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Case Report

Sick sinus syndrome associated with hypopituitarism: a case report and literature review

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Abstract

Though an association between autoimmune diseases and sick sinus syndrome has been reported, there has been no report on the association of hypopituitarism and sick sinus syndrome. Herein, we provide the first case report of hypopituitarism accompanying sick sinus syndrome in a 51-year-old woman presented to our hospital with syncope due to cardiac arrest. The patient was successfully managed by pacemaker installation and hormone replacement therapy.

Keywords: sick sinus syndrome, hypopituitarism, obstetrical hemorrhage, Sheehan's syndorome

INTRODUCTION

Sick sinus syndrome (SSS) may result from various lesions of the sinoatrial node (SN) and its surrounding tissue and mainly manifests as sinus bradycardia combined with ectopic tachycardia. Several studies[1–4] have reported an association between autoimmune diseases and SSS. Hasegawa et al. described a patient with pituitary adenoma who presented with SSS.[5] However, to our knowledge, there has been no report on the association of SSS. Herein, we provide the first case report of hypopituitarism accompanying SSS, which was treated with pacemaker installation and hormone replacement therapy.

CASE REPORT

A 51-year-old female farmer was admitted to our hospital with syncope on October 11, 2010. She reported frequent episodes of dizzy spells, amaurosis and exercise-induced syncope over the previous year. During ambulatory treatment, bradycardia (heart rate: 50–55 bpm) was repeatedly recorded on electrocardiography (ECG). A 24-hour Holter ECG recording showed sinus arrest and sinoatrial block. The longest RR interval was 7.36 seconds. SSS was diagnosed, and the patient was hospitalized for pacemaker implantation. The patient had a prematurely aged face, dry skin, and hypotrichosis; physical examination was otherwise unremarkable. The patient experienced an obstetric hemorrhage during parturition 25 years ago and the fetus died. The patient developed menoxenia after the incident and entered menopause 6 months later. No further imaging studies were performed.

We conducted a detailed search for the cause of syncope. Other factors, such as tachyarrhythmia and neurological disease, were not detected. Routine tests, including blood electrolyte and coagulant levels, were normal. To treat the bradycardia, we implanted a pacemaker (DDD) into the patient. ECG showed that the

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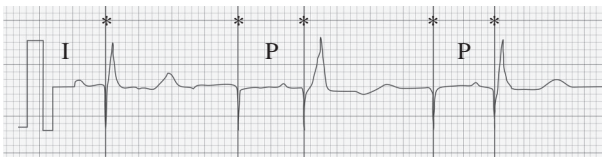

Fig. 1 **Postoperative ECG of a 51 year old woman with sick sinus syndrome associated with hypopituitarism: AV sequential pacing.** The interval between the atrial pacing signal (*) and the *P* wave was prolonged (160 ms), indicating intra-atrial block.

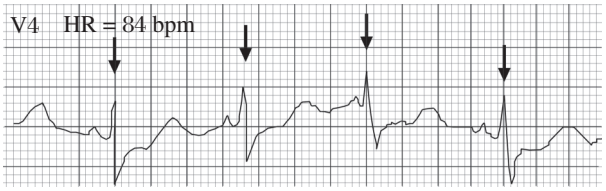

Fig. 2 **The patient's heart rate (HR) was elevated (84 bpm) after hormone replacement therapy.**

pacemaker worked normally, with intra-atrial block (***Fig. 1***). On the second postoperative day, the patient developed nausea and vomiting. The vomitus was stomach contents mixed with blood. Suspecting irritable gastritis, we prescribed fasting, fluid infusion and acid-suppression therapy, but the patient's condition worsened. As hematemesis continued, she became anorectic, weak, dehydrated, and lethargic. Blood electrolyte tests showed hyponatremia (Na: 108.6–128.0 mmol/L), hypochloridemia (Cl: 80.3–97.9 mmol/L), and hypocalcemia (Ca: 1.98–2.10 mmol/L). The severe electrolyte imbalance was not reversed by vigorous intravenous replacement.

We reevaluated the patient's clinical features, including her medical history of obstetric hemorrhage and early menopause, prematurely aged face, hypotrichosis, and stubborn postoperative hyponatremia. A diagnosis of Sheehan's syndrome was considered. Secretory function tests of the pituitary, thyroid, reproductive, and adrenal glands were conducted, which revealed hormone deficiencies (***Table 1***). The patient was started with intravenous hydrocortisone (100 mg daily) and oral levothyroxine (25 mg daily). Within 1 day of treatment, the patient's symptoms and electrolyte imbalance were effectively alleviated. Although cranio–cerebral MRI was not performed because of the presence of the pacemaker, the diagnosis of Sheehan's syndrome was credible on the basis of the patient's clinical features. At hospital discharge, the patient was prescribed continuous hormone replacement (25 mg levothyroxine by mouth daily). At the 3-month follow-up visit, the patient reported no recurrence of syncope, and she showed an elevated sinus heart rate (***Fig. 2***) and corrected hormone levels (***Table 1***).

