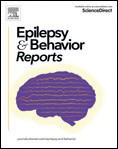
[](Journal%20logo)[](Unlabelled%20image)[Epilepsy & Behavior Reports 12 (2019) 100339](https://doi.org/10.1016/j.ebr.2019.100339)

Contents lists available at [ScienceDirect](http://www.sciencedirect.com/science/journal/25899864)

Epilepsy & Behavior Reports

journal homepage: [www.elsevier.com/locate/ebcr](http://www.elsevier.com/locate/ebcr)

Case Report

[](http://crossmark.crossref.org/dialog/?doi=10.1016/j.ebr.2019.100339&domain=pdf)No effect of electrical transcranial direct current stimulation adjunct treatment for epilepsia partialis continua in POLG disease

Lynn Marquardt [a](#_bookmark0),[⁎](#_bookmark4), Tom Eichele [b](#_bookmark1), Laurence A. Bindoff [b](#_bookmark1),[c](#_bookmark2), Henning Kristian Olberg [b](#_bookmark1), Gyri Veiby [b](#_bookmark1),

Heike Eichele [a](#_bookmark0),[d](#_bookmark3), Isabella Kusztrits [a](#_bookmark0), Marco Hirnstein [a](#_bookmark0)

a *Department of Biological and Medical Psychology, University of Bergen, Jonas Lies vei 21, 5009 Bergen, Norway*

b *Department of Neurology, Haukeland University Hospital, Bergen, Jonas Lies vei 71, 5053 Bergen, Norway*

c *Department of Neurology, Section for Clinical Neurophysiology, Haukeland*

d *Regional Resource Center for Autism, ADHD, Tourette Syndrome and Narcolepsy, Western Norway, Haukeland University Hospital, Fjøsangerveien 36, 5054 Bergen, Norway*

# a r t i c l e i n f o

*Article history:*

Received 12 July 2019

Received in revised form 30 September 2019

Accepted 4 October 2019

Available online 25 October 2019

*Keywords:* Mitochondrial disease POLG

Neurostimulation tDCS

Refractory status epilepticus

# a b s t r a c t

We report a 15-year-old female with POLG-related mitochondrial disease who developed severe multifocal epilepsia 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 ses- sions 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 only the second time that adjunct tDCS treatment of epileptic seizures has been tried in POLG-related mi- tochondrial disease. Taken together with the positive ﬁndings from the earlier case report, the present study high- lights that more data are needed to determine if, and under which parameters, the treatment is effective.

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Mitochondrial diseases are a group of genetic disorders affecting about one in 5000 people [[1](#_bookmark8)]. 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](#_bookmark8)]. In POLG-related mitochondrial disease, a genetic mutation interferes with a catalytic subunit of the mitochondrial DNA polymerase gamma, which replicates mitochondrial DNA [[2](#_bookmark7)], leading to depleted mitochon- drial DNA [[3](#_bookmark7)]. Once the resulting neuronal energy failure reaches a critical point, neuronal death ensues, causes atrophy and potentially

⁎ Corresponding author at: Department of Biological and Medical Psychology, University of Bergen, Jonas Lies vei 91, 5009 Bergen, Norway.

*E-mail addresses:* [lynn.marquardt@uib.no](mailto:lynn.marquardt@uib.no) (L. Marquardt),

[tom.eichele@helse-bergen.no](mailto:tom.eichele@helse-bergen.no) (T. Eichele), [laurence.albert.bindoff@helse-bergen.no](mailto:laurence.albert.bindoff@helse-bergen.no) (L.A. Bindoff), [henning.kristian.olberg@helse-bergen.no](mailto:henning.kristian.olberg@helse-bergen.no) (H.K. Olberg), [gyri.veiby@helse-bergen.no](mailto:gyri.veiby@helse-bergen.no) (G. Veiby), [heike.eichele@uib.no](mailto:heike.eichele@uib.no) (H. Eichele), [isabella.kusztrits@uib.no](mailto:isabella.kusztrits@uib.no) (I. Kusztrits), [marco.hirnstein@uib.no](mailto:marco.hirnstein@uib.no) (M. Hirnstein).

acts as the trigger for epilepsy that in turn increases neuronal loss [[4](#_bookmark7)]. A study found mitochondrial dysfunction in one third of patients with epilepsy that underwent metabolic testing [[5](#_bookmark7)], emphasizing that drug- resistant seizures are a frequent problem in mitochondrial disease, and that new treatments need to be developed. In a previous case re- port, focal seizures in a patient with POLG-related mitochondrial disease ceased after two weeks of transcranial direct current stimulation (tDCS) [[6](#_bookmark7)]. 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](#_bookmark7)] in a patient with POLG-related mitochondrial disease and drug-resistant multifocal epilepsy.

