A rare cause of sinus node dysfunction: Neuromyelitis optica spectrum disorder with area postrema syndrome

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Introduction

Sinus node dysfunction (SND) or sick sinus syndrome (SSS) is a condition in which there is a disorder of the sinoatrial (SA) node resulting in impaired pacemaker function and cardiac electrical impulse transmission, leading to a variety of abnormal bradyarrhythmia and atrial arrhythmias. There are many causes of SND, of which the most common is age-related degeneration of the SA node. Other common causes include cardiac infiltrative disease, electrolyte and metabolic derangements, and drug-related causes.[1] We describe a case of SND caused by a rare neurological disorder in which a patient presented with severe symptomatic bradycardia and syncope.

Case report

A 68-year-old woman presented with a 9-day history of epigastric discomfort, nausea, vomiting, hiccups, and vigorous coughing. She had a medical history of hyperlipidemia and left breast cancer, with previous mastectomy and adjuvant chemotherapy.

Initial investigations, including liver function, amylase, lipase, renal function, and extended electrolyte panel tests, were unremarkable. In view of her multiple gastrointestinal symptoms, an esophageal gastroduodenoscopy was done, which showed only a small hiatal hernia. A contrast computed tomography scan of the thorax, abdomen, and pelvis was normal apart from stable small liver and renal cysts. Throughout the hospital admission, the patient continued to have intractable nausea, hiccups, and vomiting.

KEY TEACHING POINTS

- Sick sinus syndrome (SSS) is a common cardiac arrhythmia that may be associated with an uncommon extracardiac cause.
- Identifying and addressing reversible causes of SSS will prevent unnecessary implantation of permanent pacemakers.
- Patients with acute postrema (AP) syndrome and neuromyelitis optica spectrum disorder (NMOSD) can present with sinus node dysfunction along with other classical AP syndrome symptoms of vomiting, nausea, and hiccups caused by the presence of lesions in the medulla, which affects autonomic function, thus affecting the heart rate.
- Having an index of suspicion in patients with SSS along with atypical symptoms can allow early diagnosis of NMOSD and avoid the necessity of pacemaker implantation.

On day 6 of her admission, she had 2 episodes of witnessed syncope that lasted for less than a minute. Both episodes occurred while the patient was seated. There was no reported jerking of limbs, up-rolling of eyes, or tongue biting. The patient reported that both episodes were preceded by severe bouts of retching and very vigorous coughing. In view of her syncopal episodes, an electroencephalogram was done, which showed no epileptiform activity. She was also found to have episodes of orthostatic hypotension with a supine blood pressure of 147/78 mm Hg and a standing blood pressure of 104/60 mm Hg. However, this could not account for her syncope because the episodes occurred while she was

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seated with no postural change. Cardiac cause of syncope was considered, and she was placed on telemetry monitoring. Transthoracic echocardiogram and cardiac enzymes were normal. Whilst on telemetry monitoring, multiple recurrent sinus pauses were detected, of which the longest was 9.3 seconds and for which she had symptoms of giddiness and near syncope (Figure 1). Preceding these significant pauses, she had ongoing severe nausea and coughing. A transvenous pacing wire (TPW) was inserted, and she was treated as a case of symptomatic SSS.

A permanent pacemaker (PPM) implantation was planned as the definitive treatment for her symptomatic SSS. However, considering the recurrent bouts of persistent vomiting and vigorous coughing that seemed to consistently precede these sinus pauses, further workup was done to exclude reversible neurological causes because results of the gastrointestinal and metabolic workup were normal. Blood investigations for antibodies were sent to rule out acute postrema (AP) syndrome, autoimmune causes, and paraneoplastic syndromes in view of her previous oncological history. Unexpectedly, the patient's anti-aquaporin 4 antibodies (anti-AQP4) turned out to be significantly positive. This led us to the clinical diagnosis of neuromyelitis optica spectrum disorder (NMOSD) with AP syndrome, which would then explain her intractable vomiting, coughing, and associated bradyarrhythmia. These symptoms were likely triggered by hiccups, which is typical of the syndrome.

