CASO CLÍNICO/CASE REPORT

Levodopa for Syndrome of Irreversible Lithium-Effectuated Neurotoxicity: a SILENT Recovery

Levodopa para Síndrome de Neurotoxicidade Irreversível Causada por Lítio: Uma Recuperação Silenciosa

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Abstract

Treatment of bipolar disorder with lithium requires drug level monitoring to avoid toxicity. Syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) represents neurological adverse effects persisting two months after drug cessation.

Fifty four year-old woman with bipolar disorder on lithium presented with subacute alternating prostration and agitation, and a generalized seizure. Toxic lithium levels were detected; she gradually recovered after dialysis. Three weeks afterwards, emotional lability, generalized rest tremor, rigidity and seizures ultimately led to a catatonic status. Infectious, inflammatory and metabolic causes were ruled out; a diagnosis of SILENT was presumed. Following several unsuccessful treatments, levodopa 300 mg daily produced dramatic clinical recovery.

SILENT most commonly presents with cerebellar dysfunction. We describe a patient with acute on chronic lithium intoxication, improved after dialysis, followed by subacute, severe and refractory neuropsychiatric deterioration compatible with SILENT. The surprising improvement with levodopa represents the first therapeutical trial reported for a condition previously considered irreversible.

Resumo

O tratamento com lítio da perturbação afectiva bipolar (PAB) implica monitorização sérica dos níveis para evitar toxicidade. Na síndrome de neurotoxicidade irreversível causada por lítio (SILENT), os efeitos adversos neurológicos persistem dois meses após interrupção do fármaco.

Uma mulher, 54 anos, com PAB sob lítio, apresentou-se com prostração subaguda alternada com agitação e crise. Foram detectados níveis tóxicos de lítio; a doente recuperou após diálise. Três semanas depois, instalou-se labilidade emocional, tremor de repouso, rigidez e crises, culminando num estado catatónico. Foram excluídas causas infeciosas, inflamatórias e metabólicas; assumido o diagnóstico de SILENT. Após vários insucessos terapêuticos, a levodopa 300 mg/dia levou a recuperação clínica franca.

A SILENT manifesta-se mais frequentemente com disfunção cerebelosa. Descrevemos intoxicação aguda em crónica por lítio, melhorada após diálise, seguida de deterioração neuropsiquiátrica grave e refractária, compatível com SILENT. A surpreendente melhoria com levodopa constitui o primeiro tratamento relatado para uma patologia previamente considerada irreversível.

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Introduction

Lithium is the gold standard treatment for acute mania and flare prevention in bipolar disorder. Its narrow therapeutic margin requires drug level monitoring to avoid intoxication. Neurological adverse effects can occur in acute, chronic or acute on chronic intoxication, ranging from mild tremor to seizures, stupor and coma. The rare syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) represents irreversible neurological injury induced by lithium intoxication persisting for at least two months after drug cessation, most commonly presenting with cerebellar dysfunction.[1,2]

Case Report

We present a 54-year-old woman with type I bipolar disorder, mild mental retardation, type II diabetes mellitus and hypertension. She had been treated for nine months with lithium 600 mg daily.

She was admitted to the emergency department with a tonic-clonic seizure. Family members reported periods of prostration and slurred speech alternating with psychomotor agitation in the last two weeks. Erratic/excessive medication intake could not be ruled out. At admission, she was poorly responsive, dehydrated, hypotensive and hypoglycaemic. Laboratory results revealed toxic plasmatic lithium levels (3.8 mmol/L, normal range 1.0-1.2), acute kidney injury, metabolic acidosis and elevated lactates, with normal electrolytes and liver panel. Brain computed tomography and electroencephalogram (EEG) were unremarkable. Two sessions of sustained low-efficiency dialysis cleared serum lithium levels, and gradual clinical recovery ensued. Three weeks afterwards, neurological examination was relevant for poor memory retention, dysarthria, limb spasticity, mild postural tremor and broad-based gait.

On the 24th day of hospitalization, the patient developed emotional lability with outbursts of laughter and crying, hallucinations, coarse postural and rest limb tremor, limb and axial rigidity and generalized seizures. Of note, no parkinsonian features had been previously identified on examination. Deterioration progressed to a catatonic status with generalized dystonia, fixed gaze and mutism alternating with incoherent speech.

