Case Report

No effect of electrical transcranial direct current stimulation adjunct treatment for epilepsy partialis continua in POLG disease

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ABSTRACT

We report a 15-year-old female with POLG-related mitochondrial disease who developed severe multifocal epilepsy partialis continua, unresponsive to standard anti-seizure drug treatment and general anesthesia. Based on an earlier case report, we treated her focal seizures that affected her right upper limb with 20-min sessions of transcranial direct current stimulation (tDCS) at an intensity of 2 mA on each of five consecutive days. The cathode was placed over the left primary motor cortex, the anode over the contralateral orbitofrontal cortex. Surface electromyography (EMG) were recorded 20 min before, 20 min during, and 20 min after four of five tDCS sessions to measure its effect on the muscle jerks. The electroencephalography (EEG) was recorded before and after tDCS to measure the frequency of spikes. Our results showed no statistically or clinically significant reduction of seizures or epileptiform activity using EEG and EMG, with this treatment protocol. To our knowledge, this is the only the second time that adjunct tDCS treatment of epileptic seizures has been tried in POLG-related mitochondrial disease. Taken together with the positive findings from the earlier case report, the present study highlights that more data are needed to determine if, and under which parameters, the treatment is effective.

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1. Introduction

Mitochondrial diseases are a group of genetic disorders affecting about one in 5000 people [1]. The symptoms are diverse but since mitochondria produce energy for body tissues through production of adenosine triphosphate (ATP), organs with high energy consumption, such as the brain, are often affected. For example, as many as 35% to 60% of people with mitochondrial disease develop seizures [1]. In POLG-related mitochondrial disease, a genetic mutation interferes with a catalytic subunit of the mitochondrial DNA polymerase gamma, which replicates mitochondrial DNA [2], leading to depleted mitochondrial DNA [3]. Once the resulting neuronal energy failure reaches a critical point, neuronal death ensues, causes atrophy and potentially acts as the trigger for epilepsy that in turn increases neuronal loss [4]. A study found mitochondrial dysfunction in one third of patients with epilepsy that underwent metabolic testing [5], emphasizing that drug-resistant seizures are a frequent problem in mitochondrial disease, and that new treatments need to be developed. In a previous case report, focal seizures in a patient with POLG-related mitochondrial disease ceased after two weeks of transcranial direct current stimulation (tDCS) [6]. Since these seizures are often refractory to medical treatment and the technique is non-invasive, we tested tDCS using similar parameters as in Ng et al. [6] in a patient with POLG-related mitochondrial disease and drug-resistant multifocal epilepsy.

1.1. Case report

This 15-year-old female was apparently healthy until the first admission followed two consecutive generalized tonic–clonic seizures. Prior to the seizures, she had experienced nausea, headache, reduced vision and paraesthesia in both upper limbs. She was intubated during helicopter transfer to hospital due to reduced consciousness. Following admission, she regained consciousness, but developed continuous jerking of her right arm. EEG showed ongoing epileptiform discharges over the right occipital region (Fig. 1A) that later involved most of the...
right cerebral hemisphere, and because of persisting uncontrolled epileptic activity she was loaded with phenytoin before using anesthesia with propofol and ketamine at relevant clinical dosages to provide effective serum levels, as well as lowering her core body temperature to 33 °C in accordance with the Norwegian treatment guidelines [7]. The clinical presentation with status epilepticus involving an occipital lobe focus prompted investigation for POLG mutation, which was subsequently confirmed through DNA sequencing analysis showing a homozygous genotype c.2243G>C.

