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Corticosteroid Induced Acute Symptomatic Sinus Bradycardia in a Postpartum Woman Treated for Multiple Sclerosis

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Abstract Multiple sclerosis (MS) is one of the most common neurological disorders and causes of disability among young adults worldwide. Pulse steroid therapy is commonly used to treat the acute relapses of MS. Acute Sinus bradycardia has been reported as a side effect after administration of pulse dose steroid; most of the reported cases are asymptomatic. A case of acute symptomatic sinus bradycardia was reported after administration of pulse steroid in post-partum women with multiple sclerosis.

Keywords: *multiple sclerosis, postpartum, sinus bradycardia, corticosteroid*

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1. Introduction

Multiple sclerosis (MS) is one of the most common neurological disorders and causes of disability among young adults worldwide. It affects around 2.5 million people especially in Europe and North America [1]. In Saudi Arabia, most of the available studies are hospital-based and there is a need to a regional or national study to investigate the prevalence of MS, although in 2008 some studies have estimated the prevalence of multiple sclerosis in Saudi Arabia individuals to be 40/100,000 [2]. Multiple sclerosis is an inflammatory, autoimmune, demyelinating neurological disorder that affects the central nervous system (CNS) [3]. MS, frequently present as relapsing and remitting course, is characterized by lesions disseminated in both time and location affecting any region of the CNS thus leading to unpredictable and uncertain symptoms. Furthermore, MS can be present with almost any neurologic symptom [4]. MS is not a curable disorder; however, the aim of the disease-modifying agent is to shorten the duration of acute exacerbations, decrease their frequency, and provide relief to the symptoms as well as to maintain function and improve the quality of life [5]. While High-dose intravenous corticosteroid therapy, also known as pulse steroid therapy (PST) , is commonly used to treat the acute relapses of MS [6,7], the side effects of the PST varies from patient to another due to variations in dosing, duration and routes of administration [8]. The most common adverse effects reported with intravenous pulse therapy are hypertension, hyperglycemia, hypokalemia, behavioral changes and infections. Even with multiple recognized side effect of the PST, it still considered a safe therapeutic option in multiple sclerosis [6]. Sinus bradycardia is an uncommon adverse effect following steroid infusion [8], and it's very rarely symptomatic. This case discusses a patient with symptomatic sinus bradycardia following PST during postpartum period with intravenous methylprednisolone given as a treatment of an acute flare of MS.

2. Case Presentation

A 31 years old Saudi Female (height 165 cm, weight 70 KG), known case of Relapsing Remitting MS Since 2010 (8 Years) reported to clinic. The patient's first presentation was optic neuritis, since the diagnosis she was on steroid therapy, then shifted to interferon, all her work up prior to the first dose was done showing normal heart rate and blood pressure (see Figure 1). On October 2017, the patient got pregnant and interferon was stopped. During her pregnancy she had no complications, no hypertension, no fever, didn't take any medication and didn't have any MS relapses. She delivered spontaneous vaginal delivery without any complications. The patient came to ER in the postpartum period (Day 28) complaining of diplopia, painful eye movement, circumoral numbness and unsteady gait. She was admitted and planned for Methylprednisolone (1000 MG IV over 3 hours) for a total of 5 days for a flare of MS. On the current time, she was not on interferon. She stopped the medications since she discovered her pregnancy and until the time of receiving methylprednisolone. During the third