An extensive workup ruled out infectious, inflammatory, and metabolic disturbances. Notably, immune-mediated encephalitis antibody panel was negative. EEG showed right frontal focal paroxysmal activity; body and brain FDG-PET revealed increased uptake right frontal and left parietal regions. A frontal lobe brain biopsy was performed; histopathology was negative for inflammatory activity or alpha-synuclein, TDP-43, tau or Abeta-mediated pathology.

Despite sparse evidence for an immune-mediated encephalitis, a three-day trial of intravenous methylprednisolone 1 g/day followed by five-day course of intravenous immunoglobulin 0.4 g/kg/day was carried out, but no clinical benefit was noticed. A sustained catatonic status persisted for more than 30 days; treatment with neuroleptics, benzodiazepines, baclofen, valproate and phenytoin was unsuccessful.

On the 70th day, levodopa/carbidopa (100/25 mg tid) was started because of favourable results reported in immune-mediated encephalitis. A slow but dramatic clinical improvement occurred over the next days; one month later, sitting and feeding were possible under supervision. The patient presented a predominantly euthymic mood, improved memory retention and evocation, mild spasticity and postural tremor. Follow-up brain 1H magnetic resonance imaging (MRI) spectroscopy (**Fig. 1**) showed myo-inositol peak reduction in bilateral parieto-occipital regions and pallidal high T1-weighed signal. The patient was admitted to a rehabilitation center; four months after starting levodopa, she was able to walk unaided; a mild ataxic gait persisted. Levodopa treatment was continued for the following years, given the striking initial and persistent clinical response. At the four-year follow-up, she is stable on levodopa/carbidopa 100/25 mg tid and valproate 500 mg bid, and independent in her daily activities (Supplementary Video).

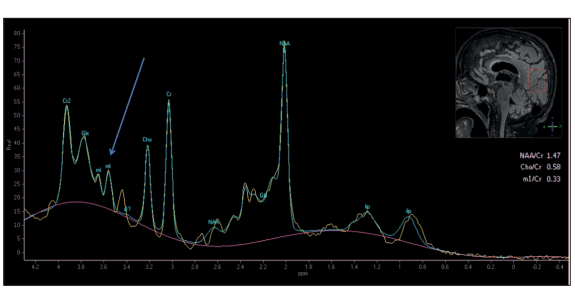

Figure 1. Magnetic resonance spectroscopy with the voxel placed on bilateral paramedian parieto-occipital regions showing a reduction of the myo-inositol peak at 3.5 ppm (arrow).

Discussion

Cerebellar dysfunction is the most frequently reported presentation of SILENT, although cognitive, extrapyramidal and brainstem symptoms have also been described.[2] Several biological explanations for lithium toxicity have been postulated[3]: competition with sodium and potassium channels, interfering in neurotransmitter

activity; upregulation of serotonin and acetylcholine and downregulation of dopamine transmission mediating neurotoxicity; changes in glutamate, inositol monophosphate, and glycogen synthase kinase 3 transduction pathways.[4] White matter lithium accumulation might explain long-term neurological adverse effects despite drug cessation. In a study including 78 patients, chronic lithium therapy increased the risk of neurologic adverse effects after an acute raise in serum lithium concentrations, even with normal plasmatic levels; advanced age, concomitant drugs and neurological illness represented risk factors for neurotoxicity.[5]

Our patient presented an acute on chronic lithium intoxication with marked improvement following clearance of toxic lithium levels. The patient subsequently developed a severe subacute neuropsychiatric picture that culminated in a catatonic status refractory to trials with immunotherapy, neuroleptics and antiepileptics. The diagnosis of SILENT was presumed; clinical features, normal blood lithium levels and presence of well-known risk factors (mild mental retardation, chronic anti-diabetic and anti-hypertensive medication, and rapid correction of lithemia) support our hypothesis.[2,3] A prior undiagnosed movement disorder such as Parkinson's disease is deemed unlikely given the absence of parkinsonian findings in earlier neurological examinations. One possible explanation for our patient's severe presentation was mainly driven either by disruption of dopamine dependent signaling in the frontostriatal functional circuit or by dopamine depletion.[6]

Surprisingly, a dramatic clinical improvement was witnessed after a levodopa trial. A spontaneous recovery with temporal coincidence to levodopa initiation cannot be ruled out.

To the best of our knowledge, this is the first case of a successful treatment approach to SILENT, a condition previously considered irreversible with no fruitful therapeutical trials described in the literature.[7] This case should raise awareness to the potential clinical benefit of levodopa in patients with SILENT presenting with frontal lobe dysfunction. ■

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