Following two episodes of propofol anesthesia and achieving burst suppression, she regained consciousness and her epilepsy was then treated with phenobarbital and oxcarbazepine while withdrawing phenytoin. After stabilization, the patient was discharged with ongoing medication treatment. She was readmitted a second and third time
with headache and visual disturbances that quickly morphed into general
tonic–clonic seizures, followed by focal motor status epilepti-
cus, both episodes treated with anesthesia and hypothermia. On the
third occasion, her MRI showed new changes in both occipital regions.
During the second prolonged admission, she still had jerking of her
right arm despite maintaining phenytoin, levetiracetam, oxcarba
apine, topiramate and clobazam at therapeutic doses. At the point where tDCS
treatment was instituted, the patient had a multifocal seizures with
multiple semiologies (Fig. 1A and B) including a multifocal, asynchro
nous myoclonus, that was dominant and most debilitating in the right
hand. We thus targeted the left primary motor cortex with tDCS, as
the myoclonus activity most likely arose from that area, with the goal
to relieve pain and disability.

1.2. Methods of tDCS and EEG

The use of tDCS was discussed with the local ethical committee who
considered it a form of supplementary experimental treatment whose
purpose was to provide care for an individual, and for which the caring
physician could take responsibility without obtaining the committees’
approval. Verbal consent was obtained from the parents and treatment
was reported in the patient’s medical journal. tDCS was applied for
20 min at 2 mA on each of five consecutive days with a DC-Stimula
ter PLUS (neuroConn, Ilmenau, Germany) through 5 × 7 cm rubber elec
trodes with saline soaked sponges giving a current density of
0.057 mA/cm². The patient displayed continuous jerking in the right
hand muscles and left shoulder muscles. To reduce the jerking of the

![tDCS montage and results](image_url)

**Fig. 2.** tDCS montage and results. Panel A) Placement of anode at Fp2 (red) and cathode at C3 (blue) within the international 10/20 system. Panel B) Means of spikes/jerks per second across all four days. Time in minutes. Panel C) Spikes/jerks per second and 95% confidence intervals before, during, and after treatment.
right hand, the cathode was placed over the contralateral left primary motor cortex at approximately C3 of the 10–20 EEG system (see Fig. 2A). The rationale was that cathodal stimulation has been shown to reduce cortical excitability in the brain area underneath the electrode and hence might reduce epileptic activity causing the myoclonus [8]. The anode was placed on the right orbitofrontal cortex (approximately Fp2). By placing the electrode on the contralateral side, the electric field between anode and cathode crosses the midline and was hoped to affect the motor cortex most effectively. Since the anode is active and expected to increase cortical excitability, a better setup would have included an extra-large anode that would effectively reduce the current strength. However, as the tDCS treatment was issued at short notice, we did not have large electrodes available at the time. We chose the orbitofrontal region, because it is often used as a control site in tDCS experiments [9] and because it was not particularly affected by epilepsy. Indeed, we did not observe a worsening in the EEG in this region after the treatment. The tDCS setup was used in accordance with safety guidelines [10,11].

Initial EEG recordings and seizure monitoring during status epilepticus were done with 25 channel clinical EEG and scored visually by experienced neurophysiologists. With the cathode placed over the left primary motor cortex, we looked for improvement particularly in the right hand. Continuous EEG was measured from C3 and C4 (right motor cortex as control) for 20 min before and 20 min after tDCS, from a clinical EEG setup following the 10/20 system with 6 + 2 (F3, F4, P3, P4, O1, O2) electrodes and video monitoring of the patient. EMG data from the right hand and left trapezius was acquired continuously for 20 min before tDCS, during 20 min tDCS, and 20 min after tDCS. EEG data was not interpretable during tDCS due to amplifier blocking. EMG and EEG data were recorded on four out of five days.

