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Severe chronic lithium intoxication in patient treated for bipolar disorder

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Abstract

OBJECTIVE: Lithium has been long used in psychiatry as an adjuvant treatment for bipolar disorder. Chronic lithium intoxication is very rare.
DESIGN: We present the case of a 72-year-old female, treated with lithium for more than 10 years for bipolar disorder, who was admitted for gait impairment with weakness of limbs, myoclonus, speech impairment and memory disturbances.
RESULTS: Diagnosis of lithium intoxication was based on clinical picture and determination of serum lithium levels. EEG showed severe encephalopathy with triphasic wave complexes. Sensory and motor axonal neuropathy was observed by EMG. Discontinuation of the drug leads to clinical improvement, although not to a fully neurological recovery.
CONCLUSION: Lithium is still very effective drug, but requires regular monitoring of serum levels to prevent overdose and symptoms of intoxication. Neurophysiological methods, including EEG and EMG, are strongly recommended to determine the level of peripheral and/or central nervous system impairment.

CASE REPORT

INTRODUCTION

Lithium is used in psychiatry as adjuvant treatment for many diseases, such as bipolar disorder (Malhi *et al.* 2016). It has very good antipsychotic and antidepressant effects. It relieves manic phase, but also decreases the frequency and depth of depression (Girardi *et al.* 2016). It has antisuicidal effects. As an adjuvant treatment, it enhances the efficacy of antipsychotic drugs, alleviates affective symptoms, impulsivity and violent behavior (Augustin 2005). It has many excellent effects, but certain requirements have to be met during the treatment. One of them is regular monitoring of serum levels to prevent overdose and symptoms of intoxication.

Symptoms of intoxication may be manifested already at serum lithium levels below 1.5 mmol/L and may include nausea, vomiting, diarrhea, polyuria, polydipsia, tremor, weight gain, leukocytosis, thrombocytosis, hypercalcemia, and hyperkalemia (Chen *et al.* 2004). Serum lithium levels from 1.5 to 2 mmol/L are associated with worsening of gastrointestinal symptoms (Freeman *et al.* 2006), as well as and neurological ones may occur (drowsiness, tremor, muscle hypertonia, slurred speech). Serum

lithium levels higher than 2 mmol/L are life-threatening; patients may experience cardiotoxicity (Hsu *et al.* 2005) (arrhythmia, AV block, bradycardia, myocarditis), difficulty swallowing, cerebellar signs, myoclonus, seizures, coma and death (Chan *et al.* 2012). Long-term use can cause thyroid dysfunction (hypothyroidism), and renal function impairment (renal tubular necrosis) (Gitlin 1999).

In our study, we report severe lithium poisoning in a 72-year-old woman, who received long-term treatment for bipolar disorder. Unfortunately, lithium levels were not checked on a regular basis. When the patient developed tremor and myoclonus, which were already the first signs of lithium overdose, she was referred to outpatient neurologist, where she was followed-up for half a year with an incorrect diagnosis of incipient Parkinson's disease. The patient's condition deteriorated and eventually the patient was acutely admitted to hospital.

CASE REPORT

A 72-year-old female treated with lithium (lithium carbonate 900 mg daily) for more than 10 years due to bipolar disorder, was admitted to the neurological department for gait impairment lasting for two days, with muscle weakness, myoclonus, impaired speech and in particular short-term memory disorders. She tried to commit suicide repeatedly in the past. Last year, she developed myoclonus and tremor, for which she was evaluated by an outpatient neurologist several times; the condition was interpreted as extrapyramidal disorder and the patient was started on biperiden 2 mg daily. The patient had a history of surgery for uterine adenocarcinoma one year ago; She was treated for hypertension (beta-blockers: bisoprolol 5 mg daily, ACE-inhibitors: perindopril 4 mg daily). She was further treated with quetiapine (400 mg daily) due to psychiatric indications. She has been followed-up for rheumatoid arthritis and previously treated with biological treatment, and autoimmune thyroiditis, atypical form of lymphocytic thyroiditis. The patient was asked about gastrointestinal difficulties before the current disease. She mentioned diarrhea and abdominal pain two months before the hospitalization. She did not see a doctor for these problems.