She underwent pre-immunosuppression evaluation and was promptly started on intravenous (IV) methylprednisolone 1 g per day for 5 days. By day 2 of IV methylprednisolone, the patient reported improvement of vomiting and coughing. The patient was kept on TPW, with a backup rate of 40 beats/min, and telemetry showed reduction in the frequency and duration of the sinus pauses by the end of day 2 of treatment. At the end of day 3 of treatment, there was no pacing requirement, and the TPW was removed. She underwent a magnetic resonance imaging (MRI) scan of the brain and the cervical and thoracic spine with contrast once the TPW was removed. The presence of T2-weighted/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in the posteroinferior medulla, dorsal midbrain, periaqueductal gray matter, as well as a long segment lesion in the cervical cord was observed and consistent with a demyelinating disease (Figure 2), further confirming the diagnosis of NMOSD.

After 5 days of IV methylprednisolone, she was switched to a tapering oral prednisolone dose, with the aim to reduce to 10 mg once daily as a regular maintenance dose. She was given a 1-month follow-up on discharge with the neurologist and planned for long-term regular review by them. She was started on a course of IV rituximab for immunosuppression for her NMOSD, with administration of her first dose in hospital just before discharge. During her inpatient treatment, the patient was on telemetry, and there was no further recurrence of sinus pauses or other bradyarrhythmia. There were no further syncopal episodes, and hence a PPM implantation was held off.

Discussion

We report a case of NMOSD with involvement of the posteroinferior medulla and dorsal midbrain presenting with AP syndrome and SSS causing recurrent symptomatic sinus pauses. NMOSD is an autoimmune inflammatory central nervous system disorder, characterized predominantly by demyelination and axonal damage, that is associated with Anti-AQP4 antibodies. Because of the varying location of lesions in the AP, diencephalon, and other brainstem areas, its broad continuum of clinical presentations led to the concept of NMOSD.[2] As per the 2015 International Panel for NMO Diagnosis in patients with a positive test of anti-AQP4 antibodies, the presence of 1 core clinical characteristic such as

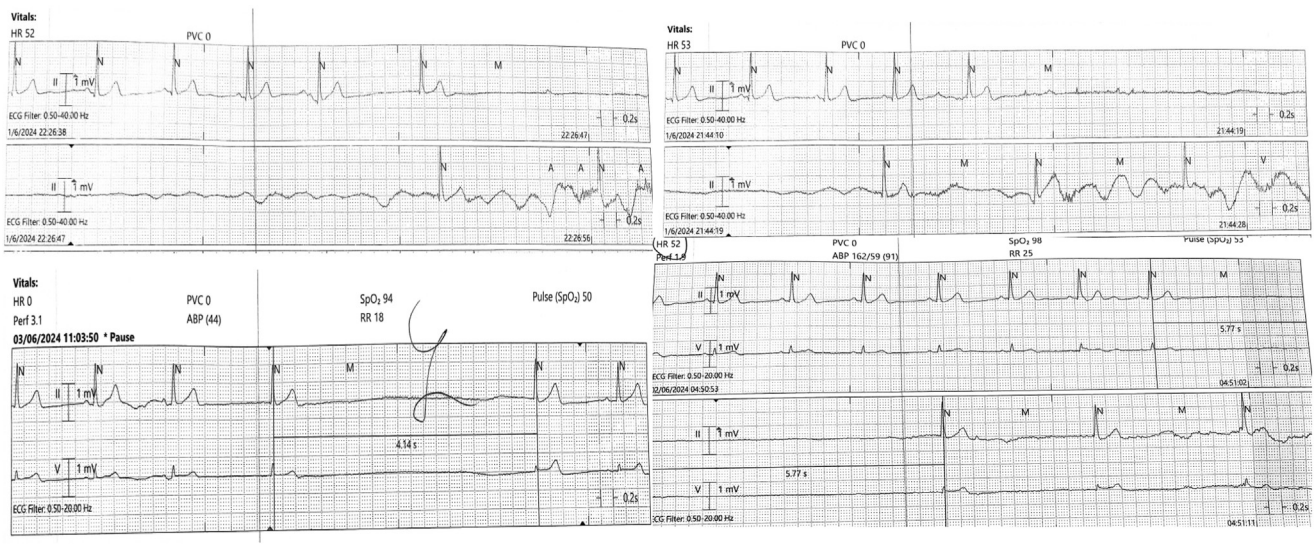

Figure 1 Telemetry strips showing multiple significant sinus pauses. Top left image shows a 9.3-second pause, top right image showing a 7.7-second pause, bottom left image showing a 4.1-second pause, bottom right image showing a 5.7-second pause.