dose of Methylprednisolone, she suddenly became unresponsive with meiotic eyes and developed sinus Bradycardia (see Figure 2). the patient received inotropic IV 5 mcg kg\per\minute. Her heart rate was fluctuating from 30 to 40 (see Figure 2); her blood pressure was 85/55, and her pulse therapy stopped. Further investigations were done and revealed normal readings in all tests. Her cardiac enzymes and electrolyte, echocardiography and CT Pulmonary were all normal without any signs of pulmonary embolism. She was followed by Cardiology and ICU teams in our hospital and nothing was active from there side apart of Sinus Bradycardia. The patient was admitted in our hospital under neurology department. During her admission, her heart rate was still fluctuating 30-40 for 3 more days after stopping the pulse therapy. She had 4 attacks bradycardia which showed in ECG (see Figure 3, Figure 4, Figure 5). Cardiac enzyme & electrolyte were repeated and showed normal results. The bradycardia resolved spontaneously and normal levels were reestablished gradually after stopping pulse steroid. The patient took pulse steroid, with same rate and dose, since she was diagnosed with MS 8 years ago. She received 7 times pulse steroid due to MS relapses, without any complications. She got discharged with stable heart rate and stable condition. Magnetic resonance imagining (MRI) with gadolinium on time of admission showed active attacks of MRI (Brain& Spine Lumbar and Sacra and Spine Thoracic & Spine Cervical). 2 New Brain Lesions were seen; one of them is enhancing plus another enhancing old one.

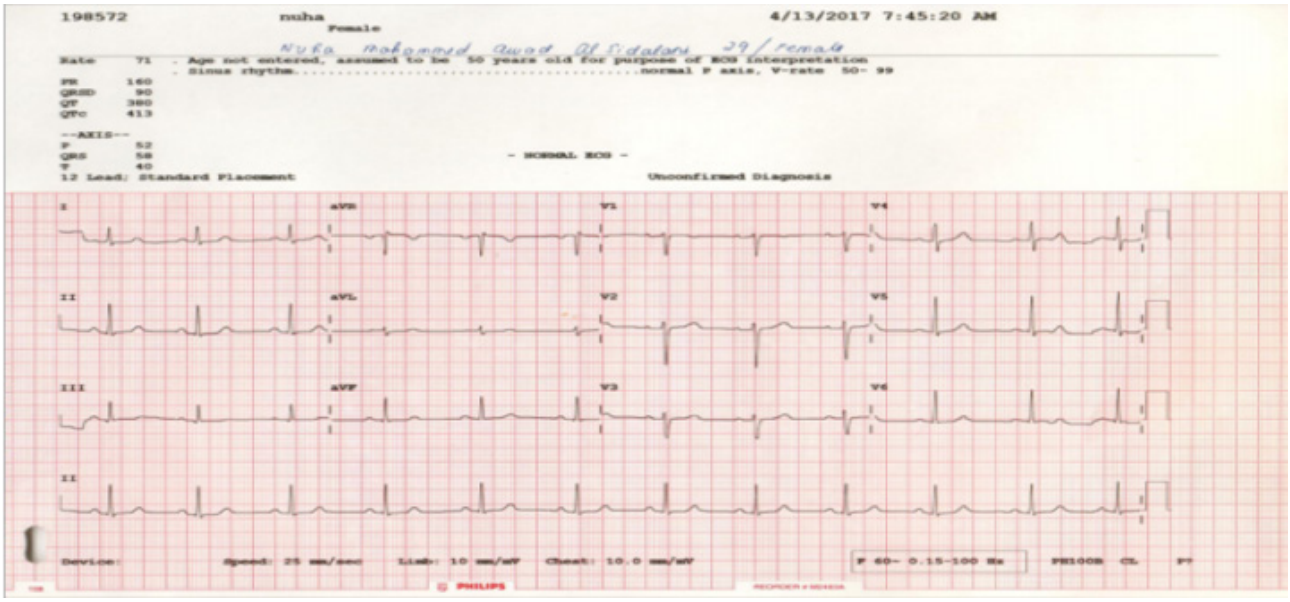

Figure 1. Her base line ECG, Heart rate was 71, vitally stable. She was a symptomatic