Three separate raters, two neurophysiologists (TE, HKO) and the tDCS clinician (LM), counted the frequency of spikes (EEG) and muscle jerks (EMG) drawn from multiple random samples. Specifically, the data were binned into 12 five-minute segments. Then, each rater picked randomly ten, artifact-free one-second periods from each five-minute segment on all four days and determined the mean number of EEG spikes and EMG jerks per second (Hz) for all four measurements (C3, C4, right hand, left trapezius). Subsequently, means were calculated across raters (see Fig. 2B) and EEG data was subjected to paired sample t-tests and non-parametric Wilcoxon tests, comparing spikes before and after tDCS. The means for EMG data were subjected to an ANOVA with across raters (see Fig. 2B) and EEG data was subjected to paired sample t-tests/Wilcoxon tests for EEG data and the ANOVAs/Friedman tests for EMG data, there were no significant differences in the means across all raters in C3 or C4 spikes (all Fs(1,30) ≤ 0.613, all ps ≥ 0.549; all χ^2(5,1) ≤ 0.091, all ps ≥ 0.763) as well as jerks in the right hand and left shoulder (all Fs(2,30) ≤ 1.74, all ps ≥ 0.192; all Zs ≥ 0.642, all ps ≥ 0.521). The mean spikes and jerks across all raters for pre-tDCS on day one (baseline) versus post-tDCS on day five were for the right hand 4.58 ± 0.32 and 4.42 ± 0.57, left trapezius 4.58 ± 0.32 and 4.08 ± 0.42 jerks/s, C3 4.50 ± 0.43 and 4.25 ± 0.32 and C4 4.25 ± 0.32 and 4.13 ± 0.17 spikes/s, respectively. None of these changes were significant (all ts ≤ 1.57, all ps ≥ 0.215; all Zs ≤ 1.34, all ps ≥ 0.180).

TDCS treatment was given in March 2018. The stimulation itself was well tolerated. The patient only reported short-term skin irritation from the net holding the electrodes in place. Four months after receiving tDCS, the patient was discharged from the hospital, still with upper limb jerking, but was readmitted in December 2018 and died due to a super-refractory status epilepticus.

3. Discussion

Neither spike nor jerk frequency changed over the course of five tDCS sessions (between before, during, and after tDCS) or when comparing baseline spike/jerk rates from day one to after treatment on day five. We therefore conclude that – in this case study – tDCS did not have a beneficial treatment effect on treatment-resistant refractory epilepsy partialis continua in POLG-related mitochondrial disease. Hence, our results are inconsistent with those of Ng et al. [6], who found that seizures stopped completely in a similar case study.

There are several differences between the two case studies that could explain the different outcomes: Ng et al. [6] placed the cathode over the right temporo-parietal–occipital junction (P4/T6), while in our study it was over the left primary motor cortex. Ng et al. provided tDCS treatment twice, once for three days and once for 14 days, while we provided tDCS treatment once for five days. However, the treatment in our case was stopped before the completion of 14 days because there was no sign of improvement and due to technical reasons/staff availability. Moreover, while the patients appeared to have similar seizure frequency their genotypes were different; the patient reported by Ng and colleagues was homoygous for the c.1399G>A whereas our patient was homoygous for the c.2243G>C genotype. Both patients were also on multiple, but different anticonvulsant regimes, raising the possibility that competing mechanisms modulated response to tDCS. Lastly, our case was severe, so by the time we started the intervention the seizures may have become refractory to both medication and tDCS treatment. We cannot rule out that cathodal stimulation elsewhere (e.g., over the right occipital region) might have yielded a better treatment response, perhaps, at an earlier stage of the disease. However, while the patient had a multifocal epilepsy with multiple semiologies, we specifically targeted the left motor cortex to reduce the myoclonic jerking of the right hand that the patient found very debilitating. Similarly, we cannot rule out that stimulating for more than five days would have worked better.

According to guidelines published by a European expert consortium in 2017, and several reviews, it is not yet possible to draw conclusions regarding the efficacy of tDCS in any kind of epilepsy, even though there are some promising results [12–15]. Similarly, it remains unclear whether transcranial magnetic stimulation (TMS), another type of non-invasive brain stimulation, is an effective treatment of epilepsy [16–18], although there are some positive findings for epilepsy partialis continua [19]. Even less is known about how these non-invasive brain stimulation techniques will affect patients with mitochondrial diseases. However, given that refractory epilepsy appears to be common in these diseases [5], finding novel treatments is highly relevant. To our knowledge, this is only the second documented attempt to use tDCS in mitochondrial disease. With one positive and one negative result, it is too early to say whether tDCS will find a place in the treatment of mitochondrial epilepsy, but during the early stages of any new treatment, all findings, negative or positive, need to be published to obtain a clearer overall picture. This is particularly relevant in this case, where almost nothing is known about the efficacy of tDCS for epilepsy in patients with mitochondrial diseases. Further, because the condition is so rare, it is difficult to realize randomized controlled trials with decent sample sizes and that could control for potential placebo effects. A final reason for why we deem it important to report this negative finding is – despite its limited contribution to the literature – that there is growing evidence that cathodal stimulation might be a viable option for patients with epilepsy.
awareness of reporting bias and replication issues in the scientific community and with it a growing recognition of the relevance of negative findings. We hope that our findings contribute to a growing body of literature and encourage other scientists to provide larger samples and proper clinical trials.