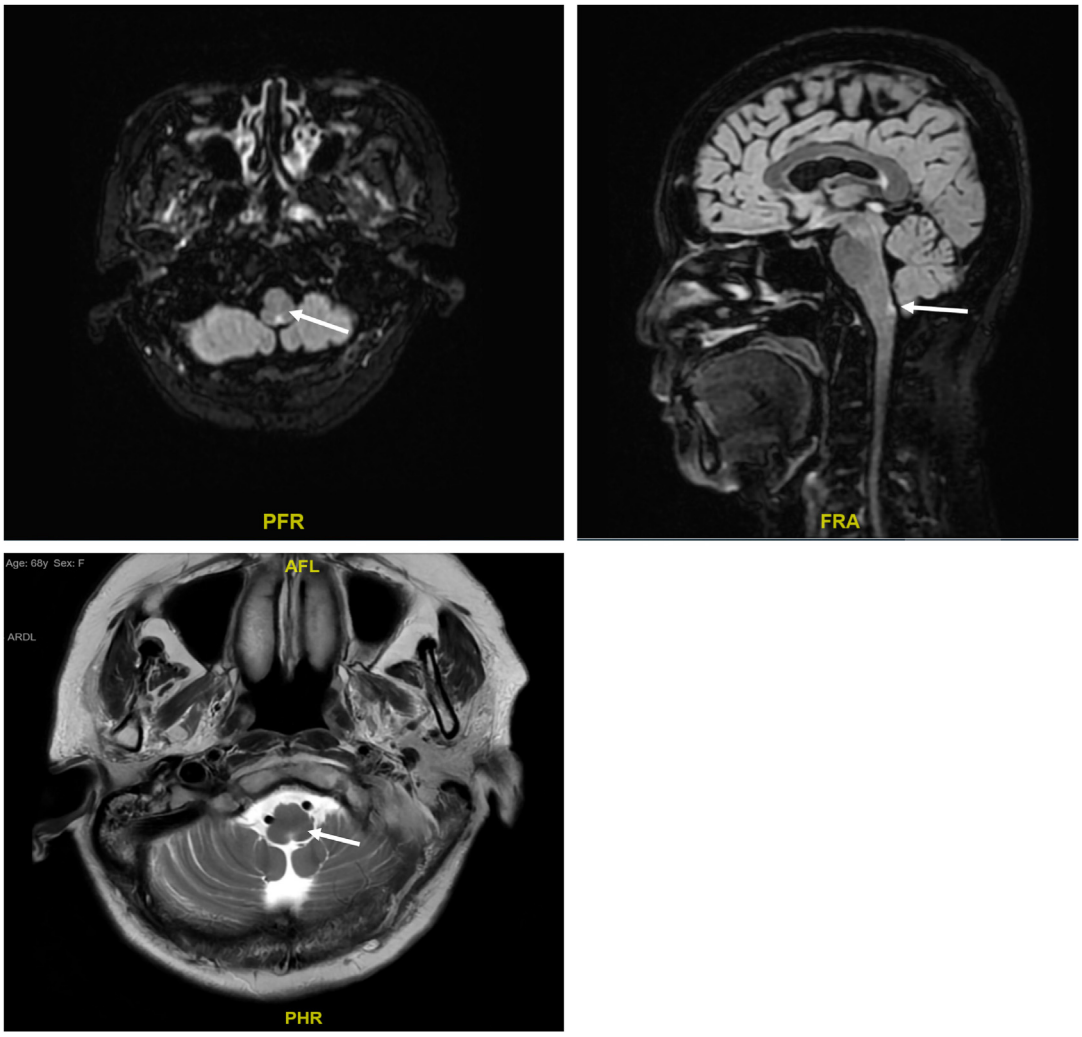

Figure 2 MRI brain showing T2W/FLAIR hyperintense lesions (*arrow*). From top left: axial view showing FLAIR hyperintense lesion in the posterior aspect of the medulla oblongata; top right: sagittal view showing FLAIR hyperintense lesion in posteroinferior aspect of the medulla oblongata; bottom left: axial view showing T2W hyperintense lesion in the posterior medulla oblongata.

either optic neuritis, acute myelitis, or AP syndrome is sufficient to make a diagnosis of NMOSD. Hence, in our patient, in the presence of a positive anti-AQP4 antibody test and presence of AP syndrome with episodes of unexplained hiccups and vomiting, she was diagnosed to have NMOSD by the neurologist.

