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Journal of Thoracic Disease and Cardiothoracic Surgery
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Case Report

A Dual Hit by Lithium: Sinus Node Dysfunction and Pulmonary Artery Hypertension

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Received date: Jun 18, 2023; Accepted date: Jun 27, 2023; Published date: July 07, 2023

Citation: Jamal Yusuf, Sunil Kumar Mandal1, Saibal Mukhopadhyay, Vimal Mehta, Rupesh Agrawall, (2023), A Dual Hit by Lithium: Sinus Node Dysfunction and Pulmonary Artery Hypertension, *Journal of Thoracic Disease and Cardiothoracic Surgery*, 4(4); DOI:**10.31579/2693-2156/054**

Abstract

Rationale: Lithium is used as an anti-manic and mood-stabilising drug in psychiatric clinical setting. It has a narrow therapeutic window with multiple side effects, which can occur even at normal therapeutic range. Among many side effects, pulmonary artery hypertension (PAH) and sinus node dysfunction (SND) is a very rare condition associated with chronic lithium use . Reversibility of PAH even after permanent drug cessation is not known.

Case presentation: We present a case of a 52-year old male on lithium therapy for last 5 years for bipolar disorder (BD) with no past history of cardiac illness, presented with moderate to severe pulmonary artery hypertension (PAH) and symptomatic sinus node dysfunction with frequent episodes of presyncope and syncope. Symptomatic sinus node dysfunction and severe pulmonary artery hypertension necessitated cessation of lithium treatment. Within two weeks, patient reverted back to normal sinus rhythm. Pulmonary artery hypertension took also improved over next six months from RVSP of 70mmHg to 35mmHg. Considering the fact that abrupt cessation of lithium therapy can lead to rebound in symptoms of bipolar disorder, he was switched to alternative antipsychotic agent Divalproex 250 mg BD under the guidance of psychiatrist.

Conclusion: Patient on chronic lithium therapy presenting with any symptoms should be properly evaluated and investigated. Even within the normal therapeutic range, patient can present with rarest of the rare side effects like in our case. Sick sinus syndrome in most cases reversible within weeks. Contrary to the only case repot published till now, this case shows that PAH is reversible with time. To the best of our knowledge this is the first case report showing reversibility of pulmonary hypertension after lithium cessation.

Keywords: lithium; bipolar disorder; sick sinus syndrome; pulmonary artery hypertension

Introduction

Lithium is still accepted to be 'gold standard' treatment for bipolar disorder(BD) [1]. Since BD is considered to be a recurrent and chronic disease, preventive lithium therapy is suggested to continue for a long time, even lifelong. Its main effect is probably through inhibition of hydrolysis of inositol phosphate, uncoupling of receptors from G-proteins or alteration of various neurotransmitters. Adverse effects of lithium include various cardiovascular, pulmonary, nervous system, endocrine, dermatological and renal side effects which can occur even at normal therapeutic range[2]. We, hereby describe a case of lithium-induced symptomatic sick sinus syndrome (SSS) and moderate-severe PAH occurring in a patient who was on lithium therapy for 5 years for BD and whose serum lithium levels were within normal therapeutic range.

Case Report

A 52 year old male, who was diagnosed with BD five years back and was receiving Lithium 800 mg/day, Aripiprazole 5 mg/day and Sertraline 200mg/day, presented with multiple episodes of presyncope and syncope since last two weeks. There was no history of dyspnoea, palpitation and

