Case report

Short-term treatment for ataxia due to Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) with cerebellar-spinal tDCS: a case report

Déborah Marques[1]
Maíra Souza[2]
Rodrigo Marques[3]
Mayara Barros[4]

[1]Corresponding author. Singular - Psiquiatria e Neuromodulação (Recife). Pernambuco, Brazil. deborahmarques@outlook.com
[2,4]Singular - Psiquiatria e Neuromodulação (Recife). Pernambuco, Brazil.
[3]Universidade Federal de Pernambuco (Recife). Pernambuco, Brazil.

ABSTRACT | INTRODUCTION: Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) may occur in patients who underwent lithium treatment for bipolar disorder. Unfortunately, SILENT can cause a progressive cerebellar degeneration culminating in permanent cerebellar symptoms as postural instability and ataxic gait. We describe, for the first time, a case of a patient suffering from SILENT whose cerebellar symptoms were treated by transcranial direct current stimulation (tDCS). The objective of the case report is to present the short-term effects of combining tDCS with physical therapy in a patient with ataxia resulting from lithium intoxication. These findings have the potential to be beneficial for both patients and clinicians, as they indicate the possibility of a new therapeutic intervention. **METHODS:** Patient underwent seven sessions of anodal cerebellar-spinal tDCS (2mA, 20min, fade-in/fade-out: 10 seconds, electrodes of 35 cm^2 for the cerebellar area and 48 cm^2 for the spinal area) plus 1-hour of daily physical therapy to treat ataxic gait, postural instability, risk of falling and impairment in standing from seated position. Clinical outcomes were assessed by items of the Scale for the Assessment and Rating of Ataxia (SARA) before and immediately after treatment sessions. **RESULTS:** Patient achieved a large motor improvement mostly perceived by a marked restoration of trunk sway as well as postural control (outstanding the time in standing – without support - increased 655 percent from 20 to 131 seconds; whereas subscores of dysmetria, action/intention tremor, dysdiadochokinesia and gait remained unchanged. **CONCLUSION:** Anodal cerebellar-spinal tDCS plus physical therapy seems to be a promising therapeutic approach to attenuate cerebellar symptoms of patients who present SILENT, mainly those with deficits in stability and postural control.

KEYWORDS: SILENT. Ataxia. Cerebellar-spinal tDCS. Physical Therapy. Case Report.

Submitted Aug. 14th, 2024, Accepted Sept. 12th, 2024,
Published Oct. 4th, 2024
Brain Imaging Stimul., Salvador, 2024;3:e5883
http://dx.doi.org/10.17267/2965-3738bis.2024.e5883 | ISSN: 2317-3394
Assigned editor: Abrahão Baptista

How to cite this article: Marques D, Souza M, Marques R, Barros M. Short-term treatment for ataxia due to Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) with cerebellar-spinal tDCS: a case report. Brain Imaging Stimul. 2024;3:e5883. http://dx.doi.org/10.17267/2965-3738bis.2024.e5883

1. Introduction

Lithium has long been a mainstay treatment for Bipolar Disorder (BD), with well-established evidence for efficacy as a mood stabilizer and in suicide prevention. However, side effects are common during its use, the most worrying being those secondary to acute intoxication, which can cause several life-threatening clinical conditions, such as renal failure. However, neurotoxicity has also been described, with over 120 reported cases of neurological sequelae, a clinical condition called Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT).[1] SILENT frequently occurs in patients with lithium plasma levels within safety limits and has as main risk factors the onset of fever and age >50 years. About 80% of SILENT patients will present with permanent cerebellar symptoms and some will progress with cerebellar degeneration.

Transcranial direct current stimulation (tDCS) is a safe tool that allows for modulation of corticospinal excitability, with effects that are dependent on polarity.[2] The potential benefits of this approach are particularly promising in treating ataxias with different underlying causes.[3] Protocols ranging from only one to 10 sessions of stimulation which used montages exclusively over cerebellar or cerebellar-spinal areas showed improvements in motor performance (i.e. as measured by clinical scales such Scale of the Assessment and Rating of Ataxia - SARA and International Cooperative Ataxia Rating Scale), upper limb coordination, manual dexterity (i.e. as measured by 9-Hole Peg Test) and walking speed (i.e. as measured by 8-Meter Walking Test) in such patients.[3-6] Here, we report for the first time a case of a patient suffering from SILENT whose cerebellar symptoms were treated by tDCS. We aimed to assess the effects of seven sessions of physiotherapy associated with tDCS on the motor rehabilitation of a patient with ataxia resulting from lithium intoxication.