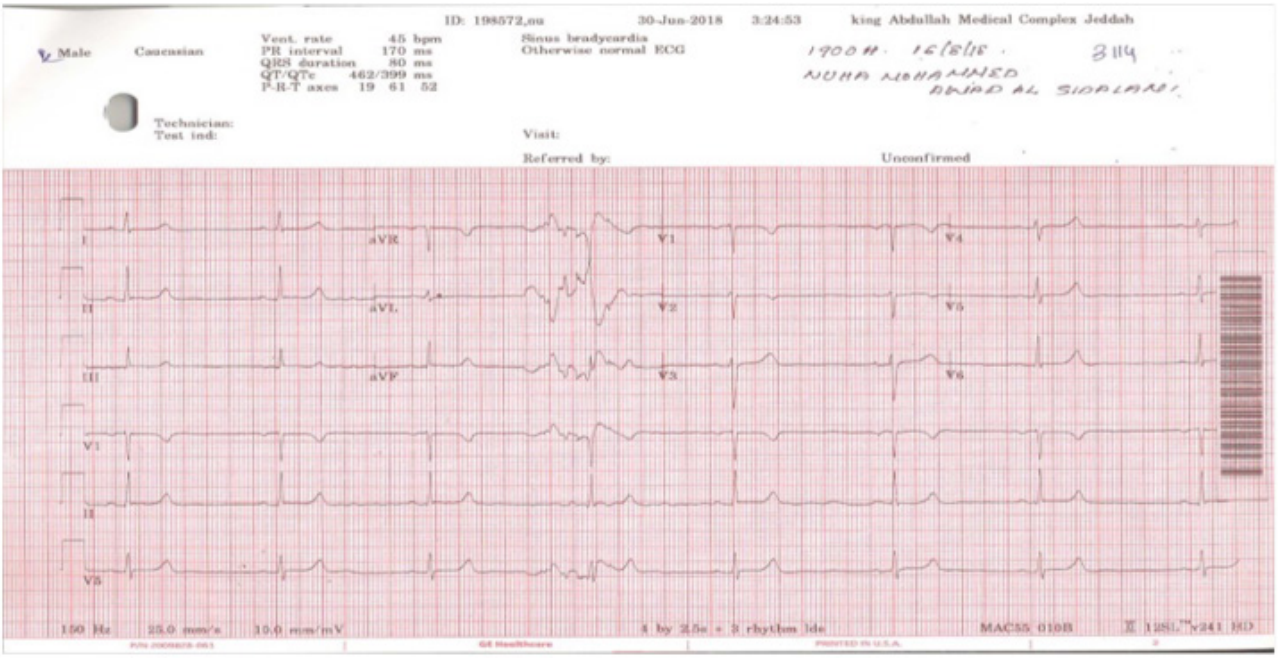

Figure 2. The Patient ECG during admission (1st attacks of Bradycardia): Heart rate was fluctuating 30 to 40 **beats per minutes, Blood pressure 92\54**. She was unresponsive with meiotic eyes and developed sinus Bradycardia.

