## CLINICAL NOTE: Lithium: An old treatment for a new indication

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## ABSTRACT

Subacute necrotising encephalopathy or Leigh syndrome is a congenital neuro-metabolic disease that is part of a group of diseases called mitochondrial encephalopathies. The form inherited is variable and it has a multisystemic effect, although with a predominance of lesions in the central nervous system. Prognosis is poor and there is no specific treatment for it. In 2007, we published the case of a 23-year-old patient, with severe psychomotor agitation crises, who responded favourably to lithium[1] after the failure of several previous treatments. Here, we describe the follow-up of this patient during the 5 years after discharge from hospital, until her death at 29 years of age. Her improvement was maintained, she was not hospitalised again and the patient's level of autonomy increased. The possible relationship of this improvement to new data on the neuroprotective and neurotropic effects of lithium are discussed.

**Key words.** Leigh syndrome, aggressive behaviour, lithium, mechanism of action.

*Actas Esp Psiquiatr 2021;49(3):125-27 | ISSN: 1578-2735*

## NOTA CLÍNICA: LITIO: UN TRATAMIENTO ANTIGUO PARA UNA NUEVA INDICACIÓN

### RESUMEN

La encefalopatía necrotizante subaguda o síndrome de Leigh es una enfermedad neuro-metabólica congénita que forma parte de un grupo de enfermedades llamadas encefalopatías mitocondriales. Presenta una forma de herencia variable y se produce una afectación multisistémica, aunque con predominio de lesiones en el sistema nervioso central. El pronóstico es malo y no existe un tratamiento específico. En el año 2007, publicamos el caso de una paciente de 23 años de edad con graves crisis de agitación psicomotriz, que tras el fracaso de varios tratamientos previos respondió favorablemente al litio[1]. Ahora describimos el seguimiento de esta paciente durante los 5 años posteriores tras el alta hospitalaria, hasta su fallecimiento a los 29 años. La mejoría se mantuvo, no volvió a ser hospitalizada y el nivel de autonomía de la paciente aumentó. Se discuten las posibles relaciones de esta mejoría con los nuevos datos sobre el efecto neuroprotector y neuroregenerador del litio.

**Palabras clave.** Síndrome de Leigh, conducta agresiva, litio, mecanismo de acción.

## INTRODUCTION

Subacute necrotising encephalopathy or Leigh syndrome is a congenital neurometabolic disease that is part of a group of diseases called mitochondrial encephalopathies[2]. It is a genetically heterogeneous syndrome, with more than 75 genes responsible being known[2]. The most frequent mutations occur in nuclear DNA (75%) with autosomal recessive transmission. In other cases, mutations appear in the mitochondrial DNA with maternal transmission. In Leigh syndrome, the genetic mutation affects the enzyme complexes involved in oxidative phosphorylation and the synthesis of adenosine triphosphate: specifically, the pyruvate dehydrogenase complex and/or the mitochondrial respiratory chain complexes, with the complexes I and IV being affected[3] more frequently.

Clinical symptoms and the course of the disease vary. Onset usually occurs in the first year of life, but in some cases can occur during adolescence, or even early adulthood. In the different cells of the same individual, mitochondria can coexist with non-mutated and mutated DNA, so that when the percentage of mutant DNA is lower, the onset is later and the phenotype is milder. The prognosis is poor and the affectation progressive until serious psychomotor deterioration is reached. The usual life expectancy is no more than 2 years.

The affectation is multisystemic, although lesions of the central nervous system predominate, mainly in the basal ganglia and brainstem. In classic forms, there is a delay in psychomotor development, hypotonia, seizures, respiratory distress, ataxia, peripheral neuropathy and optic atrophy. The later-onset forms are more heterogeneous with regression of acquired psychomotor skills, behavioural disturbances and psychiatric symptoms. The aetiological diagnosis is based on biochemical analysis of tissue samples, usually muscle,

in search of the underlying enzyme defect. Brain magnetic resonance imaging shows bilateral and symmetrical T2 signal increases in typically affected areas[2]. There is no specific treatment for this disease and only palliative measures can be taken. Thus, this description of the clinical improvement obtained with lithium treatment in a patient with this diagnosis is of great interest.