Reports of NMOSD with SSS are scarce, likely because of the fact that lesions in NMOSD can occur in different locations. Not all NMOSDs involve the medulla, and hence there is a variation in clinical presentation, and not all manifest cardiac arrhythmias. We did a literature review on NMOSD cases with associated SSS, and there was a total of 10 previous case reports (Table 1).[3–11] An attempt to uncover common characteristics between these patients was inconclusive because of the small sample size.

In previously published case reports, none of the patients had history of cardiac arrhythmias, and only 1 had an underlying cardiac condition of ischemic heart disease. This highlights that the SND was likely the result of autonomic dysfunction caused by the underlying neurological condition. There is a high probability that with treatment and control of the neuroinflammation a PPM may be avoided. The patients reported by Tsouris et al[8] and Hamaguchi et al[10] had PPM implantation for SSS. However, in both of these cases, the implantation was made during the patients' first presentation, when they presented solely with syncope along with hiccups or nausea. The diagnosis of NMOSD was made eventually when they presented a second time with new neurological symptoms that only manifested later. In our case, after treatment was initiated, the patient's sinus pauses completely resolved within days. This highlights the possibility of SND being the first presentation of NMOSD and the need to have a high index of suspicion so that premature PPM implantation may be avoided if the arrhythmias are reversible with treatment. However, there are not many case reports of long-term follow-up of patients with NMOSD with SA node involvement. Data that show the recurrence rate of SSS in patients on active treatment is limited, and further studies are thus required.

Table 1 s[3-11]Previous case reports of patients with NMOSD and arrhythmias

Author, year (ref)	Age (years)	Sex	Symptoms	Previous cardiac disease	Cardiac arrythmia	MRI lesion	Treatment	Pacemaker implantation
Bigi et al, 2012[3]	16	M	Vomiting, hiccups	No	Sinus bradycardia	Medulla oblongata	IVMP	No
Okada et al, 2012[4]	78	F	Nausea, hiccups, orthostatic hypotension, dysarthria, dysphagia, syncope	No	Cardiac arrest	Medulla oblongata	IVMP, IVIG	No
Kazumasa et al, 2019[5]	61	F	Vomiting, nausea, syncope, hiccups	No	Sinus pauses	Medulla oblongata	IVMP, oral prednisolone	No
Talhami et al, 2020[6]	21	M	Nausea, vomiting, hiccups	No	Cardiac arrest	Medulla oblongata	IVMP, RTX	No
Ryouhei et al, 2020[7]	77	M	Nausea, vomiting, hiccups	IHD	Sinus arrest	Medulla oblongata	Oral prednisolone	No
Tsouris et al, 2020[8]	42	F	Hiccups, reduced visual acuity, retrobulbar pain, syncope	No	Sinus pauses	Medulla oblongata, left optic nerve	IVMP and oral prednisolone	Yes
Endo et al, 2020[9]	22	F	Nausea, vertigo, nystagmus, diplopia, dysarthria, limb paraesthesia, syncope	No	Sinus arrest	Dorsal part of medulla oblongata	IVMP and oral prednisolone	No
Hamaguchi et al, 2022[10]	77	M	Nausea, syncope, limb weakness, sensory disturbances, syncope	No	Sinus pauses	Dorsal part of medulla oblongata, cervical cord	IVMP, PLEX, oral prednisolone	Yes
Lin et al, 2023[11]	45	M	Syncope, nausea, vomiting, hiccups	No	Sinus arrest	Medulla oblongata	IVMP, IVIG	No
Lin et al, 2023[11]	26	F	Nausea, vomiting, hiccups, limb weakness, dysphagia, diplopia	No	Cardiac arrest	Medulla oblongata, pons, mesencephalon	IVMP, IVIG, PLEX	No
Our patient	68	F	Vomiting, nausea, hiccups, syncope, orthostatic hypotension	No	Sinus pauses	Medulla oblongata, dorsal midbrain, periaqueductal gray matter, cervical cord	IVMP, RTX, oral prednisolone	No

F = female; IHD = ischemic heart disease; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; M = male; PLEX = plasmapheresis; RTX = rituximab.