Neurological examination revealed remarkable generalized muscle myoclonus in upper and lower extremities and mild memory impairment. Severe tremor was present in the upper extremities with mild ataxia; tendon reflexes were symmetrical and normally elic-

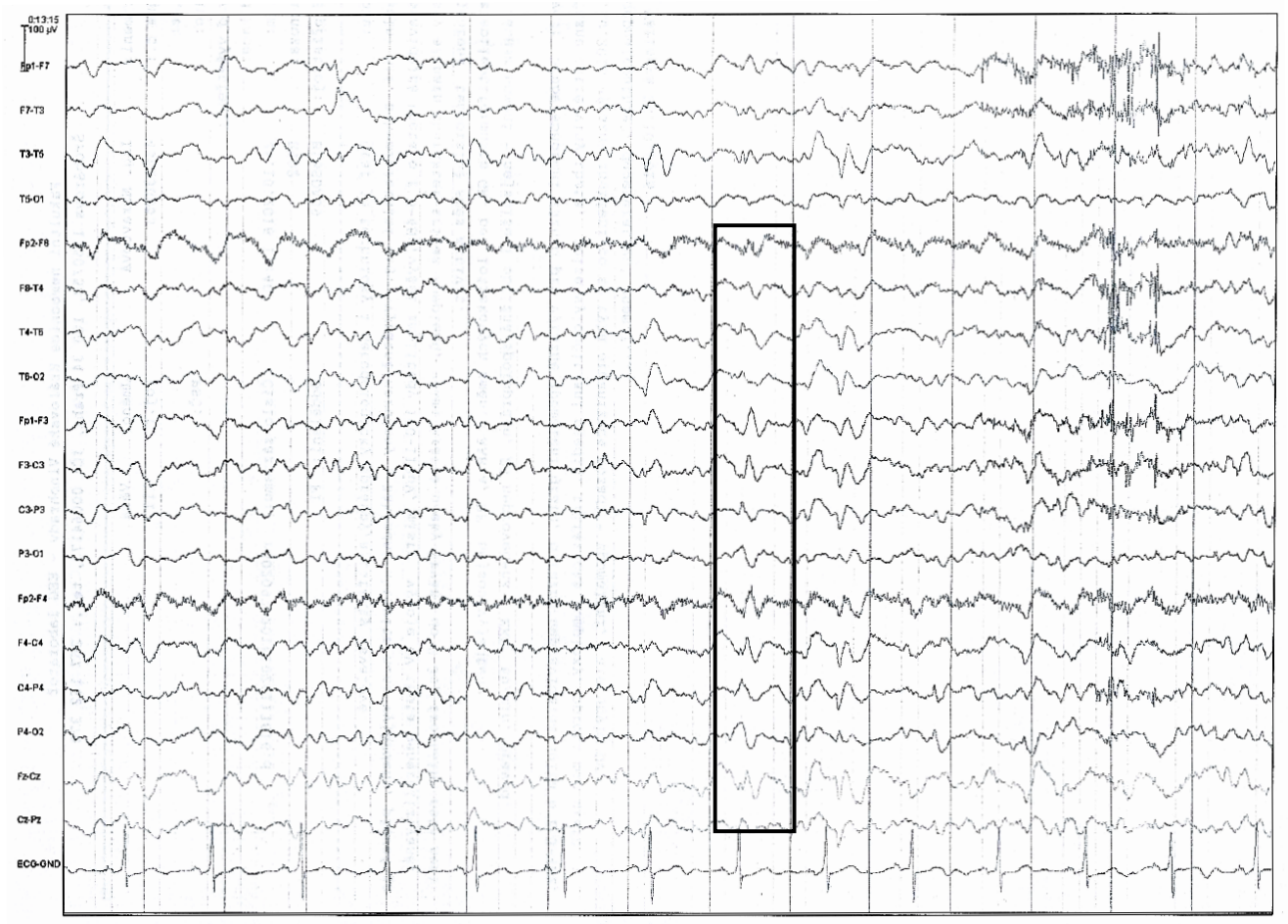

Fig. 1. EEG with diffusely irregular delta frequency of 3-4 Hz and presence of theta triphasic isolated complexes.

