardia in a child admitted to our hospital suffering from Multisystem Inflammatory Syndrome in Children (MIS-C) after receiving normal therapeutic anti-inflammatory dose of corticosteroid as a part of MIS-C management protocol. During the 4th day, after commencing intravenous methylprednisolone, he developed asymptomatic bradycardia with elevated blood pressure measurements. The electrocardiogram revealed sinus bradycardia. There was concomitant increase in the level of inflammatory biomarkers including ferritin, D-dimer and Lactate dehydrogenase as well as troponin I and B-type natriuretic peptide; nevertheless, the echocardiography was normal. Bradycardia and high blood pressure resolved over 24 h after discontinuing intravenous methylprednisolone therapy. This case suggests that the use of normal therapeutic dose of corticosteroid might induce bradycardia in management of MIS-C. Cardiovascular monitoring during administration of normal therapeutic dose of corticosteroids in MIS-C is highly recommended.

Key words: Bradycardia, case report, COVID-19, multisystem inflammatory syndrome in children, steroids

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a serious pediatrics health problem that can be linked to the Coronavirus Disease 2019 (COVID-19).[1] The syndrome is an illness that causes inflammation of different body parts and might lead to severe complications such as cardiac dysfunction, coronary artery aneurysms, acute kidney injury, and coagulopathy.[2,3] Children with MIS-C, presenting as Kawasaki-like and toxic shock syndrome, may develop various symptoms including fever, abdominal pain, vomiting, diarrhea, rash, conjunctivitis, lethargy, swollen joints, and lymph nodes. It is unknown what causes MIS-C.[4] Onset may be varied, either delayed or concomitant with ongoing COVID-19 infection.[1]

According to the American College of Rheumatology, the treatment protocol of MIS-C involves frequent use of anti-inflammatory medications including intravenous immunoglobulins (IVIG) and intravenous (IV) steroids.[4] Other anti-inflammatory medications and anti-coagulation therapy can be also used; however, their use is still controversial.[5] During the course of illness, there is a high possibility of coronary artery involvement; therefore, aspirin has commonly been prescribed. Antibiotics are routinely used to treat potential sepsis. Anti-thrombotic prophylaxis is usually prescribed because of hypercoagulable state is typically associated with MIS-C.[4]

Corticosteroids are widely used to treat various clinical conditions including immune-mediated inflammatory diseases.[6] The use of high dose of corticosteroid can induce several cardiac adverse reactions including bradycardia.

Address for correspondence:
Manaf S. Kadori, Riyadh 11541, PO Box 42142, Kingdom of Saudi Arabia

However, bradycardia is not a known adverse effect of a normal therapeutic dose of administered steroids.[7] To date, there are little evidences available on all corticosteroids potential adverse effects, due to variations in dosing, duration, and routes of administration.[8]

In this report, we are reporting the pattern of bradycardia that developed in a child while receiving therapeutic dose of IV steroid for treatment of MIS-C.

CASE PRESENTATION

An 8-year-old boy presented to the emergency department (ER) in Riyadh Care Hospital, Saudi Arabia, on August 21, 2020, with 1-day history of fever and malaise. He received symptomatic treatment and discharged home.

On August 23, the patient attended ER again complaining a high fever and generalized body ache, received oral azithromycin and antipyretics then discharged.