chest pain. During emergency visit his index ECG was suggestive of junctional escape and atrial ectopic showing bigeminy pattern suggestive of sick sinus syndrome (SSS) with multiple sinus pauses of 2-3 seconds. On physical examination, pulse rate was around 40 bpm (regularly irregular), blood pressure was 130/84 and there was grade 3/6 pansystolic murmur (during inspiration and leg raising) in left parasternal region. Reverse transcription -polymerase chain reaction for COVID 19 was negative. Patient was monitored continuously in CCU for rhythm. Transthoracic echocardiography showed normal systolic and diastolic LV function, dilated right atrium and right ventricle with severe tricuspid regurgitation (TR) and moderate -severe PAH with pulmonary artery systolic pressure(PASP) of 70mmHg [Fig 1]. Transoesophageal echo showed no structural heart defect. Other cause of PAH were excluded by lab test and other investigation like CT pulmonary angiography and HRCT. Routine lab test showed normal electrolytes (Na+, K+, Ca+2) and TSH. Other drugs causing sinus node dysfunction were excluded. He was a non-smoker and had no history of infectious disease. Cardiac rhythm was analysed on 24 hour Holter monitoring and the analysis showed sinus bradycardia, atrial escape rhythm and ectopic atrial rhythm, non-conducted p wave, paroxysmal atrial fibrillation with fast ventricular rate followed by a pause which ultimately ended with atrial escape and long sinus pause of more than 3 seconds associated with syncope, all suggestive of SSS [Fig 2]. Patient was put on temporary pacemaker. Previous records of patient reveal normal ECG and normal echocardiogram. Serum lithium level [0.78 mmol/L] was within normal therapeutic range [0.5-1.2 mmol/L].

Based on drug history and investigations, the patient was diagnosed as a case of lithium-induced PAH and symptomatic SSS. Lithium was stopped and patient was monitored in CCU continuously. SSS disappeared gradually over the next 10 days (Fig 3) but PAH persisted as such at time of discharge. Pre-discharge Holter study revealed normal sinus rhythm without any prolonged pauses. He was started on Divalproex sodium 250 mg twice a day in place of lithium, aripiprazole 5 mg once a day, sertraline 150 mg OD and discharged after two weeks. At the end of six months of follow-up, repeat echocardiogram showed marked decrease in PAH with PASP decreasing significantly from 70 mmHg to 35 mmHg (Figure 4).

