CASE SERIES

Panhypopituitarism presenting as sick sinus syndrome: A case series

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Abstract

The objective of this study is to report the cases of three patients who presented with sick sinus syndrome associated with secondary hypothyroidism, requiring permanent pacemaker insertion and hormone replacement therapy.

Three patients were diagnosed with sick sinus syndrome and permanent pacemaker insertion was planned. All three were in their sixth and seventh decades, with clear features of long-standing neglected panhypopituitarism. They had inappropriately low thyroid stimulating hormone (TSH) elevation for the low free thyroid hormonal levels. But since their initial screening was with TSH alone, which was normal in two patients, the diagnosis of central hypothyroidism was missed. Despite all these, all three improved dramatically just with steroids and thyroxine supplements, proving the endocrinological drive in rhythmicity, despite other propositions.

This article highlights the importance of multiple endocrinological drivers of sino-atrial nodal rhythmicity and how the possibility of pituitary insufficiency should be considered before going in for an invasive approach like pacemaker insertion.

Keywords: Panhypopituitarism, Cardiac arrhythmia, Sick sinus syndrome.

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Introduction

Cardiac arrhythmias are common with endocrinological emergencies like diabetic ketoacidosis, adrenal crisis, myxoedema, thyrotoxicosis, hypertensive crisis, hypoglycaemia, and dyselectrolytaemia.[1] The dyselectrolytaemias commonly associated with arrhythmia include hypocalcaemia, hypercalcaemia, hypokalaemia, hyperkalaemia, and hypomagnesaemia.[2] The underlying cause for the dyselectrolytaemia very often happens to be an endocrine dysfunction.[3] Among these, tachyarrhythmia happens to be more common than bradyarrhythmia. Rhythm disturbances like sinus bradycardia, QT prolongation, second-degree atrioventricular block, complete heart block, and sick sinus syndrome caused by primary hypothyroidism is a well-known phenomenon. Even sick sinus syndrome (SSS), presenting in hyperthyroidism has been reported in literature.[4] However, literature regarding secondary hypothyroidism presenting as SSS is scarce. To the best of our knowledge, there is only one case report of SSS induced by secondary hypothyroidism on a panhypopituitarism background.[5]

We present a case series of three patients who presented with SSS associated with secondary hypothyroidism, requiring permanent pacemaker insertion (PPI) and hormone replacement therapy.

Case Series

Case-1: A 70-year-old male, presented with recurrent giddiness and altered gait. He had a history of trans-nasal trans-sphenoidal surgery for pituitary adenoma (details lost) at Sri Ramachandra Medical Centre (SRMC), Chennai, India, on April, 1993. He was lost to follow-up and was later diagnosed with Parkinsonism and hypothyroidism elsewhere, and started on anti-parkinsonism drugs and thyroxine supplements. The patient had a history of hyponatraemia and was admitted and managed with Vasopressin receptor antagonists (Tolvaptan) on and off. During the current admission (December 2021) it was noticed that he had bradycardia, and after a detailed Holter assessment, he was diagnosed with intermittent sinoatrial block suggestive of sick sinus syndrome and permanent pace-maker insertion (PPI) was planned. Due to altered gait, a thorough neurological re-assessment was done which revealed cerebellar ataxia and imaging revealed a pituitary macroadenoma (Figure1). Lab findings were suggestive of pan-hypopituitarism and non-functioning pituitary adenoma. Medical management with replacement steroids and escalated thyroxine doses was initiated, which resolved his sick sinus syndrome, eliminating the need for permanent pacemaker insertion. Subsequently, he underwent successful trans-sphenoidal pituitary mass resection, and histopathology confirmed pituitary adenoma. The patient recovered and is doing well post-operatively.

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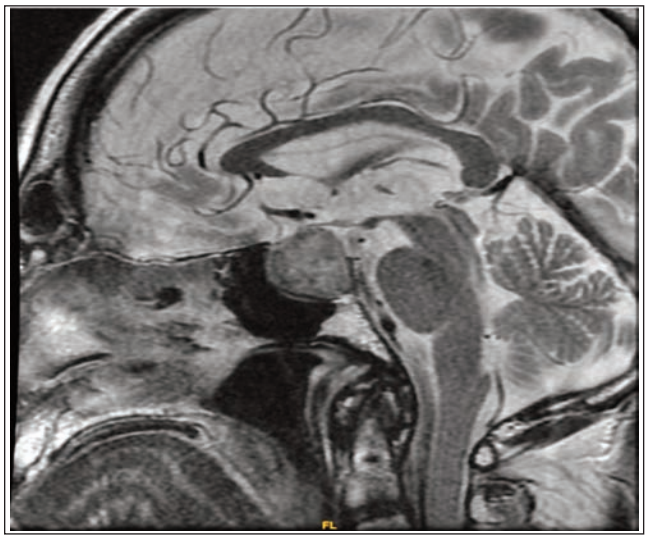

Figure-1: MRI Brain -sagittal view showing a well-defined heterogenous mass within the sella with suprasellar extension suggestive of pituitary macroadenoma.