On August 26, 2020, the patient returned to ER complaining of high fever, generalized blanching maculopapular rash, poor oral intake, generalized body ache, backache, neck pain, and abdominal pain. His parents and one sibling tested positive for COVID-19 on July 21, 2020. He developed 2 days fever from July 25, 2020, but he did not require COVID-19 swab. He remained asymptomatic from July 27 to August 21, 2020. The initial physical examination revealed high fever of 39.7°C, heart rate (HR) 160 beats/min, respiratory rate (RR) 25 breaths/min, Glasgow Coma Scale 15/15, oxygen saturation 95% on room air, the child was agitated, had neck stiffness, muscles tenderness, generalized blanching maculopapular rash, strawberry tongue, diffuse abdominal tenderness, clear chest with no added sounds, and normal cardiac examination. The patient received a bolus of IV fluid in ER then admitted to the ward as a suspected case of MIS-C versus meningitis with septicemia. After admission, the child was rapidly deteriorated. He developed hypotension and tachycardia that required strict monitoring in Pediatric Intensive Care Unit (PICU). He received two boluses of normal saline followed by epinephrine then norepinephrine infusions with 2 L/min oxygen support through nasal cannula. As a suspected case of MIS-C versus septic shock, we started high dose of ceftriaxone (100 mg/kg/day), IV methylprednisolone 1.4 mg/kg/day, IVIG 2 gm/kg slow infusion over 12 h, and aspirin 5 mg/kg/day. The initial laboratory workup showed a white blood cell (WBC) count 17000 with 89% neutrophils and 6% lymphocytes, high D-dimer 2.66 µg/ml, high ferritin 587.16 ng/ml, high C-reactive protein 231 mg/l, normal plain CT brain, and Chest X-ray revealed bilateral peri-hilar shadows with increased bronchovascular marking. Lumbar puncture was postponed as the patient was hemodynamically unstable, blood and urine cultures were performed and COVID-19 swab was negative.

On August 27 (the 2nd day of admission), the patient dramatically improved, inotropes gradually weaned, and

Table 1: Investigations of the reported case

	26/08	28/08	30/08	02/09	03/09	05/09	Normal values
D-DIMER	2.66	2.18	3.22	3.48	2.35	1.57	< 0.5 ug/ml
FERRITIN	587.16	604.15	322.38	197.91	---	---	7 – 140 ng/mL
LDH	---	253	280	378	334	294	125 – 220 U/L
TROPONIN I	---	0.074	0.020	0.012	---	---	< 0.03 ng/mL
BNP	---	62	30	59	---	---	0 – 125 pg/mL
ALBUMIN	---	20	25	36	---	---	35 – 52 g/L
URINE	---	Proteinuria	Normal	---	---	---	
ESR	20	25	32	40	35	25	0 – 10 mm/hr
CRP	231	147	46	14	---	---	0 – 5 mg/L
CBC:							
WBC	17	16	9.3	18.3		15.4	4.5 – 13.5 x 109/L
Neutrophils	89%	82%	44%	69%	---	67%	40% – 75%
Lymphocytes	6%	14%	40%	27%		23%	25% – 40%
Platelets	183	193	264	609		692	150 – 450
ECHOCARDIOGRAPHY	NORMAL	---	---	NORMAL	---	---	Normal
BLOOD CULTURE				No growth			
URINE CULTURE				No growth			
CT BRAIN				Normal			

BNP: brain natriuretic peptide, CBC: complete blood count, CRP: C-reactive protein, CT: computed tomography, ESR: erythrocyte sedimentation rate, WBC: white blood cells.

discontinued at 14:00. The rash started to subside, fever reduced and less severe neck, and back and abdominal pain. Pediatric cardiology examination along with echocardiography and ECG all were normal. The aspirin was continued due to high cardiac enzymes levels (troponin 0.074 ng/mL and BNP 234.8 pg/mL). Lumbar puncture was performed to confirm the diagnosis of MIS-C.

During hospital stay, inflammatory biomarkers, cardiac enzymes, and CBC were monitored every 2 days [Table 1]. The patient was observed in PICU with normal records of vital signs until the morning of August 30, and then transferred to the pediatric ward on IV methylprednisolone 1.4 mg/kg/day and oral aspirin 5 mg/kg/day while the antibiotic was discontinued.

On the evening of August 30 (the 4th day of admission), the patient started to develop asymptomatic bradycardia (HR 46 beats/min) associated with occasional higher side systolic blood pressure readings [Figure 1]. However, the patient was clinically stable. The laboratory results showed improvement of the inflammatory biomarkers. Both PICU and Pediatric Cardiology physicians were suggested that the bradycardia was most likely an adverse effect of the IV steroid and recommended no further interventions except for patient monitoring.