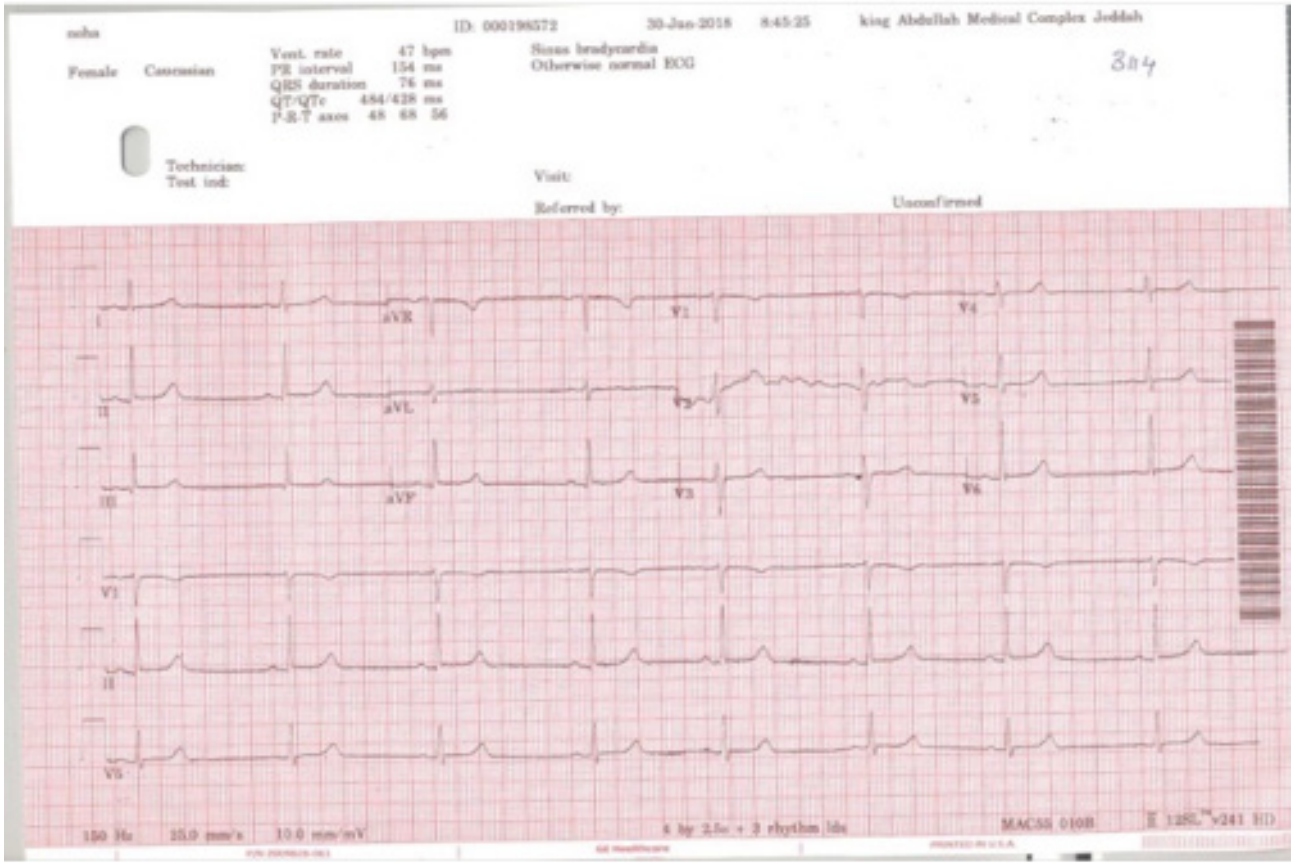

Figure 3. The patient ECG during 2[ND] Attack of Bradycardia: Her heart rate was 45 beat per minute, blood pressure 101/72. She was complaining of chest pain on and off