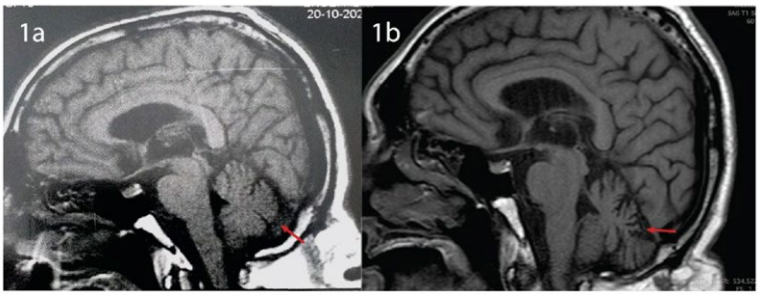
2. Case report

Mr. A., currently 66 years old, was first diagnosed with BD type I (ICD-10 F31 and DSM-5 F31) at 64 years of age, being prescribed lithium 600mg and aripiprazole 5mg. He had a history of several depressive and manic episodes but had never sought help before and was otherwise healthy. After about 2 weeks, the patient underwent an unsuccessful dental procedure and, on the following days, presented fever and several motor abnormalities (cervical dystonia, superior limbs ballism, ataxic gait).

He was hospitalized and progressed with high fever and low arousal, being admitted to the intensive care unit, where he presented hypotension due to suspected sepsis, drug-induced hepatitis and several seizures, but rapidly recovered over a period of 12 hours. Mechanical ventilation was not necessary and he was transferred to a ward after 48 hours, receiving hospital discharge within 13 days from admission. He did not undergo hemodialysis and lithium plasma levels were not assessed. Brain magnetic resonance imaging (MRI) during this period was unremarkable (Figure 1a) and laboratory tests were normal at discharge, but ataxic symptoms were noted upon physical examination. The main diagnostic impression was that the patient had developed neurological complications of sepsis.

Over the following months, the patient worsened of motor symptoms, including dysmetria, dysarthria, intention tremor, ataxic gait, postural instability, and impairment in standing from seated position. He came under the care of our team 11 months after hospital discharge severely disabled and entirely dependent on others. MRI showed atrophy of the cerebellar vermis as the sole abnormal finding (Figure 1b). SILENT was established as the main diagnosis at this time, due to the previous exposure to lithium during fever, age >50 years, and the progressive nature of the ataxic symptoms with evidence of cerebellar degeneration.

Figure 1. 1a displays a midline sagital T1 MRI with normal cerebellum (red arrow) acquired during hospitalization; 1b shows noticeable vermian atrophy (red arrow) after 11 months from discharge



Source: the authors (2024).

Regarding the treatment for BD, he had continuously been prescribed desvenlafaxine 100mg and aripiprazole 5mg by a neurologist since hospital discharge. History taking showed that he had been presenting several mood episodes, becoming very agitated, irritated, uncooperative and expressing suicidal intentions at times, and bedridden, unmotivated, apathetic, barely communicating, with psychomotor slowing and depressed mood at others. He became stable from BD symptoms and slightly better of dysarthria after switching to sertraline 50mg and quetiapine 50mg, also occasionally using clonazepam 0,25mg when agitated or anxious.

His main complaint, however, remained the cerebellar symptoms, due to impaired mobility, limited verbal expression and overall dependence on the full-time care of others. Therefore, tDCS associated with physical therapy was indicated as a treatment for ataxia.

3. Methods

3.1 Trial registration

This case report was retrospectively registered in the local ethics committee (CAAE N° 7.006.605). Additionally, written informed consent has been obtained from Mr. A to publish the details of its case.