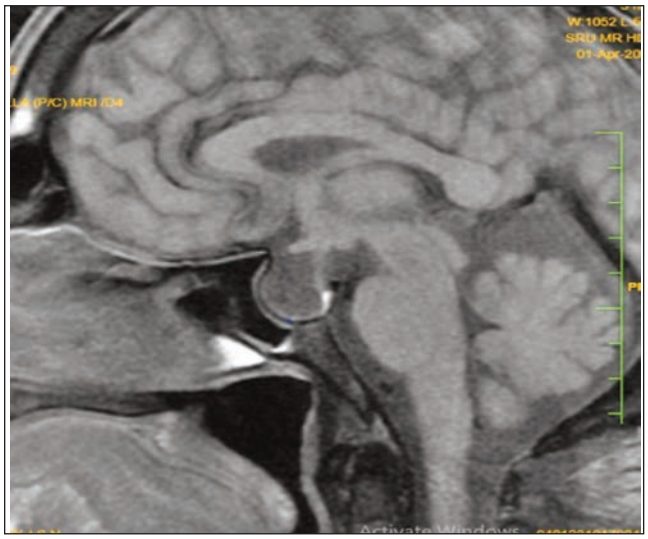

Figure-2: MRI of the brain sagittal view showing empty sella with preserved posterior pituitary bright spot.

Case-2: A 60-year-old gentleman, with a history of hypothyroidism and on irregular treatment, presented with abdominal distension and pedal oedema on June, 2022, to SRMC, Chennai. On evaluation, he had sinus rhythm with ectopics and couplets signalling sick sinus syndrome and was planned for PPI. He also had non-cirrhotic portal fibrosis (NCPF) with portal hypertension. Biochemistry tests showed evidence of panhypopituitarism. MRI revealed an empty sella (Figure 2). The patient was started on replacement steroids, and thyroxine supplementation, following which his cardiac rhythm reverted to normal on follow-up visit, rendering PPI unnecessary. The patient still has sinus rhythm on two-year follow-up.

Case-3: A 70-year-old gentleman presented to the emergency room at Sri Ramachandra Medical Centre, Chennai, in August 2021 with giddiness and dyspnoea. He had a history of systemic hypertension, dyslipidaemia, coronary artery bypass graft (CABG) 20 years ago, and trans-nasal trans-sphenoidal pituitary mass resection for a non-functioning pituitary adenoma 12 years ago. He was lost to follow-up and was not on hormone replacement therapy for two years. He was diagnosed with sick sinus syndrome and initiated on Orciprenaline, with plans for permanent pacemaker insertion (PPI) due to inadequate response. However, during subsequent endocrinological follow-up, he was started on replacement steroids and Thyroxine supplements, addressing his underlying hypopituitarism. Remarkably, his sick sinus syndrome reverted, allowing discontinuation of Orciprenaline therapy. MRI revealed an empty sella (Figure3). The patient's condition stabilised with hormone replacement therapy, and he was doing good on follow-up.

Discussion

The heart rate is 100 beats per minute without any regulatory factors. The regulation is effected by cardiac reflexes and neuroendocrine factors. Any structural abnormality or perturbation in blood gas, acid-base balance, electrolytes, or ion channel dysfunction predisposes an individual to dysrhythmia.[6]

The central cardiac stimulatory centre acts via the sympathetic nervous system through nor-epinephrine which opens the ligand-gated sodium and calcium channels and increases the chronotropic, dromotropic, and inotropic effects. The cardio-inhibitory centre acts via the para-sympathetic nervous system through acetylcholine which opens ligand-gated K^+ channel and reduces the heart rate. During the resting phase, vagal stimulation is predominant keeping the heart rate at 72-75 bpm.[7] Any issue with proprioceptors, chemoreceptors, and baroreceptors, which relay the afferent signals to cardio-regulatory centres, and higher control like limbic system and cortical regulation, which controls the cardiac regulatory centres, may also alter an individual's cardiac rate and rhythm.