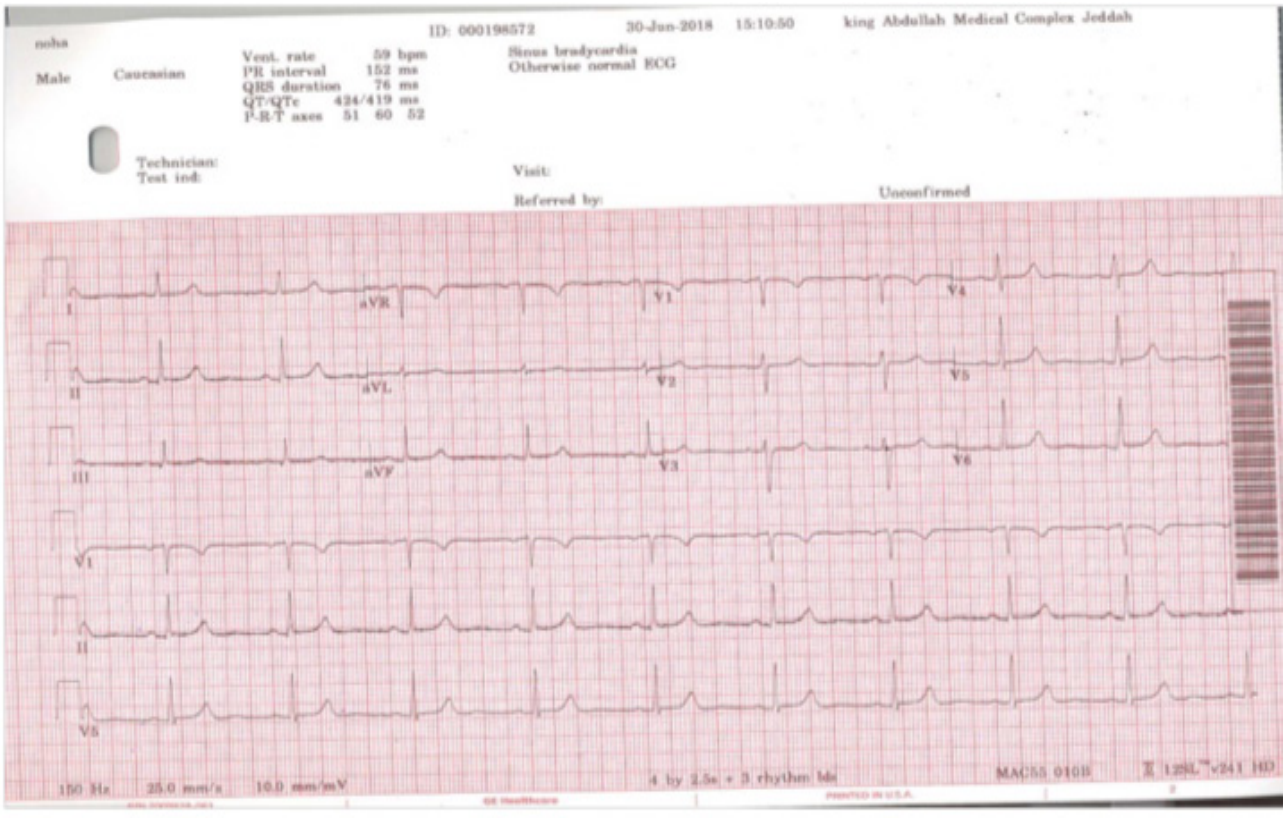

Figure 4. The patient ECG during 3[RD] attack of Bradycardia: Her heart rate 46 beat per minutes, blood pressure 101/55. She was complaining of chest pain on and off

