RESIDENT & FELLOW SECTION

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Clinical Reasoning: Heart to swallow

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SECTION 1

A 55-year-old woman was admitted to our intensive care department after intoxication with lithium. Her medical history was relevant for bipolar disorder for which she received medical treatment with lithium, haloperidol, and citalopram. In the week before admission, she had developed a clinical picture of gastroenteritis with diarrhea and vomiting, which resulted in dehydration and a marked deterioration in kidney function. During the last days before admission, she had become progressively lethargic and had developed dysarthria as well as postural tremors of the extremities. The tremors were coarse and irregular, most clearly present in the hands with a frequency of approximately 8 Hz. At admission, she opened her eyes spontaneously, localized pain, and showed normal verbal responses (E4M5V5). Physical examination showed severe dysarthria, ataxia, and no focal neurologic deficits. Reflexes were normal. Laboratory investigation revealed a de novo elevated creatinine level (220 μmol/L, normal 49–90) corresponding to an estimated glomerular filtration rate of 22 mL/min/1.73 m^2 (normal >60) and a lithium level that was 5.8 mmol/L (target value 0.6–0.8 mmol/L). ECG at admission was normal except for a prolonged QTc interval of 533 milliseconds (normal <450).

Questions for consideration:

1. What is the causal relationship between the observed symptoms and lithium and creatinine levels?
2. What is the treatment of this disorder?

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SECTION 2

Potential explanations for altered consciousness and tremors include intoxications (lithium, serotonergic, or antiepileptic drugs) and alcohol withdrawal. The tremor described here has the typical characteristics of a lithium tremor.[1] These symptoms, in combination with elevated lithium levels led to a diagnosis of severe lithium neurotoxicity due to hypovolemia-induced renal failure. Since the excretion of lithium is almost uniformly renal, acute lithium toxicity may be initiated by a loss of renal function. Patients with lithium intoxication often develop gastrointestinal symptoms, e.g., nausea and vomiting. If these symptoms are severe, dehydration and decreased renal function may develop. This impairs the ability to excrete lithium and exacerbates lithium toxicity. Therapeutic intervention should focus on rehydration and the removal of lithium from the body. Restoration of electrolyte and water balance by rehydration in hypovolemic patients with lithium toxicity is mandatory to maintain or restore kidney function and maximize lithium clearance. Removal of lithium should be achieved by discontinuation of the drug as well as extracorporeal removal by means of hemodialysis or continuous veno-venous hemofiltration (CVVH). Lithium is readily dialyzable since it is nonprotein bound and has a low molecular weight and a small volume of distribution. Usually one session of hemodialysis or 24 hours of CVVH is sufficient, although some experts advise to continue dialysis after normal (<1 mmol/L) levels of lithium have been achieved to prevent a rebound effect.[2]

In our patient, treatment was initiated with rehydration as well as CVVH and the patient was admitted to our intensive care unit (ICU). CVVH was continued for 24 hours, which resulted in a decrease of lithium levels toward therapeutic levels. However, severe lethargy as well as neurologic sequelae persisted for 14 days despite normalization of lithium levels.

Question for consideration:

1. Should a different diagnosis be considered in view of the persistence of neurologic symptoms?

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SECTION 3

Neurologic complications of lithium intoxication usually develop later in the clinical course because of the relatively slow absorption in the CNS. Furthermore, they may persist despite removal of lithium by hemodialysis of hemofiltration. This "syndrome of irreversible lithium effectuated neurotoxicity" (SILENT) is characterized by prolonged neurologic and neuropsychiatric sequelae, which may persist for months. Demyelination at multiple sites in the CNS has been suggested to be the cause and can sometimes be observed on MRIs as focal white matter abnormalities.[3,4] In our patient, in addition to her neurologic symptoms, episodic symptomatic bradycardias and atrioventricular (AV) blocks associated with hypotension were observed during her stay at the ICU. Upon careful analysis, we observed a close relationship of bradycardias with swallowing. The patient denied ever having symptomatic bradycardias or presyncopal complaints when swallowing before the current episode of lithium intoxication. A representative ECG after swallowing is shown in the figure; also see the video on the *Neurology*® Web site at Neurology.org (which was recorded relatively late in the clinical course). These bradycardias persisted during the first week of admission but eventually diminished and disappeared. After 2 weeks of admission, her neurologic symptoms slowly improved as well and she was discharged toward a psychiatric care facility for rehabilitation, reinstitution, and optimization of medical therapy for her bipolar disorder.

Questions for consideration:

1. What is the phenomenon observed in the figure and the video?
2. What is the presumed pathophysiology of this phenomenon and what is its relation to lithium intoxication?

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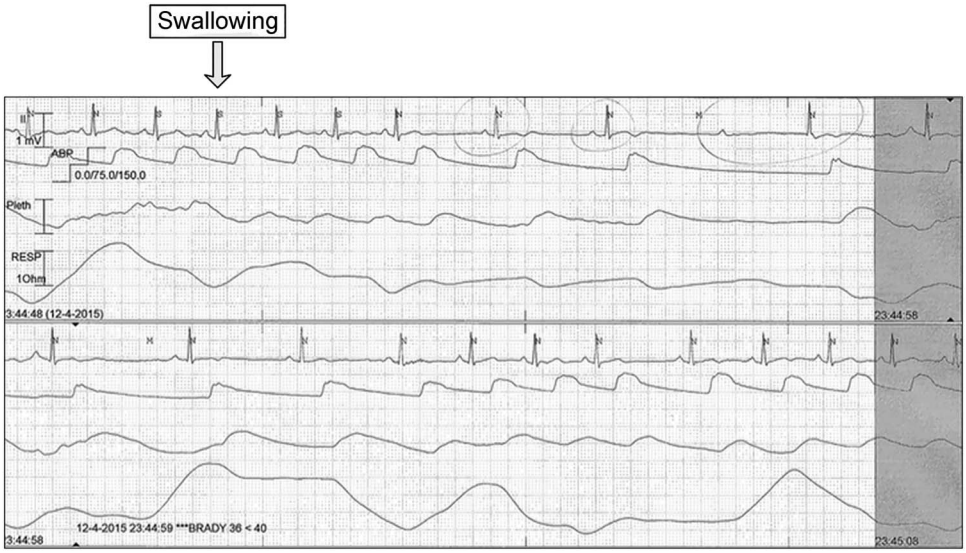
Figure **Bradycardia and atrioventricular block during swallowing**