Numerous endocrine conditions are known to cause rhythm change. Among diabetics, autonomic neuropathy, associated comorbidities like hypertension, chronic kidney disease in a long-standing diabetic patient, spontaneous hypoglycaemia or hypoglycaemia secondary to insulin, and sulphonylureas, cause QT prolongation. Drugs like Dipeptidyl Peptidase inhibitors (Teneligliptin at higher doses) and Glucagon-like Peptide -1 agonist are known to increase the heart rate; and even atrial fibrillation (with the

use of Albiglutide) have been reported in various studies.[8] Thyroid hormones, especially T3 regulate several myocardial ion channels directly and augment adrenergic sensitivity through upregulation of Beta-1 Adrenergic receptors. Thyrotoxicosis predisposes the patients to sinus tachycardia and numerous tachyarrhythmias like paroxysmal atrial tachycardia, atrial and ventricular ectopics, atrial fibrillation, and left ventricular hypertrophy.[9] Hypothyroidism, on the other hand, slows the cardiac pace and predisposes the individual to varying degrees of conduction blocks. In extreme variants, patients may develop cardiac tamponade which worsens the haemodynamic stability and causes dysrhythmia. Growth hormone acts via IGF-1 which is involved in left atrial remodelling. Growth hormone excess states, like acromegaly, predispose the patients to late potentials and thereby cause ventricular ectopics.[10] Recurrent arrhythmias as a presenting feature in phaeochromocytoma have been reported in the literature.[11] Hypokalaemia and aldosterone-mediated myocardial fibrosis in primary hyperaldosteronism causes arrhythmias even to the extent of polymorphic ventricular tachycardia and ventricular fibrillation. Cortisol directly modulates the rapid and delayed rectifier potassium channels regulating outward potassium current;[12] hence, Cushing's syndrome and adrenal insufficiency predispose individuals to arrhythmias through direct effects as well as secondary to haemodynamic changes and dyselectrolytaemia. Hyperparathyroidism and hypoparathyroidism are also notorious to cause arrhythmias through dysregulated calcium metabolism.

Oestrogen suppresses apoptosis of cells, especially those maintaining auto rhythmicity, and testosterone increases ryanodine receptor type-2, late Na^+ current, and prolongation of action potential and has proven effects over sinoatrial node through various animal studies.[1]

In this case series, we have reported three cases of sick sinus syndrome associated with secondary hypothyroidism. All were in their sixth and seventh decades, with clear features of long-standing neglected pan-hypopituitarism, and presented with symptomatic SSS requiring PPI. Neither of them had a history of alcohol, smoking, and illicit drug abuse. Drugs predisposing to rhythm disturbances were excluded. One of the patients had a critical coronary disease and had undergone CABG a few years back. The other patient had evidence of fibrosis in the form of NCPF. All three patients had inappropriately low TSH elevation for the low free thyroid hormonal levels (Table). But since their initial screening was with TSH alone, which was normal in two patients, the diagnosis of central hypothyroidism was missed. Despite all these, all three patients improved dramatically just with steroids and thyroxine supplements, exemplifying the hormonal role in driving cardiac rhythm, despite other propositions.

Table: Laboratory investigations.

Lab values	Patient 1	Patient 2	Patient 3	Reference Ranges
Thyroid Stimulating Hormone (TSH)	0.40	3.4	3.44	0.27-4.2 µIU/ml
Free T4	0.73	0.55	0.36	0.93-1.7 ng/dl
Free T3	2.2	1.22	1.38	2-4.4 pg/ml
Follicle Stimulating Hormone (FSH)	1.62	9	0.878	1.5-12.4 mIU/ml
Luteinizing Hormone (LH)	0.57	4.4	0.2	1.7-8.6 mIU/ml
Testosterone	5.4	49	<2.5	175-781 ng/dl
Prolactin	5.42	10.1	167	4.0-152 ng/ml
8 AM Cortisol	2.43	5.0	2.8	6.7-22 µg/dl
ACTH stimulated cortisol	8.4	9.0	7.4	>18 µg/dl
Corrected Calcium	9.5	8.9	9.1	8.8-10.6 mg/dl
Sodium	128	138	1 34	136-146 mmol/L
Potassium	4.0	3.6	3.9	3.5-5.1 mmol / L
Magnesium	1.8	2.0	1.9	1.8-2.6 mg/dl
Haemoglobin	11.4	11.5	10.1	13-17 g/dl

Conclusion

This article highlights the importance of multiple endocrinological drivers of sino-atrial nodal rhythmicity and how the possibility of pituitary insufficiency should be considered before going in for an invasive approach like PPI. Physicians may easily be carried away by the inappropriately elevated TSH values (which would still be in the normal reference range) for the low normal /low free T4 levels when evaluating for sick sinus syndrome. So astute history taking, and prompt identification of hormonal causes will eliminate the need for PPI.

Disclaimer: No case presented herein is individually identifiable. Verbal consent was taken from patients during the hospital stay and interaction.

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Author Contribution:
PR: Concept, design, data acquisition, interpretation, drafting, final approval and agreement to be accountable for all aspects of the work.
AS: Data acquisition, analysis, interpretation, drafting, final approval and agreement to be accountable for all aspects of the work.
ARA & SM: Concept, design, data acquisition, revision, final approval and agreement to be accountable for all aspects of the work.
AR: Concept, design, data interpretation, revision, final approval and agreement to be accountable for all aspects of the work.