Lithium for Leigh syndrome – damage, benefit, or both?

Running title: Lithium for Leigh syndrome

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Key words. Leigh syndrome, mitochondrial disorder, respiratory chain, mtDNA, intoxication

Dear Editor,

With interest we read the article by Basterreche et al. about a 23yo female with Leigh syndrome diagnosed at age 4y and manifesting with severe psychomotor impairment, severe self-harm, hetero-aggressions, bilateral hypodensities of the basal ganglia, and cerebellar atrophy[1]. The patient was treated with lithium and experienced a beneficial effect with regard to psychosis. The study is appealing but raises the following comments and concerns.

The main limitation of the report is that the diagnosis "Leigh syndrome" was not genetically supported. Currently, mutations in >75 genes have been made responsible for Leigh syndrome[2]. Thus, for diagnosing Leigh syndrome it is crucial to know the genetic defect, if it occurred sporadically or was inherited, and which other first degree relatives were clinically affected and carried the defect as well. An extensive family history is required and in case Leigh syndrome was inherited, we should be informed about the trait of inheritance and if the causative mutation occurred in the homozygous or heterozygous form and if it was located on the mtDNA or on the nDNA.

Furthermore, Leigh syndrome is characterised by elevated lactate in the cerebro-spinal fluid (CSF) or brain, why the results of CSF lactate determination and magnetic resonance spectroscopy (MRS) should be provided. In a meta-analysis of 385 patients with Leigh syndrome the most frequent clinical manifestations were elevated blood/CSF lactate (72%), developmental delay (57%), hypotonia (42%), respiratory dysfunction (34%), epileptic seizures (33%), poor feeding (29%), and weakness (27%)[3]. Rarely, Leigh syndrome patients may present with elevated CSF protein or positive oligoclonal bands[4].

Missing in the article is a report about the electro-encephalography (EEG) findings. Since seizures can be a phenotypic features of Leigh syndrome in one third of the cases[3] and since the patient manifested with psychiatric abnormalities, it is crucial to present the results of EEG recordings to rule out epilepsy.

Which were the "respiratory complications" the patient died from at age 29y? We should be informed about the autopsy findings. It should be discussed if lithium was involved in the decease. We should be informed about serum lithium levels at the time of death. Frequent side effects of lithium include tremor, ECG abnormalities[5], renal insufficiency, hypothyroidism, hyperparathyroidism, infertility, decreased libido, dysgeusia, or glossalgia. In a study of mice it has been shown that lithium causes oxidative stress and thus mitochondrial dysfunction[6]. Thus, the effect of lithium on mitochondrial functions should be clarified.

Furthermore, it should be discussed if the beneficial effect of lithium for Leigh syndrome was simply the beneficial effect of lithium for psychosis. We should be told if lithium is only beneficial in patients with a mitochondrial disorder (MID) who exhibit psychiatric disease, or if it is generally beneficial to all patients with Leigh syndrome, irrespective of whether they manifest with psychiatric disease or not. Since it was proposed to generally treat Leigh syndrome with lithium, we should be told if the authors have treated other Leigh syndrome patients or MID patients other than Leigh syndrome with lithium, and which was the effect.

Overall, this interesting study has several limitations which challenge the interpretation of the results. The diagnosis Leigh syndrome should be genetically confirmed, an EEG should be recorded, first degree relatives should be investigated clinically and genetically, a cerebral MRI is crucial, and lactate levels in the CSF or brain tissues should be provided.

DECLARATIONS

Acknowledgement: none

Statement of ethics: was in accordance if ethical guidelines

Conflicts of interest: none

Funding sources: no funding was received

Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval, CM: literature search, discussion, critical comments, final approval

Informed consent: was obtained

The study was approved by the institutional review board

REFERENCES

1 Basterreche N, Arrúe A, Arnaiz A, Olivas O, Zumárraga M. Lithium: An old treatment for a new indication. Actas Esp Psiquiatr. 2021 May;49(3):122-127.

2 Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol. 2008 Oct;39(4):223-35. doi: 10.1016/j.pediatrneurol.2008.07.013.