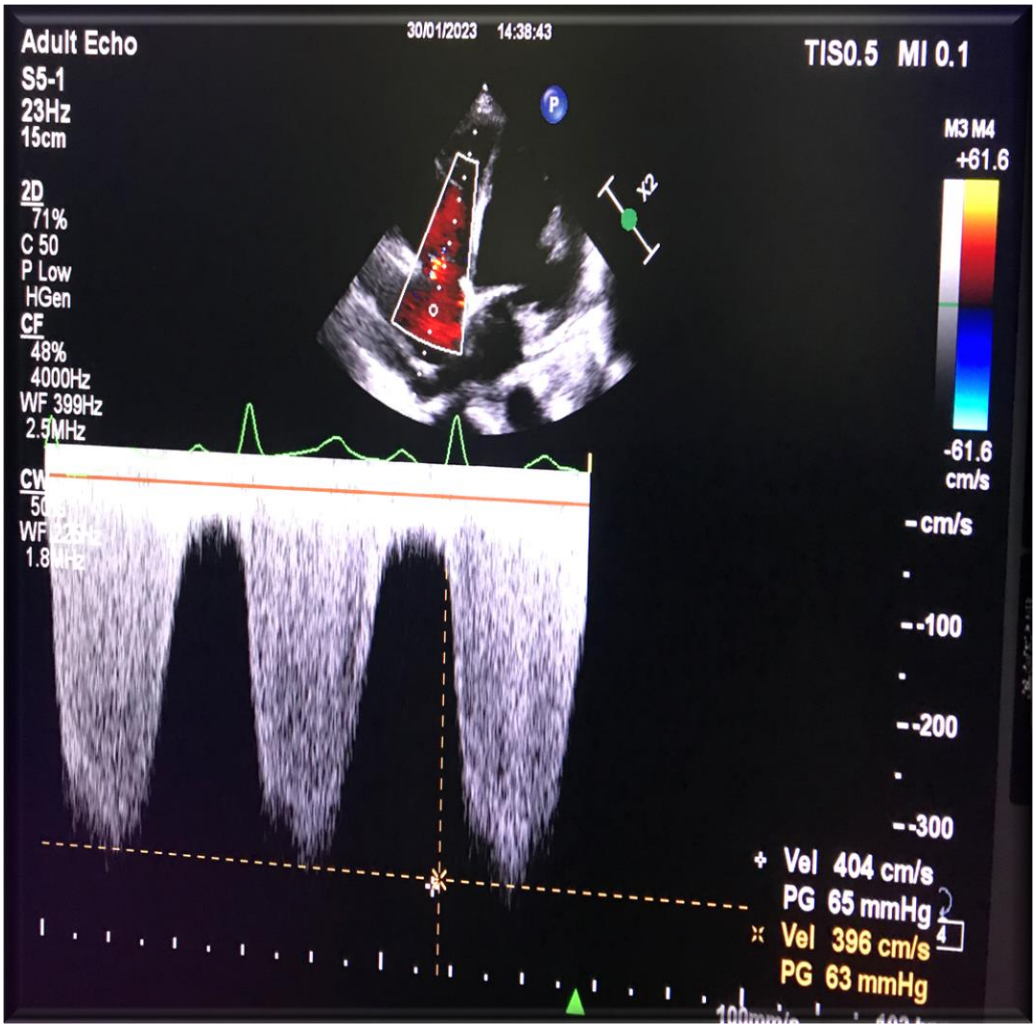

Figure 1: Two-dimensional echocardiography showed dilated RA and RV with severe tricuspid regurgitation with TR velocity 4.2 m/sec and moderate-severe PH with PSAP of 70 mmHg. PASP, pulmonary artery systolic pressure. RA, right atrium. RV, right ventricle. TR, tricuspid regurgitation.