* 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. 1](#_bookmark5)A) that later involved most of the

<https://doi.org/10.1016/j.ebr.2019.100339>

2589-9864/© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

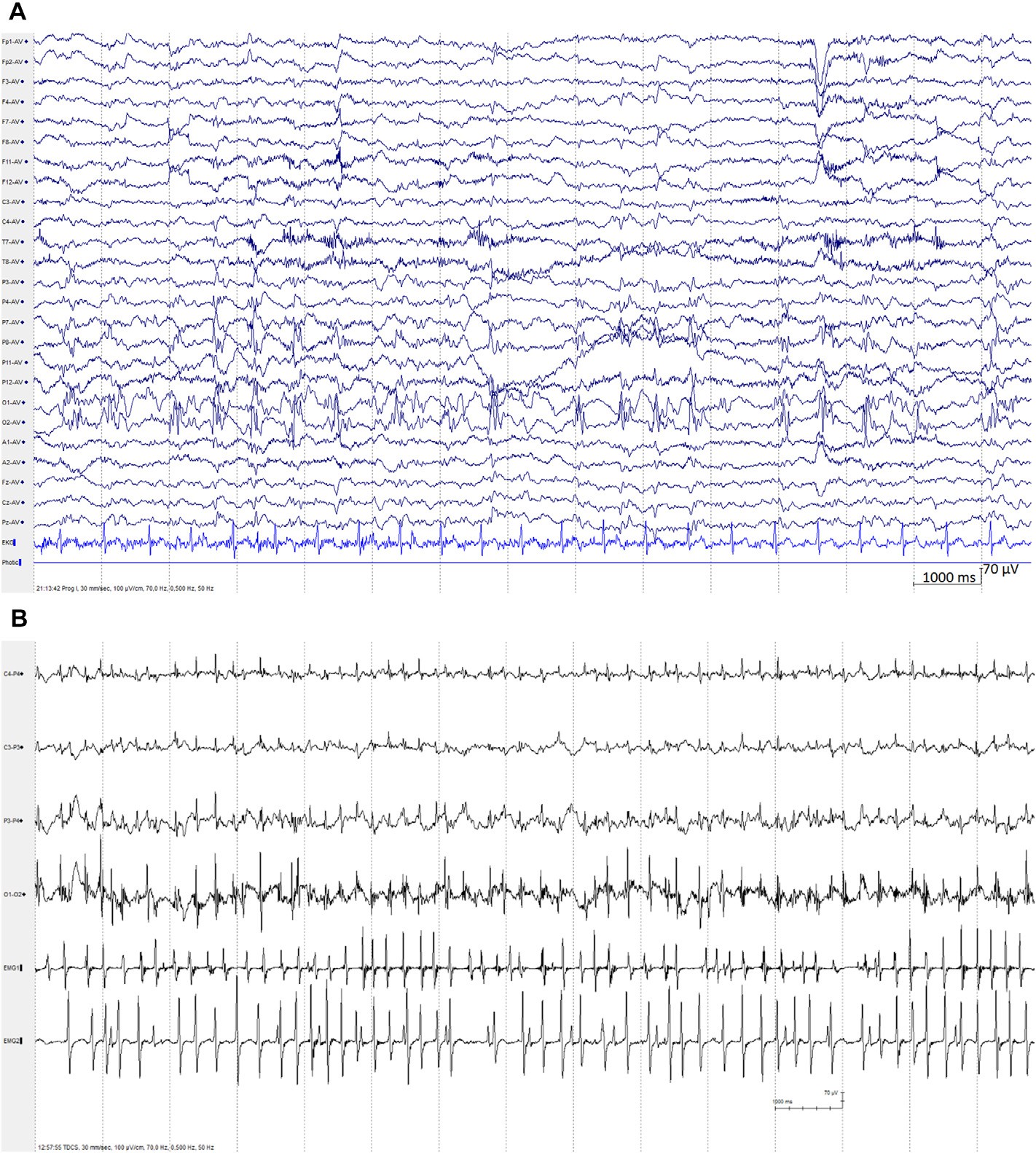
[](Image%20of%20Fig.%201)

Fig. 1. POLG disease visualized through EEG examples. Panel A) EEG sample from the patient from an early clinical recording, showing almost continuous 2 Hz polyspike-and-slow waves mainly over the right parieto-occipital region. Panel B) Continuous EEG recording from the tDCS experiment showing channels (from top to bottom) C4, C3, P3, O1 and EMG1 and EMG2 being the right hand and left trapezius, respectively.

right cerebral hemisphere, and because of persisting uncontrolled epi- leptic activity she was loaded with phosphenytoin before using anes- thesia with propofol and ketamine at relevant clinical dosages to provide effective serum levels, as well as lowering her core body tem- perature to 33 °C in accordance with the Norwegian treatment guide- lines [[7](#_bookmark7)]. The clinical presentation with status epilepticus involving an occipital lobe focus prompted investigation for *POLG* mutation, which

was subsequently conﬁrmed through DNA sequencing analysis show- ing a homozygous genotype c.2243GNC.