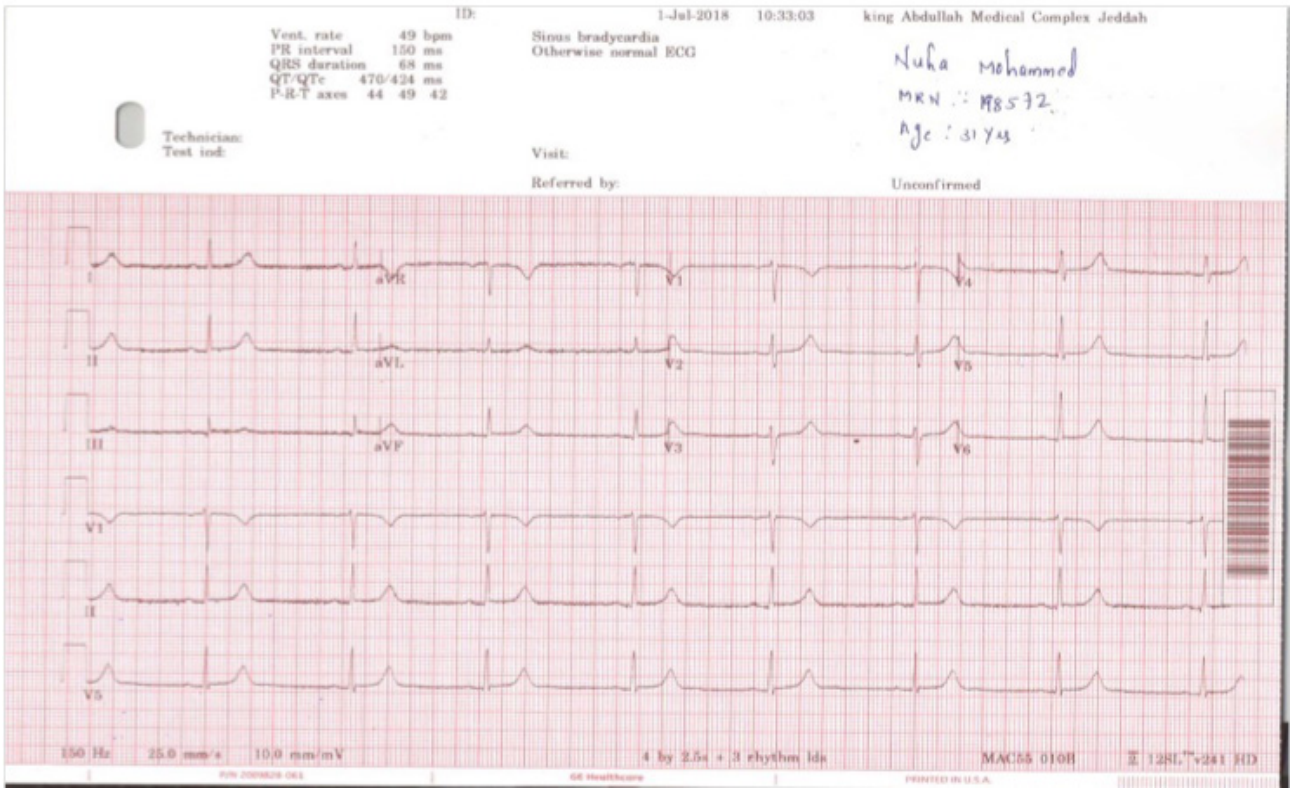

Figure 5. The patient ECG during 4th Attack of Bradycardia: Her heart rate 46 beat per minutes, blood pressure 139\97. She was asymptomatic

3. Discussion

Pulse steroid therapy (PST) is commonly used to treat the acute relapses of MS. It's typically given in a short course (3 to 5 days) of high-dose intravenous corticosteroid such as methylprednisolone in order to enhance the therapeutic effect and lower the long-term adverse effects [8]. The PST is commonly used to treat other condition such as rheumatoid arthritis and psoriasis as well as some renal, neurological, ophthalmic, hematological, pulmonary, gastrointestinal and neoplastic disecuases [9]. The side effects of PST varies from patient to another due to variations in dosing, duration and routes of administration. The most common adverse effects that have been reported with intravenous pulse therapy are hypertension, hyperglycaemia, hypokalaemia, behavioural changes and infections [6]. Yet the most serious adverse effects reported in the one literature include arrhythmias and sudden death [10,11]. Even with multiple recognized side effect of the PST, it is still considered as a safe therapeutic option in multiple sclerosis [6]. Sinus bradycardia is an uncommon side effect of steroid infusion [8], but it has been previously reported in some cases [10,12]. Most of the prior reported cases are asymptomatic [13,14], while other cases presented late onset of bradycardia, ranging from 1 to 7 days after the administration of PST [12]. Gardiner and Grith [11] have stated that bradycardia can take up to 6 days after the administration of pulse corticosteroids to become apparent. This "silent" bradycardia could be present for many of the sudden deaths associated with pulsed corticosteroids [10,11]. Another study was conducted to determine the effect of PST on cardiac rhythms in patients with MS. The study involved 52 patients who were admitted to the hospital to take methylprednisolone for an acute flare of MS. Patients receiving beta blockers or antiarrhythmic drugs or those with a history of cardiac disease were excluded. All patients included in this study went under continuous cardiac monitoring and a total of 167 sessions of PST were monitored. The results of this study showed that the most common cardiac arrhythmia was sinus tachycardia (83.8%) and sinus bradycardia was found in (41.9%) of the recorded rhythms [15]. The underlying mechanism of corticosteroid inducing bradycardia is still unclear, although there are many factors that may contribute to the development of bradycardia after a PST according to multiple theories that have been established. Yet it is more likely to be multifactorial in causes. None of the reported case was related to postpartum period but some other studies have shown that the rapid rate of the infusion, the presence of underlying cardiac disease or renal disease may increase the incidence of bradycardia after the PST [13,16]. One study suggests that transient direct damage to the myocardium is a possible mechanism leading to bradycardia after the administration of PST. In two reported cases, patients who developed bradycardia following intravenous methylprednisolone did technetium-99m pyrophosphate myocardial scanning. It showed diffusely increased radionuclide accumulation in the myocardium that resolved on follow-up a few weeks later [17]. Our patient didn't have a technetium-99m pyrophosphate myocardial scanning, but her echocardiography showed normal left ventricular function, making this explanation less likely. Another possible mechanism can be due to the changes in sodium and water physiology induced by corticosteroids, in which it can cause sodium retention and hypertension due to their intrinsic mineralocorticoid activity, which result in the expansion of plasma volume and in turn activate low-pressure baroreceptor [18]. The patient of this study didn't