## CLINICAL CASE

A 23-year-old woman diagnosed with Leigh syndrome at age 4 had the classic symptoms of the disease, with serious psychomotor impairment. Her brain CT scan showed bilateral hyperdensity of the basal nuclei and cerebellar atrophy. At the end of adolescence, she began to display behavioural disturbances and over a period of 5 years, from 18 to 23 years of age, was admitted to a short-stay psychiatric unit 17 times. The reason for her hospitalisations throughout this period was a psychomotor agitation crisis with serious self-harm and heteroaggressions of increasing intensity. During hospitalisation, no other psychiatric symptoms were observed and acute organic processes were ruled out by the internal medicine service. She was initially treated with benzodiazepines (clonazepam and diazepam) at increasing doses. Later, as the severity increased, she took antipsychotics: haloperidol (10 mg), perphenazine (24 mg) and olanzapine (20 mg) that were not well tolerated due to their extrapyramidal side effects. She also took carbamazepine (1200 mg) with an incomplete response. Finally, a treatment with lithium was established, due to the efficacy described in self and hetero-aggressive behaviours in patients with different diagnoses[4]. Unlike previous treatments, the response, at a moderate dose (lithaemia: 0.4 mEq/L), was complete and early, and the patient was able to be discharged. Details of the case were published in Biological Psychiatry in 2007[1].

Clinical evolution was followed during the subsequent 5 years. She returned to the institution where she lived, with the previous psychosocial approach, receiving lithium (0.6 mEq/L) as pharmacological treatment to prevent aggressive behaviour and lorazepam (2 mg) for insomnia. At 29 years of age, the patient died following respiratory complications of her illness. During the 5 years of follow-up, she did not need to be hospitalised again for a psychomotor agitation crisis. In addition to her physical limitations (ataxia, muscle weakness, loss of vision), the patient had an intellectual deficit and limited social interaction. For all these reasons, her autonomy was limited and she needed help with activities of daily living. The staff at the institution where she lived described a progressive improvement in her degree of autonomy throughout the follow-up time. In fact, it was possible to relocate her to a less dependent patient unit until the moment of her death.

## DISCUSSION

The utility of lithium for self and hetero-aggressive behaviour in patients with various medical and psychiatric diagnoses has been documented for a long time[4,5]. We began treatment with lithium in the case described with this relatively broad indication. However, today it is known that lithium can exert a neurotropic and neuroprotective effect[6,7,8]. These effects of lithium have been proposed to be associated with the inhibition of two main enzymes, inositol monophosphatase and glycogen synthase kinase 3 (GSK-3). The molecular mechanisms involved in the action of GSK-3 have been the most studied, but have not yet been fully elucidated. Inhibition of GSK-3 by lithium protects the neuron from oxidative stress, excitotoxicity, DNA damage and alterations in mitochondrial function[6,7]. Furthermore, GSK-3 itself regulates 100 other enzymes that could be involved in the therapeutic mechanism, which could explain the wide range of lithium effects. In this case, lithium was able to exert a neuroprotective and neurotropic effect. The good response, the speed with which it was established and at such a small dose (0.4 mEq/L) were striking. In addition, throughout the 5 years the patient survived, her condition and autonomy increased. It may be thought that lithium slowed down the neuroprogression of her disease while it was being used. Recently, the rapid effect on agitation that occurs has been described[9] as well as the ability of micro-doses of lithium to improve cognitive symptoms in patients with dementia at initial stages[6,8]. Although we do not have genetic data on our patient, the relatively late age of onset of the disease and the long survival are compatible with a lower percentage of mutant DNA than that of the classic presentation. And, as happens with patients in the initial stages of dementia, lithium is capable of preserving or regenerating the function of partially intact neurons. The immediate effect of lithium in combating agitation, and the subsequent improvement we describe in the degree of autonomy of the patient, may be due to different mechanisms of action. Chronic inhibition of GSK-3 has been proposed to have a neuroprotective effect by stimulating gene and protein expression that acts as an antiapoptotic factor[6]; however, other authors consider other mechanisms, independent of GSK-3 inhibition[11].

Finally, given that Leigh disease has no aetiological treatment, lithium may be a therapeutic option to improve the quality of life of these patients.

## CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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