On September 1, we started gradual tapering IV steroid and switched to oral prednisone (0.7 mg/kg/day) while the pediatric cardiologist repeated the echocardiography (reported normal) and ECG (showed sinus bradycardia). The normal fundus examination test excluded the possibility of increased intracranial pressure as a possible side effect of steroids which can cause hypertension and bradycardia. In general, the patient was active with no new concerns; however, bradycardia was still documented.

On September 2 and within 24 h of receiving the last dose of IV methylprednisolone (and shifting to oral lower dose of steroid), the patient's heart rate started to increase up to 70 beats/min and returned to normal for age readings over the next few days [Figure 1].

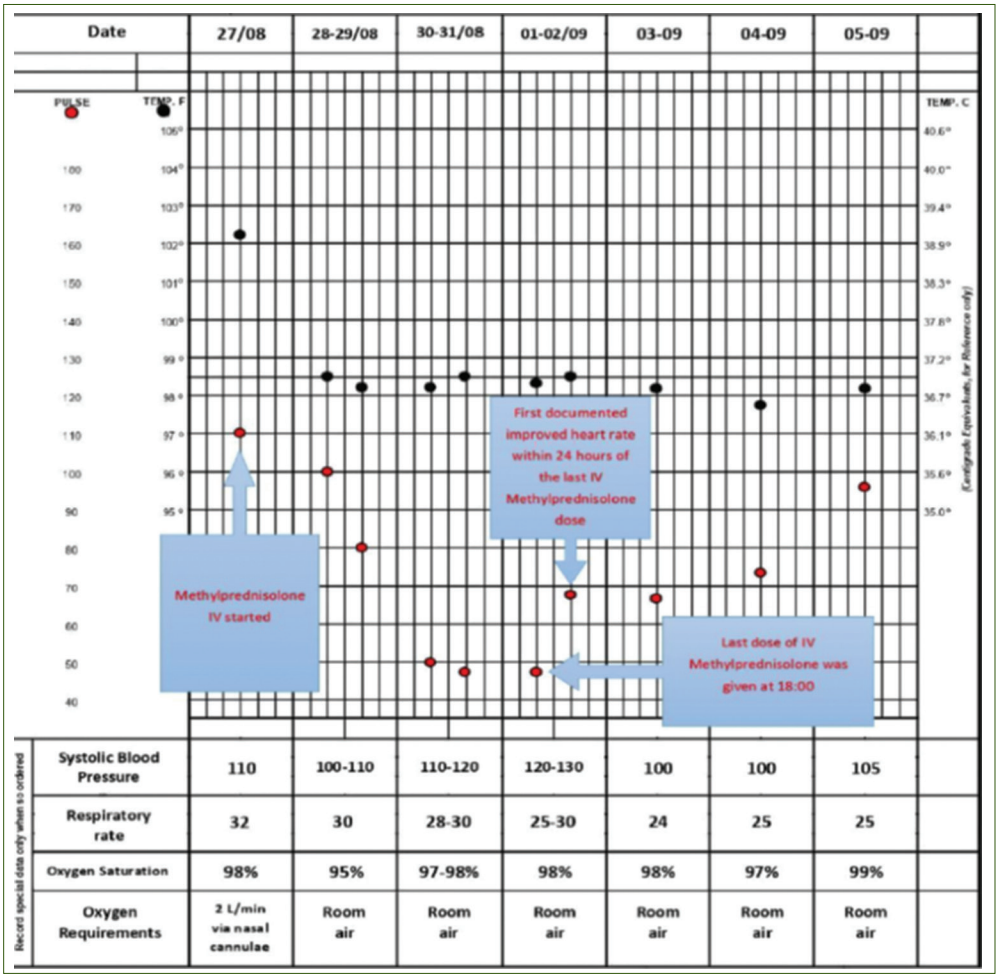

Figure 1: Vital signs recording chart

DISCUSSION

This case of asymptomatic bradycardia developed in a school-aged male child after receiving a course of protocol-defined IV methylprednisolone. We found a significant drop of heart rate after 72 h of starting conventional IV methylprednisolone (1.4 mg/kg/day) as a part of MIS-C treatment. The heart rate gradually improved within 24 h of switching to oral prednisone 0.7 mg/kg/day.