3.2 tDCS protocol and physical therapy

Cerebellar-spinal tDCS was delivered by a battery-driven constant current stimulator (NeuroSTIM/MEDSupply-Brazil). The patient underwent seven daily cerebellar-spinal tDCS sessions using a pair of saline-soaked (0.9% NaCl) surface sponges electrodes (7x5 cm^2 for the anodal cerebellar electrode; 8x6 cm^2 for the cathodal spinal electrode), with an intensity of 2mA, during 20 minutes, fade-in/fade-out 10 seconds. The anode was placed over the cerebellum area (2 cm under the inion), while the cathode was placed over the spinal lumbar enlargement (2 cm under T11).[5] The anode was placed using a customized head strap and the cathode using elastic gauzes. Incidence of adverse effects such as tingling, burning and itching, among others, was assessed daily after each cerebellar-spinal tDCS session.

During and immediately after each cerebellar-spinal tDCS session, physical therapy (totalizing one hour per day) was performed using Proprioceptive Neuromuscular Facilitation techniques aiming to improve trunk control, dynamic and static balance, anticipatory and reactive balance control, transition from sitting to standing (with and without support), gait and core/pelvic strengthening.

3.3 Clinical measures

Before and immediately after the seven combined treatment sessions, items of the SARA[7] were used to evaluate the patient's clinical progressions. The presence of dysmetria, action/intention tremor, dysdiadochokinesia, trunk sway, postural ataxia and gait were evaluated using the following tests: (i) index-index test; (ii) nose-finger test; (iii) fast alternating hand movement test; (iv) heel-shin slide test; (v) transition from sitting to standing; (vi) time in standing – without support; (vii) gait with support.

4. Results

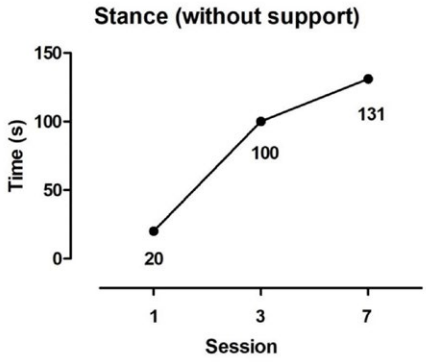
Mr. A. showed a large motor improvement after only seven sessions of combined treatment (cerebellar-spinal tDCS plus physical therapy), mostly perceived by a marked restoration of trunk sway as well as postural control (better in static balance). The evolution of clinical scores (before and after treatment sessions) are shown in Table 1: outstanding the time in standing – without support increased 655 percent (from 20 to 131 seconds - see figure 2), whereas subscores of dysmetria, action/intention tremor, dysdiadochokinesia and gait remained unchanged. Tolerability to cerebellar-spinal tDCS was good, with no serious adverse effect reported by the patient after treatment sessions.

Table 1. Clinical measures before and after the seven sessions of cerebellar-spinal tDCS plus physical therapy

	1st session	7th session
Index-index test	0	0
Nose-finger test	0	0
Fast alternating hand movement test	3	3
Heel-shin slide test	1	1
Transition from sitting to standing	Qualitative description	Qualitative description
Time in standing – without support	20sec	131sec
Gait with support	7	7

Source: the authors (2024).

Figure 2. Patient's evolution for the time in standing (without support) from the first to the last session of combined treatment



Source: the authors (2024).

5. Discussion

The results demonstrated that cerebellar-spinal tDCS was effective in reducing cerebellar symptomatology. The intervention was also safe and tolerable, with no reported discomfort and no change regarding mood stabilization.

The pathophysiology of SILENT involves toxic intraneuronal levels of lithium ions. When a lithium overdose occurs, high availability is widespread, and this may result in damage to a variety of brain regions. When lithium plasma levels are low or moderate, the onset of fever seems to be a defining factor for the occurrence of SILENT, in this case having a clear tropism for the cerebellar cortex, probably due to its higher sensitivity to heat and hyperthermia. The most consistent findings in the postmortem study of these cases are cerebellar atrophy and loss of Purkinje cells.[7,8]

Cerebellar tDCS has been shown to increase the excitatory tone of Purkinje cells, changing activity in the deep cerebellar output nuclei. Anodal tDCS over the cerebellum seems able to increase physiologic inhibitory tone over the primary motor cortex through the inhibition of the dentate nucleus.[9] Furthermore, there is evidence that transcutaneous spinal tDCS can induce prolonged functional neuroplastic changes by modulating the ascending and descending spinal pathways and spinal reflex excitability.[10] Cathodal spinal tDCS has been used to improve gait training in chronic stroke patients as well as functional outcomes in chronic spinal cord injury.[11]

Cerebellar degeneration caused by SILENT is a disabling and largely untreatable clinical condition that predominantly occurs in patients with BD, due to the frequent use of lithium as a treatment in this population. The high prevalence of cerebellar sequelae makes tDCS an interesting therapeutic alternative since it may act directly on the presumed pathophysiology of these symptoms. It is also a safe non-pharmacological intervention that may prove useful in the context of BD since this mental disorder imposes limitations on the use of medications due to the risk of compromising mood stabilization or imposing harmful side effects.