have a history of hypertension not even during her pregnancy; she was following with prenatal care throughout her pregnancy regularly without any changes in her blood pressure nor her heart rate or electrolytes. Furthermore, her blood pressure level was normal throughout the course of observation making this explanation unlikely. Interestingly, Fingolimod, also causes sinus bradycardia and even second-degree atrioventricular block. It is recommended that patients receive 6 hours of continuous ECG and blood pressure monitoring after the first dose of this oral disease-modifying agent [19]. Our patient used to take Fingolimod but it's unlikely to relate the incidence of symptomatic bradycardia post PST with the history of Fingolimod use since she didn't have any changes in her heart rate following first dose of Fingolimod (see Figure 1). She also stopped taking Fingolimod at the time of discovering her pregnancy and didn't take it again in the postpartum period which makes the connection unlikely. In fact, symptomatic bradycardia with Fingolimod occurs only in about 0.5% of cases and is most often self-limiting [20]. Moreover, the magnitude of bradycardia did not increase with repeated dosing despite of increase in its blood concentration [21], and with continued treatment, heart rate would return towards baseline values [22,23]. Lastly, it has been suggested that bradycardia maybe an idiosyncratic reaction to high-dose steroid infusion in a certain population of patients, which maybe the case in our patient in her postpartum period since she did receive PST 7 times before due to MS relapse with the same rate and dose without any complications [24]. The incidence of bradycardia after the administration of PST is starting to raise the concern of weather routine cardiac monitoring is necessary for patients receiving high-dose steroid therapy, especially as many of PST sessions take place in the outpatient setting. In fact, monitoring the patient's heart rate and telemetry as well as slow rate of steroid infusion may be indicated and should be considered for certain high-risk individuals such as patient with history of cardiac disease or who have experienced adverse effects following PST in the past. Most of reported cases were earthier resolved spontaneously or managed effectively with conservative regimen. It is believed that this case highlights the importance of monitoring the patient during the PST as well as being careful in proper evaluation and assessment of the patient's overall condition. It's not very clear weather postpartum period can be considered as a predisposing factor for developing bradycardia after PST or not. Yet a retrospective study involving 47 patients with MS who had documented pregnancies were assessed in the role of Postpartum Intravenous methylprednisolone (IVMP) in order to prevent of relapses during the first postpartum trimester. Cases were divided into two groups: the group who received 1 g of IVMP after delivery and the group who did not receive IVMP after delivery. The steroids were administered within the first 6 hours after delivery and none of the patients have reported Bradycardia after the administration. In fact, the relapses were seen in 17.9% of the IVMP cases compared to 46.2% of the no-IVMP cases [25]. Our case raises the question to weather postpartum period should be considered to be one of the high-risk patients who may require continuous heart rate monitoring or not. Moreover, slow rate of steroid infusion should be considered in order to lower the risk of developing bradycardia after PST, especially with the recent practice of prophylactic use of intravenous methylprednisolone in postpartum trimester to reduce the relapses in this period.

4. Conclusion

In conclusion, our patient had sinus bradycardia, in post-partum period with MS relapse, which was started with pulse steroid. The majority of prior reported cases have been asymptomatic and thus, symptomatic sinus bradycardia remains an extremely rare adverse effect of PST. It does not warrant any treatment as most cases are self-limiting and resolve after discontinuing steroid infusion. Cardiac monitoring is generally not needed if patients are young and free of active cardiac conditions; however, patient-specific factors, such as the use of concomitant medications (that is, beta blockers) and smoking status should be considered when making this decision. As a feedback to our case, post-partum period has to be one of the cases to be monitored during PST. Finally, the patient should be evaluated according to his clinical condition if he/she needs continuous monitoring.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Consent

Written informed consent was taken from the patient directly for publication of this case report and any related images.

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