The association between bradycardia and high-dose corticosteroids was first documented in 1986.[9] The available case reports of corticosteroid induced bradycardia in pediatric age group were associated with the use of pulse steroid therapy. A retrospective study conducted by Gugten *et al*. 2008 has reported bradycardia developed in 63.9% of children after receiving prednisone (mean dose, 2.03 mg/kg/d) or dexamethasone (mean dose, 0.28 mg/kg/d (1.86 mg/kg/d prednisone equivalent)) for the treatment of acute lymphoblastic leukemia, Non-Hodgkin Lymphoma, and graft versus host disease.[10]

The exact cause of steroid-induced bradycardia is unclear; but some mechanisms have been hypothesized. Published studies have shown that high-dose of methylprednisolone had a significant cardiac effects that may be mediated by its direct effect on the myocardial membrane and alterations in cardiovascular sensitivity to catecholamine.[11] Furthermore, corticosteroids may have the ability to produce sudden electrolyte shifts, giving rise to cardiac arrhythmias including bradycardia.[12] Another proposed theory is that pulse corticosteroids can induce changes in sodium and water physiology, which result in the expansion of plasma volume and in turn activate baroreceptors. Hence, it seems that corticosteroid-induced bradycardia might have a multifactorial origin.

Since corticosteroid therapies are frequently used in the treatment of a wide-range of illnesses, including MIS-C, this case report raises the alert of potential bradyarrhythmia side effect while using conventional doses as well as high (pulse) doses of steroids. Thus, such patients should be strictly monitoring their vital signs for this rare but potentially serious side effect.

Future research is needed to determine the exact cause of this serious corticosteroids induced bradycardia side effect (since the bradycardia is not a manifestation of the primary illness) and to improve the intervention measures.

CONCLUSION

Protocol-defined systemic steroid dose can induce bradycardia in MIS-C. This is a rare but potentially serious side effect. Close monitoring of vital signs, in particular the heart rate, is highly recommended for MIS-C patient's receiving IV steroid therapy.

ETHICAL APPROVAL

Signed informed consent for participation and publication of medical details was obtained from the parents of this child. Confidentiality of patient's data was ensured at all stages. The authors declare that ethics approval was not required for this case report.

AUTHOR'S CONTRIBUTIONS

MK, AG, IM and OA have contributed to development study design, literature search, data collection, interpretations of the findings, and writing of the report.

REFERENCES

1. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol 2020;16:413-4.
2. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, *et al*. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet 2020;395:1771-8.
3. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, *et al*. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259-69.
4. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, *et al*. American college of rheumatology clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19: Version 1. Arthritis Rheumatol 2020;72:1791-805.
5. Sperotto F, Friedman KG, Son MB, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: A comprehensive review and proposed clinical approach. Eur J Pediatr 2020;15:1-6.
6. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: Review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel) 2020;7:69.
7. Al Shibli A, Al Attrach I, Hamdan MA. Bradycardia following oral corticosteroid use: Case report and literature review. Arab J Nephrol Transplant 2012;5:47-9.
8. Sinha A, Bagga A. Pulse steroid therapy. Indian J Pediatr 2008;75:1057-66.
9. Tvede N, Nielsen LP, Andersen V. Bradycardia after high-dose intravenous methylprednisolone therapy. Scand J Rheumatol 1986;15:302-4.
10. van der Gugten A, Bierings M, Frenkel J. Glucocorticoid-associated bradycardia. J Pediatr Hematol Oncol 2008;30:172-5.

11. Akikusa JD, Feldman BM, Gross GJ, Silverman ED, Schneider R. Sinus bradycardia after intravenous pulse methylprednisolone. Pediatrics 2007;119:e778-82.
12. Bocanegra TS, Castaneda MO, Espinoza LR, Vasey FB, Germain BF. Sudden death after methylprednisolone pulse therapy. Ann Intern Med 1981;95:122.

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