In conclusion, cerebellar-spinal tDCS may be a viable, safe and tolerable option to reduce cerebellar symptomatology in patients with SILENT. Other reports/studies with a higher sample and reliable methodology (as randomized controlled trials) are needed to draw more consistent conclusions.

Authors contributions

The authors declared that they have made substantial contributions to the work in terms of the conception or design of the research; the acquisition, analysis or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsibility for all aspects of the study.

Conflicts of interest

No financial, legal, or political conflicts involving third parties (government, private companies, and foundations, etc.) were declared for any aspect of the submitted work (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

References

1. Verdoux H, Debruyne AL, Queuille E, De Leon J. A reappraisal of the role of fever in the occurrence of neurological sequelae following lithium intoxication: a systematic review. Expert Opin Drug Saf. 2021;20(7):827–38. http://dx.doi.org/10.1080/14740338.2021.1912011

2. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(3):633–9. http://dx.doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

3. Benussi A, Dell'Era V, Cotelli MS, Turla M, Casali C, Padovani A, et al. Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia. Brain Stimul. 2017;10(2):242–50. http://dx.doi.org/10.1016/j.brs.2016.11.001

4. Benussi A, Koch G, Cotelli M, Padovani A, Borroni B. Cerebellar transcranial direct current stimulation in patients with ataxia: A double-blind, randomized, sham-controlled study. Mov Disord. 2015;30(12):1701–5. http://dx.doi.org/10.1002/mds.26356

5. Benussi A, Dell'Era V, Cantoni V, Bonetta E, Grasso R, Manenti R, et al. Cerebello-spinal tDCS in ataxia: A randomized, double-blind, sham-controlled, crossover trial. Neurology. 2018;91(12):e1090–101. http://dx.doi.org/10.1212/WNL.0000000000006210

6. Portaro S, Russo M, Bramanti A, Leo A, Billeri L, Manuli A, et al. The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation: A case report. Medicine. 2019;98(8):e14447. http://dx.doi.org/10.1097/MD.0000000000014447

7. Braga-Neto P, Godeiro-Junior C, Dutra LA, Pedroso JL, Barsottini OGP. Translation and validation into Brazilian version of the Scale of the Assessment and Rating of Ataxia (SARA). Arq Neuropsiquiatr. 2010;68(2):228–30. http://dx.doi.org/10.1590/s0004-282x2010000200014

8. Rossi FH, Rossi EM, Hoffmann M, Liu W, Cruz RR, Antonovich N, et al. Permanent Cerebellar Degeneration After Acute Hyperthermia with Non-toxic Lithium Levels: a Case Report and Review of Literature. Cerebellum. 2017;16(5-6):973–8. http://dx.doi.org/10.1007/s12311-017-0868-3

9. Grimaldi G, Argyropoulos GP, Bastian A, Cortes M, Davis NJ, Edwards DJ, et al. Cerebellar Transcranial Direct Current Stimulation (ctDCS): A Novel Approach to Understanding Cerebellar Function in Health and Disease. Neuroscientist. 2016;22(1):83–97. http://dx.doi.org/10.1177/1073858414559409

10. Cogiamanian F, Ardolino G, Vergari M, Ferrucci R, Ciocca M, Scelzo E, et al. Transcutaneous spinal direct current stimulation. Front Psychiatry. 2012;3:63. http://dx.doi.org/10.3389/fpsyt.2012.00063

11. Nardone R, Höller Y, Taylor A, Thomschewski A, Orioli A, Frey V, et al. Noninvasive Spinal Cord Stimulation: Technical Aspects and Therapeutic Applications. Neuromodulation. 2015;18(7):580–91. http://dx.doi.org/10.1111/ner.12332