Table 1 **Secretory function tests of the pituitary, adrenal, thyroid, and reproductive glands**

Hormone	Pre-treatment	Post-treatment	Normal range
ACTH (ng/L)	15.3	42.8	0–46
Corisol (μmol/L)	0.60	0.28	0.14–0.69
TSH (mIU/L)	2.6	0.263	0.3–4.2
FT3 (pmol/L)	1.5 ↓	4.0	3.1–6.8
FT4 (pmol/L)	8.7 ↓	13.2	12–22
FSH (IU/L)	7.4 ↓	/	21–104
LH (IU/L)	2.5 ↓	/	10.9–58.6
PRL (μg/L)	2.59 ↓	/	3.1–14.1
E2 (pmol/L)	31.70	/	12–136.0

ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; FT3: free triiodiothyronine; FT4: free thyroxine; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin; E2: estradiol; /: not done; ↓: deficiency; pre-treatment: after pacemaker implantation and before hormone replacement therapy; post-treatment: after 3 months of hormone replacement therapy with levothyroxine (25 μg by mouth daily).

DISCUSSION

The etiology of SSS can be divided into intrinsic causes and extrinsic factors that disrupt the function of the SN[1]. Intrinsic causes include degenerative fibrosis of the SN, ion channel dysfunction, and remodeling of the SN. Extrinsic factors include the use of certain pharmacologic agents, metabolic disturbances, and autonomic dysfunction. This patient was only 51 years old and had no history of ischemic or non-ischemic cardiomyopathy, and she also had no positive family history or showed any evidence of infiltrative disease. These considerations suggested that internal lesions of SN were not likely responsible for SSS in the patient. There were also none of the extrinsic factors mentioned above. Therefore, absolute or relative lack (during physiological or trauma stress) of hormones of the pituitary and its downstream target glands, the most significant clinical abnormality of the patient, was very likely the cause of bradycardia and the metabolic disturbances. Effectiveness of hormone replacement further supported this argument.

Neurohumoral regulation plays an important role in maintaining normal cardiac rhythm. Many studies have described neuroregulation of cardiac rhythm, but few have discussed humoral regulation. Hormones secreted by the pituitary and its downstream target glands (i.e., the thyroid, reproductive and adrenal glands) have recently been implicated in helping maintain sinus

rhythm and regulating the conduction of endocardial excitation. The thyroid hormone acts on cardiac rhythm in several ways. It has positive chronotropic actions by acting on cardiac ion channels. A study[6] of the newborn mouse heart illustrated that T3 can enhance the pacemaker current and the Na^{+}-Ca^{2+} pump activity, thereby strengthening the autorhythmicity of myocardial cells. The thyroid hormone was also shown to improve sinus heart rate by enhancing the sensitivity of the heart to the sympathetic nervous system and adrenaline[7,8]. Long-term, severe hypothyroidism may cause degeneration of the mucous membranes of the SA node and adjacent tissues, thereby blocking sinus rhythm generation and conduction. In the present case, sinus bradycardia and cardiac arrest may be partly ascribed to her hypothyroidism. It also remains likely that intra-atrial block in the patient was associated with myocardial mucoid degeneration due to hypothyroidism.

Estrogen has been recognized as a protective factor against coronary heart disease[9,10] and injury from myocardial ischemia[11–13]. Recently, sex hormones have been shown to play important roles in regulating cardiac rhythm. A recent study in mammals[14] showed that sex hormones could improve the heart rate and atrioventricular conduction velocity, and estrogen has been found to play a role in cardiac chronotropicity during physical activity and stress[15,16]. The detailed mechanism of this process, whether through ischemic myocardial protection or direct regulation of cardiac electrophysiology, is still not clear. In the present case, the patient's estrogen level was low (***Table 1***). The pathogenesis of SSS in our case could be partially attributed to the insufficiency of estrogen levels, which are required to exert a protective effect against chronic myocardial ischemia and to suppress apoptosis of cells, especially autorhythmic cells[13]. However, the question whether the degeneration of the SN in the elderly is associated with the physiological withdrawal of sex hormones requires further research.

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in body stress and fluid homeostasis[17]. When the body is under stress, the HPA axis is activated, elevating the heart rate through activating the cardiac sympathetic nervous system.[18,19] On the other hand, glucocorticoids are required for normal cardiovascular reactivity to angiotensin II, epinephrine, and norepinephrine[20]. Although surgical stress should stimulate the HPA axis by increasing cortisol secretion[20], this approach did not work in our patient. Her pituitary gland did not respond to surgical stress and her ACTH did not increase, compared to baseline (***Table 1***). Consequently, the patient showed manifestations of postoperative stress disorder: nausea, vomiting, weakness, and severe electrolyte imbalance. The sinus bradycardia and arrest may have been manifestations of a poor ability to respond to stress.

After obtaining the patient's relevant medical history and ascertaining her physical appearance, we did not check her pituitary function to evaluate the pathogenesis of syncope or her ability to tolerate surgery. We also did not perform an electrophysiology study to evaluate the function of the SA node. SSS is common in the elderly and its pathogenesis is still not clear. For patients with SSS who show signs of early-onset aging, it may be necessary to assess the functionality of the pituitary and the SA node. The results of these analyses can have important clinical significance when making a definitive diagnosis, selecting a treatment strategy, and evaluating the surgical risk.

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