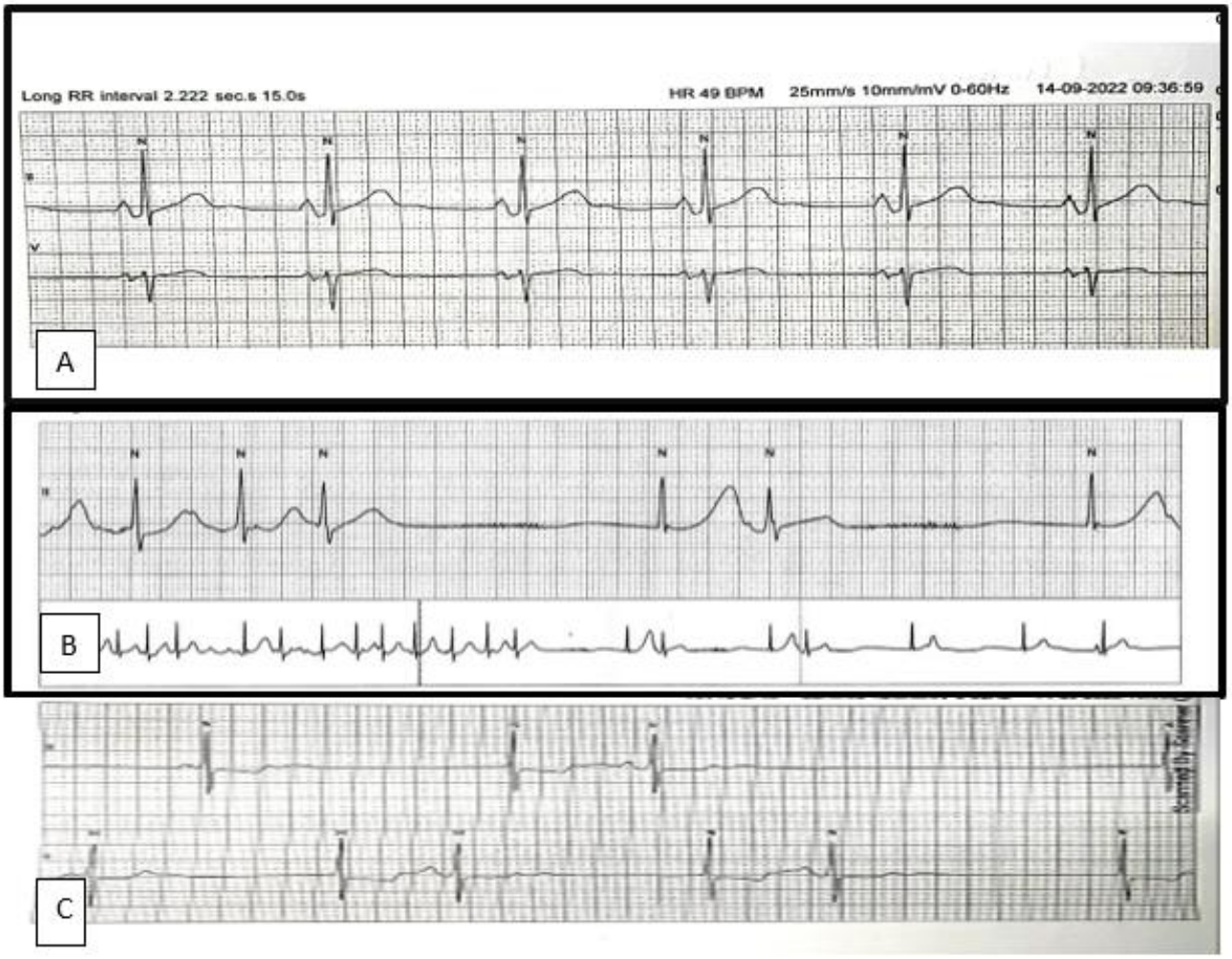

Figure 2: Showing multiple rhythm suggestive of sick sinus syndrome. A. Ectopic atrial rhythm from coronary sinus ostia, atrial escape rhythm and non-conducted p wave. B. Atrial fibrillation with fast ventricular rate followed by sinus pause of 2.2 sec and terminated by atrial escape rhythm, C. Long sinus pause of more than 3 seconds.

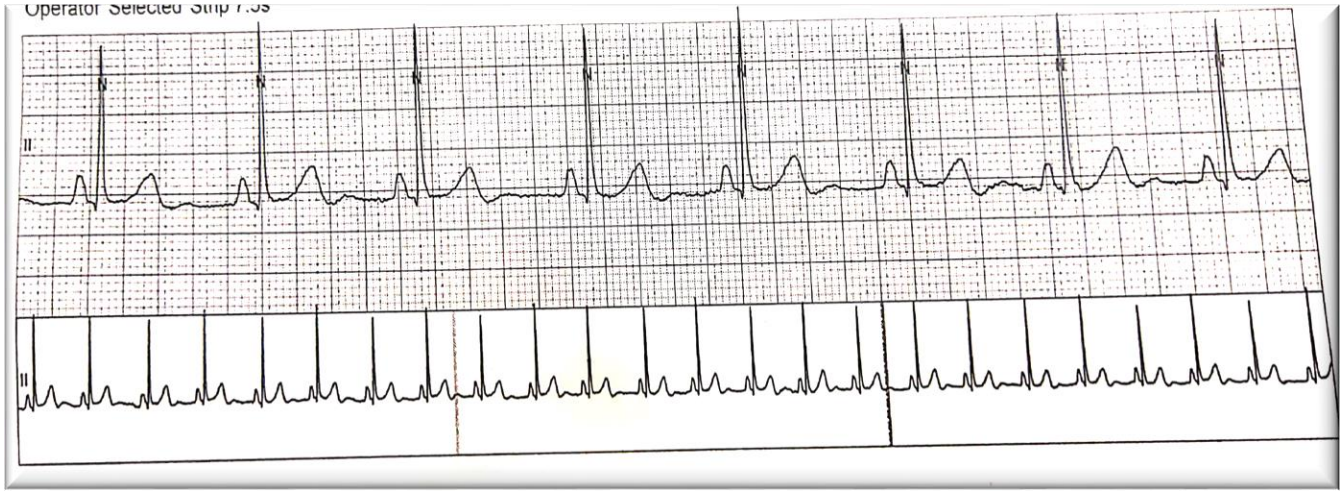

Figure 3: Twenty-four hour Holter monitoring strip showing return of sinus rhythm after 7 days of lithium cessation.