itable, spastic pyramidal signs were negative with generalized muscle weakness. During the hospitalization, the patient developed bulbar symptoms with dysarthria and dysphagia, and worsening of cerebellar symptoms. Within a few days, the clinical picture (myoclonus, dysphagia) progressed into somnolence with the need for intubation and mechanical ventilation; the patient was transferred to the resuscitation unit.

Numerous laboratory tests were performed. Baseline levels were determined for urea 11.8 mmol/L (reference range 2–6.7), creatinine 159 μmol/L (reference range 46–90), and beta2-microglobulin 5540 μg/L (reference range 800 to 2200); over the next 3 days, renal values decreased: urea 5.4 mmol/L, and creatinine 100 μmol/L. Lithium level was 2.7 mmol/L on day 3 of hospitalization, 1.0 mmol/L on day 10, and below 0.5 mmol/L on day 12 of hospitalization. Only mild inflammatory changes were seen in cerebrospinal fluid samples. Paraneoplastic antibodies against SOX1 and PNAM2 were found in the serum, which often occur in relation to small cell lung cancer. EEG revealed abnormal pattern with diffusely irregular delta frequency of 3–4 Hz, presence of occasional sharp waves and theta triphasic isolated complexes (Figure 1). CT scan of the chest and abdomen revealed a focal lesion in the right mediastinum, suspected tumor or enlarged lymph nodes. MRI scan of the brain revealed no clear pathology, only findings of minor diffuse atrophy and a few nonspecific lesions in both hemispheres. EMG examination showed low amplitude of motor responses (CMAP) in the lower and upper extremities; the histogram provided a higher percentage of myogenic units in the right tibialis anterior muscle. No myoclonic jerks were found in the vasus lateralis muscle, MUPs were normal in size and shape.

Initially, autoimmune encephalitis was considered due to myoclonus, memory impairment, abnormal EEG findings with signs of severe encephalopathy (marked reduction of basic activities), the presence of paraneoplastic antibodies in the cerebrospinal fluid and suspected tumor findings in the mediastinum. The corticosteroid and antiepileptic treatment (valproate) had a modest effect but the patient continued progressing into somnolence with the need for mechanical ventilation. Diagnosis of lithium toxicity (chronic intoxication) was determined based on extremely high serum lithium levels, progressive neurological clinical picture and EEG findings.

The patient was on mechanical ventilation for one week. Improvement of the clinical condition was observed more pronounced after extubation. One month after the lithium intoxication, she was still significantly weak, but had no dysarthria and myoclonus, was capable of standing by the bed and making few steps with the help of two persons.

The patient was referred for long-term rehabilitation. Three months after the intoxication, she was able to walk 40–50 m alone with a cane. Her condition significantly improved. She remains under supervision for bipolar disorder, for which she is currently taking quetiapine and valproate. Mild sensitive-motor neuropathy, mild cognitive impairment and signs of ataxic gait remain as residual symptoms following lithium intoxication.

DISCUSSION

Lithium is one of the effective drugs in psychiatry used to treat bipolar disorder. At present, it is used less because of a narrow therapeutic range, requiring regular monitoring of serum lithium levels (Girardi *et al.* 2016, Malhi *et al.* 2016). Lithium is used as an adjuvant in the treatment of bipolar disorder to control the manic phase. It can be added to other drugs, for example, for treatment of schizophrenia or depression.