3 Chang X, Wu Y, Zhou J, Meng H, Zhang W, Guo J. A meta-analysis and systematic review of Leigh syndrome: clinical manifestations, respiratory chain enzyme complex deficiency, and gene mutations. Medicine (Baltimore). 2020 Jan;99(5):e18634. doi: 10.1097/MD.0000000000018634.

4 Yiş U, Seneca S, Dirik E, Kurul SH, Ozer E, Cakmakçi H, De Meirleir L. Unusual findings in Leigh syndrome caused by T8993C mutation. Eur J Paediatr Neurol. 2009 Nov;13(6):550-2. doi: 10.1016/j.ejpn.2008.10.009.

5 Altinbas K, Guloksuz S, Caglar IM, Caglar FN, Kurt E, Oral ET. Electrocardiography changes in bipolar patients during long-term lithium monotherapy. Gen Hosp Psychiatry. 2014 Nov-Dec;36(6):694-7. doi: 10.1016/j.genhosppsych.2014.07.001.

6 Ommati MM, Arabnezhad MR, Farshad O, Jamshidzadeh A, Niknahad H, Retana-Marquez S, Jia Z, Nateghahmadi MH, Mousavi K, Arazi A, Azmoon MR, Azarpira N, Heidari R. The Role of Mitochondrial Impairment and Oxidative Stress in the Pathogenesis of Lithium-Induced Reproductive Toxicity in Male Mice. Front Vet Sci. 2021 Mar 24;8:603262. doi: 10.3389/fvets.2021.603262.

AUTHORS' REPLY

Lithium: An old treatment for a new indication

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Dear Editor:

We appreciate Dr Finsterer's interest and comments on the clinical case "Lithium: An old treatment for a new indication" published in this journal (Basterreche et al, 2021). Dr Finsterer finds a number of limitations in our note that we will try to clarify in this reply.

The patient was diagnosed with Leigh Syndrome in the neurology department of a general hospital in our province, and with this diagnosis already established, she was admitted to our monographic hospital, which exclusively treats patients with psychiatric disorders.

We do not know the specific mutation that caused her pathology, but we do know that she had a sister with the same mutation who had not developed the disease, so we can presume that this was not a sporadic case. It is true that we do not know whether it was a mitochondrial or nuclear DNA mutation. We do not know if elevated lactate levels were detected in cerebrospinal fluid, although, as she was diagnosed in a first line general hospital, we are sure that all the necessary diagnostic tests were performed.

With regard to the presence of possible epileptic seizures, these are not included in her clinical history, therefore it does not seem necessary to include electroencephalographic data, but it is true that we should have mentioned it.

The patient died at the age of 29 years and we do not have the autopsy data, nor do we know if an autopsy was performed. We do know that the cause of death was respiratory pathology. Adverse effects of lithium in humans do not include respiratory disease (McKnight et al, 2012). On the other hand, the blood levels of 0.6mEq/L that this patient maintained are, in principle, far from the level of lithium toxicity.

We agree that the role of lithium on mitochondrial function should be studied and understood. In our case the patient did not worsen, but clearly improved, so it does not seem compatible with a negative effect of lithium on the already altered mitochondrial function she was suffering from. This does not exclude that this may be the case in other cases.

Dr Finsterer wonders whether the improvement in the patient's general behaviour when treated with lithium could be due to the improvement of her psychiatric symptomatology alone. We cannot deduce from a single case what were the causes of this improvement, which we discussed from a biological point of view in the original note. An improvement in the severe but occasional episodes of agitation, not psychosis, that she suffered, does not seem sufficient to produce a progressive and sustained change over time in her autonomy and in her ability to relate to others, although it cannot be radically excluded. Whether treatment with low-dose lithium favours the preservation of neurological function in these patients is something that would be interesting to test in a larger study, which is beyond the possibilities of our psychiatric unit at this time.

In short, our case is of purely clinical content and, although it lacks certain genetic, electroencephalographic or necrological data, we believe it is of interest as the patient has shown a very significant improvement in her quality of life.