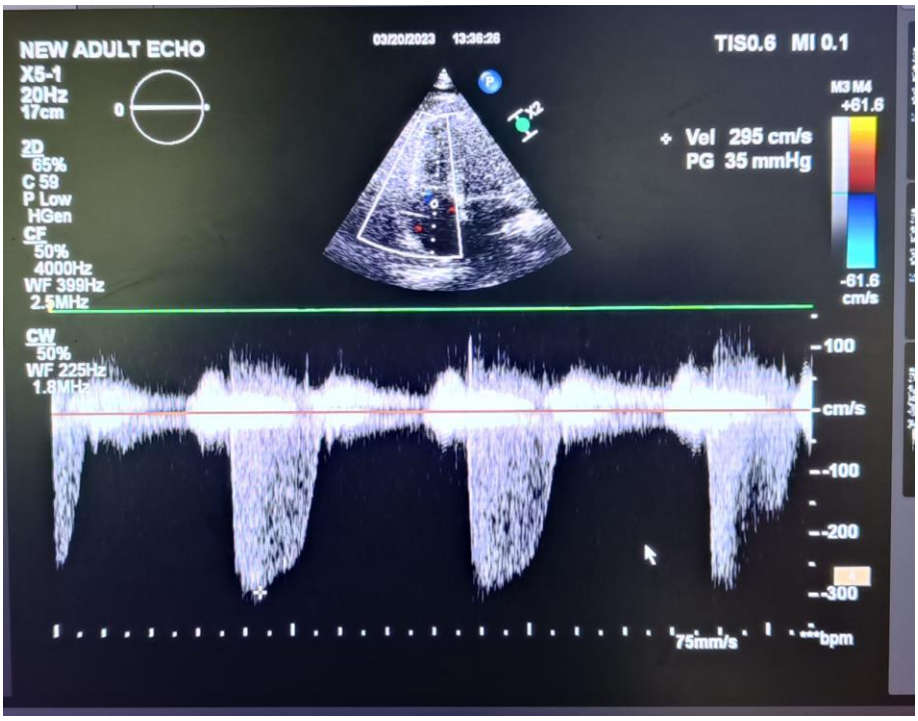

Figure 4: Repeat transthoracic echocardiogram showing marked decrease in PAP from 70mmhg to 35mmHg.

Discussion

BD is an episodic illness with a very heterogeneous clinical course. It often begins in late adolescence and young adulthood. It usually requires lifelong treatment including pharmacotherapy and psychosocial intervention. The estimated lifetime prevalence ranges from 0.6% to 2.4% worldwide [3]. Lithium is one of the most widely used drugs for maintenance therapy reflected by its status as the first line treatment in many international guidelines like Canadian Network for mood And Anxiety (CANMAT) [4] and German S3 guidelines [5]. They recommends lithium as a first line treatment option in bipolar depression but there are many undesirable side effects. It includes metabolic side effects (weight gain with diabetes, high blood pressure, hyperlipidaemia, insulin resistance), neurological problems (abnormal body movements, cognitive dulling, tremors, seizures, ataxia etc), renal dysfunction (interstitial nephritis), cardiac side effects and pulmonary fibrosis[6]. Among several cardiac side effects (atrial arrhythmia, ventricular arrhythmia, sudden cardiac death, myocarditis), PAH and SSS is infrequent but most serious. To the best of our knowledge, only one case report is available in world literature of lithium causing both PAH and SSS by Vohra et al [7]. In that case, patient had only mild-moderate PAH with no follow-up available. On the contrary, this is the first case report with follow-up of six months showing reversibility PAH from severe to mild. PAH is a progressive disease of lung vascular system, primarily affecting small arterioles. Vasoconstriction, vascular remodelling and thrombosis are the main pathophysiology behind the development of PAH [8]. PAH is defined as the mPAP > 20 mmHg at rest. Although the increased PAH can be asymptomatic, dyspnoea with exertion, fatigue, pre-syncope/syncope and features of right heart failure (fluid retention and lower extremity oedema, hepatomegaly, raised JVP) can be the presentation in advanced PAH. The vascular remodelling, mitogenic effect of serotonin and regulation of VEGF are the three main possible mechanisms for lithium causing PAH.