Author contribution

Conception and design of the study: LAB, GV and MH. Acquisition of data: LM, IK, TE, HKO, MH and LAB. Analysis and interpretation of data: LM, IK, TE, HKO and MH. Drafting the manuscript or figures: All authors. Critical review and revision: All authors.

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Ethical statement

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). We confirm that we have read the journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

None.

References

[1] Rahman S. Mitochondrial disease and epilepsy. Dev Med Child Neurol 2012;54: 397–406.
[2] Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. Epilepsia 2012;53: 92–7.
[3] Tzoulis C, Tran GT, Coxhead J, Bertelsen B, Lillegård PB, Falakrani N, et al. Molecular pathogenesis of polymerase gamma-related neurodegeneration. Ann Neurol 2014; 76:66–81.
[4] Hikmat O, Eichele T, Tzoulis C, Bindoff LA. Understanding the epilepsy in POLG related disease. Int J Mol Sci 2017;18:1845.
[5] Parikhi S, Cohen BH, Gupta A, Lachhwani DK, Wylie E, Kotagal P. Metabolic testing in the pediatric epilepsy unit. Pediatr Neurol 2008;38:191–5.
[6] Ny YS, van Ruiten H, Lai HM, Scott R, Ramesh V, Horridge K, et al. The adjunctive application of transcranial direct current stimulation in the management of de novo refractory epilepsy partialis continua in adolescent-onset POLG-related mitochondrial disease. Epilepsia open 2018;3:103–8.
[7] Torgirsens E, Stensland B, Ljøstad U, Mygland A. Epilepsi – anfallsklassifisering og akutbehandling til pasienter med epileptiske anfall. In. 22.09.2017 ed. helsebiblioteket.no: Folkehelseinstituttet; 2017. p. 6.
[8] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9.
[9] Horvath JC, Forte JD, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 2015;8:535–50.
[10] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17:37–53.
[11] Bikson M, Grossman P, Thomas C, Zannou AI, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016;9:641–61.
[12] San-Juan D, Morales-Quezada L, Garduño AJO, Alonso-Varegas M, González-Aragón MF, López DAE, et al. Transcranial direct current stimulation in epilepsy. Brain Stimul 2015;8:455–64.
[13] Liu Y, Wang Y. Neurostimulation as a promising epilepsy therapy. Epilepsia open 2017;2:371–87.
[14] Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol 2017;128:36–92.
[15] San-Juan D, Sarmiento CI, González KM, Baraza O, Manuel J. Successful treatment of a drug-resistant epilepsy by long-term transcranial direct current stimulation: a case report. Front Neurol 2018;9:65.
[16] Chen R, Spencer DC, Weston J, Nolan SJ. Transcranial magnetic stimulation for the treatment of epilepsy. Cochrane Database Syst Rev 2016(8):CD011025. https://doi.org/10.1002/14651858.CD011025.pub2.
[17] Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206.
[18] Fisher R, Zhou J, Fogarty A, Joshi A, Markert M, Deutsch G, et al. Repetitive transcranial magnetic stimulation directed to a seizure focus localized by high-density EEG: a case report. Epilepsy Beh Case Rep 2018;10:47–53.
[19] Rotenberg A, Rae EH, Takoea M, Tormo JM, Schachter SC, Pascual-Leone A. Repetitive transcranial magnetic stimulation in the treatment of epilepsy partialis continua. Epilepsy Behav 2009;14:253–7.