The cause of SND in NMOSD remains unclear. However, in all the case reports of NMSOD with bradyarrhythmia, AP syndrome was 1 of the neurological symptoms, with the MRI findings consistently showing lesions in the medulla oblongata. Hence, it may be assumed that the involvement of the AP, which is a sensory circumventricular organ located in the dorsal region of medulla, is a crucial component in its effects on the SA node and the cause of bradycardias. The mechanism postulated is that SND occurs because of autonomic dysfunction from lesions in the medulla, specifically in the AP, which connects to the nucleus tractus solitarii (NTS). As shown in studies, the NTS controls the neurotransmission of cardiovascular reflexes and plays an important role in regulation of cardiovascular function.[12] The SA node is directly influenced by parasympathetic and sympathetic divisions of the autonomic nervous system. The cell bodies of preganglionic parasympathetic nerves are located in the nucleus ambiguous and the dorsal motor nucleus of the vagus in the medulla. Therefore, lesions in the medulla would lead to parasympathetic effects on the SA node.[13] The NTS, however, plays a role by transmitting stimuli via efferent fibers to the rostral ventrolateral medulla (RVLM) after receiving input through sympathetic afferent fibers. Stimulation of the NTS can inhibit neurons in the RVLM, resulting in reduced sympathetic outflow causing bradycardia.[14] Our patient experienced significant sinus pauses and orthostatic hypotension, with subsequent MRI of the brain showing lesions in the posterior medulla and the AP region. It was therefore evident that her symptoms were likely caused by the inflammation and its subsequent damage to the NTS and its many projection fibers to the RVLM, the nucleus ambiguous, and the dorsal motor nucleus of the vagus. Consequently, this resulted in significant arrhythmias and cardiac disturbances. Severe orthostatic hypotension could also be a cause of syncopal episodes in patients with NMOSD with AP syndrome,[15] and consideration of further testing

with autonomic tests and tilt table is a possibility for confirmation of diagnosis. However, in our case, because presentation was acute and the patient was in high dependency with a TPW, this was not carried out. A method of distinguishing intrinsic SA nodal disease from vagally mediated bradyarrhythmia would be to consider atropine testing. In our patient, because episodes of the sinus pauses were intermittent and transient and resolved after early introduction of steroids, this was not done. Atropine testing could be a consideration in other cases of more persistent bradyarrhythmia where there is a suspicion that the bradycardias could be vagally mediated. Atropine works by blockade of the parasympathetic autonomic tone resulting in increased rate of discharge of the SA node, and hence an appropriate response to atropine would suggest a vagally mediated bradyarrhythmia.

Our patient's presentation and comorbidities very closely resembled the case reported by Kazumasa et al.[5] They were both women, of similar age, and presented with nausea, hiccups, and SSS a year after undergoing mastectomy and radiation therapy for breast cancer. Both cases were taking regular estrogen-inhibiting medications. However, our case was not considered to have paraneoplastic NMOSD because paraneoplastic neurological syndrome strictly refers to cases in which the neurological symptoms occurred before the development of cancer. Therefore, whether a paraneoplastic mechanism was involved in the immunopathogenesis of these 2 patients who had NMOSD with AP syndrome with manifestation of SSS within 1 year of breast cancer diagnosis and treatment is uncertain.

Conclusion

SSS is a common cardiac arrhythmia but may be associated with an uncommon cause. We present a rare cause of SSS and emphasize the need to search for reversible causes, especially if the initial presentation is atypical. One must take into account extracardiac causes of SND. Neurological disorders causing autonomic dysfunction should be considered as a cause of bradyarrhythmia. Additionally, we highlighted important clinical signs such as the triad of intractable vomiting, nausea, and hiccups leading to vigorous coughing in patients with AP syndrome and NMOSD. This is a rare cause of SND that requires a high clinical index of suspicion. The recognition of this syndrome with proper treatment may allow resolution of the associated bradyarrhythmia and avoid the need of a PPM implantation.

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