A real-time ECG recording during swallowing is shown. Initial normal sinus rhythm changes after swallowing, and bradycardia as well as high-degree atrioventricular block are observed.

SECTION 4

Our patient had episodes of swallow-induced transient bradycardia. As bradycardia was not severe enough to cause loss of consciousness, these episodes do not fulfill the criteria for syncope. Nonetheless, episodes of swallow-induced bradycardia are characteristic for "swallow syncope," a rare syndrome that belongs to the reflex syncope syndromes.[5] The pathophysiology of swallow syncope is incompletely understood but likely involves a vagal reflex that is initiated by activation of the glossopharyngeal nerve during swallowing.[5–7] Efferent impulses lead to the sinoatrial node (right vagus nerve) or the AV node (left vagus nerve) and may lead to various types of paroxysmal bradycardias and reduction of cardiac output. The importance of vagal pathways in this reflex is stressed by studies in which pretreatment with atropine or other anticholinergic drugs is effective in preventing swallow-induced bradycardia. A recent review of all 80 published cases of swallow syncope showed that the majority of cases (62%) had underlying cardiac or gastrointestinal disease, although a substantial minority of patients did not have any underlying pathology.[5] Treatment of the syndrome may involve implantation of a permanent pacemaker. In patients in whom quality of life is severely affected by recurrent syncopal events, this treatment is usually effective.

DISCUSSION Herein, we report a case of a patient who had been chronically treated with lithium who developed severe neurologic as well as cardiac symptoms due to an intoxication of lithium, which was caused by prerenal kidney insufficiency-related reduced elimination of lithium. Lithium salts have been used for the treatment of psychosis and bipolar disorder since the 19th century. Although effective, it has a narrow therapeutic index. This is illustrated by the fact that a majority of patients chronically treated with lithium experience at least one episode of toxicity during their course of treatment.[8] Patients may be relatively asymptomatic despite very high serum concentrations, and severe clinical toxicity may develop despite lithium concentrations in the therapeutic range. Therefore, the diagnosis and treatment of this syndrome should rely on a combination of clinical symptoms as well as drug levels.

Despite rapid normalization of plasma lithium levels, neurologic symptoms persisted for several weeks, which is consistent with the SILENT syndrome as discussed above. Potential neurologic symptoms include lethargy and coma, ataxia, confusion or agitation, and neuromuscular excitability.[9]

In addition to neurologic symptoms, she developed cardiac toxicity: she presented with a markedly prolonged QTc time, which did not lead to rhythm disturbances initially and normalized rapidly after plasma lithium levels were corrected. Of note, however, during her stay at the ICU, she developed symptomatic sinus node bradycardias as well as AV blocks that were provoked by swallowing. Cardiac toxicity may cause changes in the ECG. Although arrhythmias are rare, prolonged QTc intervals and bradycardia have been reported.[10] Whereas swallow-induced bradycardia has been described previously, provocation of this syndrome by lithium toxicity has not. Lithium exerts its actions through the alteration of sodium transport in neurons, which increases intraneuronal metabolism and reduces stores of catecholamines. In the heart, lithium is a potent blocker of cardiac sodium channels. This lithium-related blockade of sodium channels can unmask conduction abnormalities in the heart such as conduction delays as well as Brugada syndrome although other mechanisms of lithium-associated bradycardias have been described as well.[11] Plans were made to perform extensive autonomic nervous system tests in our patient to evaluate the effects of vagal maneuvers on her symptoms and heart, but unfortunately these were hampered by her persistent neurologic and psychiatric symptoms. By the time her neuropsychiatric status improved, her episodes of swallow syncope had resolved completely. Finally, we aimed to exclude whether genetic defects in ion channels contributed to the observed clinical phenomena. Recent molecular insights have defined a molecular basis for sinoatrial and AV node dysfunctions and several mutations in the genes encoding for cardiac sodium channels have been described that contribute to these dysfunctions.[12] To analyze whether such mutations may have had a role in our patient's symptoms, we performed genetic testing of our patient and tested for mutations in 48 genes (next-generation sequencing arrhythmia panel, http://amsterdamgenomedx.com) that are associated with arrhythmias but were unable to find genetic polymorphisms that predispose to arrhythmias in this specific case. We postulate that lithium provoked episodes of swallow-induced bradycardia in our patient due to the combined effects of swallowing-induced vagal efferent activity and an increased susceptibility to bradycardia caused by lithium.

AUTHOR CONTRIBUTIONS

Dr. van Westerloo: concept and design of the report, data accrual, wrote the manuscript. Dr. Barge-Schaapveld: analysis of genetics, critical revision of the manuscript for important intellectual content. Dr. Bikker: performed DNA analysis, critical revision of the manuscript for important intellectual content. Dr. van Noorden: critical revision of the manuscript for important intellectual content. Dr. Tannemaat: concept and design of the report, data accrual, cowrote the manuscript.

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DISCLOSURE

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