Serum lithium levels should be from 0.4 to 0.8 mmol/L and should not exceed 1.5 mmol/L (El Bakhi *et al.*2009). In addition to regular monitoring of lithium levels, it is also necessary to check renal, heart and thyroid function. Special caution is required when taken concomitantly with some antipsychotic agents (haloperidol, chlorpromazine, clozapine), which can lead to malignant neuroleptic syndrome (Miodownik *et al.* 2008). Derivatives and triptans and serotonergic antidepressants (SSRIs, such as fluvoxamine, fluoxetine) may lead to serotonin syndrome. Lithium levels also increase the levels of calcium channel blockers or carbamazepine.

Lithium intoxication (Chen *et al.* 2004, Freeman *et al.* 2006) includes a) gastrointestinal symptoms (nausea, vomiting, diarrhea), b) neurological symptoms (drowsiness, muscle weakness, blurred vision, dysarthria, myoclonus, nystagmus, cerebellar signs, signs of encephalopathy, extrapyramidal disorder, seizures, coma), c) cardiac symptoms, such as ECG changes (flat or inverted T wave, QT prolongation), AV block, and d) overall symptoms – dehydration, electrolyte disturbances.

The diagnosis of lithium intoxication is based on the clinical picture and on the determination of serum lithium levels. If the blood lithium level is above 2–3 mmol/liter, it may cause renal insufficiency, confusion, seizures, coma and death.

The diagnosis of lithium poisoning (intoxication) in our patient was based on a relatively typical clinical picture (myoclonus, tremor, muscle weakness, dysarthria, cerebellar syndrome, somnolence), repeated high serum lithium levels with gradual reduction (lithium level was extreme on day 3 of hospitalization, with 2.7 nmol/L), and mild renal insufficiency at baseline. EMG findings demonstrated a mild, predominantly axonal sensory motor neuropathy, which may occur in chronic lithium poisoning (Vanhooren *et al.* 1990, Farawelli *et al.* 1999). No neuromuscular transmission disorder was detected. EEG revealed isolated triphasic wave complexes, occurring in severe metabolic encephalopathies

or in Creutzfeldt-Jakob disease (Ikeda *et al.* 2003). They are a sign of a marked deterioration of brain functions. Confusion and epileptic seizures have been described in literature in lithium intoxication (Shibasaki *et al.* 2003). Lithium can induce confusion by direct toxic action, non-convulsive status epilepticus, or when used concomitantly with neuroleptics or antidepressants, it may lead to a malignant neuroleptic syndrome or serotonin syndrome (Gansauer *et al.* 2003*)*. EEG is a suitable method that can help differentiate these conditions (Kaplan *et al.* 2006).

No specific antidote is available for treatment of lithium poisoning. If the patient develops signs of lithium overdose, the drug should be discontinued and the level of lithium should be checked. In severe intoxication, the patient should be placed on ICU to monitor basic vital signs, correct body fluid balance, or initiate hemodialysis treatment in the presence of renal failure (Decker *et al.* 2015). Hemodialysis must be continued until the serum lithium level is not detectable. Serum lithium levels should be monitored for additional one week, because its levels can increase due to delayed diffusion from tissues. A small number of patients may develop an irreversible damage to the nervous system (SILENT, a syndrome of irreversible lithium-effectuated neurotoxicity), which is characterized by cognitive deficits, sensory and motor neuropathy and damage to the cerebellum (Chan *et al.* 2012, Vahhooren *et al.* 1990). These symptoms also remained in our patient. It has been published that cognitive problems have improved after discontinuation of lithium therapy (Soriano-Barcelo *et al.* 2015).

Lithium treatment in psychiatry is still important, but requires long-term monitoring of serum levels and careful monitoring of clinical symptoms of overdose (gastrointestinal disorders, neurological symptoms). Checks of serum lithium levels and determination of renal and thyroid functions are required at least on a 6-month basis; or earlier when increasing the doses of lithium. We also recommend neurophysiological methods, including EEG and EMG, which can help to determine the level of peripheral and/or central nervous system impairment.

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