Asymptomatic ECG changes are the most common and include T wave changes (example- flattening, inversion, isoelectricity etc). Cardiac side effects of lithium can range from asymptomatic sinus bradycardia to lethal arrhythmias. Conduction system abnormalities include sinus node dysfunction (SND), AV block, RBBB and LAFB. SND ranging from benign to severe has been described usually at toxic serum levels, but can occur at therapeutic level also[9] in both paediatric and adult patients. Symptomatic SND and AV block may require sudden interruption of lithium and can lead to rebound of bipolar symptoms, hence this should be done under close medical supervision and psychiatrist guidance. Multiple mechanisms have been proposed for sinus node dysfunction. Voltage gated sodium channel is a major determinants of myocardial conduction velocity and sinus nodal pacemaker activity. Lithium causes concentration dependent block of this peak sodium current which is consistent with permeation in negative voltage gated Na+ channel via multi-ion mechanism[10], hence blockage of this ion channel is an important mechanism for SND and failure to impulse generation. Hypercalcemia, and hypothyroidism leading to decrease in depolarisation rate impulse propagation by lithium can cause various electrophysiological changes. In our patient, electrolyte and TSH level was within the normal range so other putative mechanisms described above can be the cause of SND. In clinical practice cardiac effects attributed to lithium toxicity occur in 20 to 30 percent of patients. Fluctuation in serum lithium levels; intrinsic parasympathetic and sympathetic tone, age-related interstitial fibrosis and decrease in sinus rate, variations in cardiac sodium channel expression, underlying pre-existing cardiac disease, and medications that affect renal function, such as nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACE-I), or receptor blockers (ARB) are the possible mechanisms for the development of SND. Haemodialysis may be required in patients who developed severe toxicity in the form of ventricular arrhythmia or encephalopathy.

In this case, chronic use of lithium resulted into development of symptomatic SSS and PAH. SND improvement is well documented in most of the cases but reversibility of pulmonary vascular changes after drug cessation is still debatable. Meanwhile in our case PAH also improved significantly over a period of time. This proves the relationship

between usage of lithium and sinus node dysfunction along with PAH and its reversibility.

Conclusion

Regular serum lithium level monitoring along with ECG and echocardiography should be done for early diagnosis of asymptomatic PAH and conduction system abnormalities in patients on chronic therapy. Timely diagnosis and necessary intervention can prevent lethal consequences of this rare side effects. Even advance PAH can be reversible and no need to start drugs to decrease PAH and instead close follow-up with echocardiogram is needed. Likewise, pacemaker implantation usually not needed for SND. Patient should be kept on alternative antipsychotic agent to prevent from rebound phenomenon.

Conflicts of interest:

The authors declare that there is no conflict of interest.

Consent: Written informed consent was obtained from the patient(s) for publication of this case report, including accompanying images.

References:

1. Young AH, Hammond JM., (2007).Lithium in mood disorders:increasing evidence base, declining use? Br J Psychiatry;191:474-476.
2. Meyer JM., (2011).Pharmacotherapy of Psychosis and Mania. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th edn. New York: McGraw-Hill Companies:445–447.
3. Grande I, Berk M., Birmaher B.,Vieta E.,(2016).Bipolar disorder. Lancet 387 (10027):1561–1572
4. Yatham LN., Kennedy SH., Parikh SV., Schaffer A., Bond DJ., Frey BN., et al. (2018) .Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)guidelines for the management of patients with bipolar disorder. Bipolar Disord 20 (2):97–170.
5. Bschor T., Baethge C., Grunze H., Lewitzka U., Scherk H., Severus E, Bauer M., (2020).S3 guideline on bipolar disorders - 1st update 2019: What's new in pharmacotherapy? [German S3 guidelines on bipolar disorders-first update 2019: What is new in pharmacotherapy?]. neurologist. Mar;91(3):216-221. German.
6. Volkmann C., Bschor T and Köhler S ., (2020). Lithium Treatment Over the Lifespan in Bipolar Disorders. Front. Psychiatry 11:377
7. Vohra S., Pradhan A., Sethi R., Bhandari M., (2021).sinus node dysfunction and pulmonary hypertension- "Double Trouble" with lithium therapy. International Journal of angiology, case report
8. Humbert M., Kovacs G., Marius M., Hoeper M., Badagliacca R., M.F. Berger r et al. (2022).ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2022) 00, 1–114
9. Shetty RK., Vivek G., Parida A., et al. (2013).Lithium induced sinus node dysfunction at therapeutic level. BMJ case report jan 22.
10. Darbar D., Yang T., Churchwell K., Wilde AA., Roden DM.(2005) Unmasking of brugada syndrome by lithium. Circulation;112:1527-1531.

DOI:10.31579/2693-2156/054