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 phe- nytoin. 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 gen- eralized 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, oxcarbazepine,

topiramate and clobazam at therapeutic doses. At the point where tDCS treatment was instituted, the patient had a multifocal seizures with multiple semiologies ([Fig. 1](#_bookmark5)A 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. *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-Stimulator 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

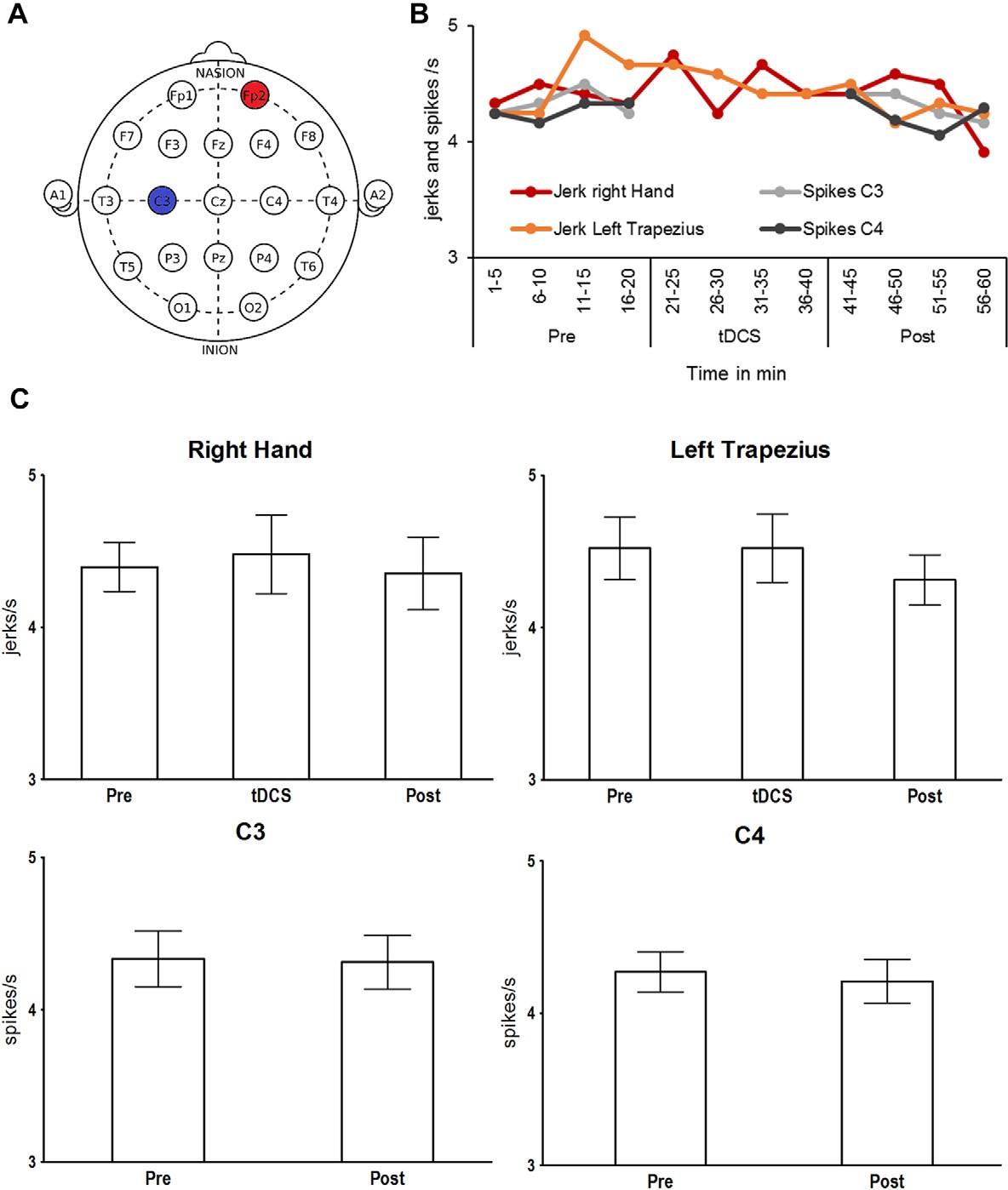
[](Image%20of%20Fig.%202)

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. 2](#_bookmark6)A). 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](#_bookmark7)]. The anode was placed on the right orbitofrontal cortex (approximately Fp2).

By placing the electrode on the contralateral side, the electric ﬁeld be- tween 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 re- gion, because it is often used as a control site in tDCS experiments [[9](#_bookmark7)] 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](#_bookmark7),[11](#_bookmark7)].

Initial EEG recordings and seizure monitoring during status epilepti- cus were done with continuous 25 channel clinical EEG and scored visu- ally 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 continu- ously 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. 2](#_bookmark6)B) 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 the repeated measures variable *Time* (before, during after tDCS) and a non-parametric Friedman test. Non-parametric Friedman and Wilcoxon tests were included because not all variables met the normal distribu-

tion criterion necessary for *t*-tests and ANOVAs — due to the limited

range of values for spikes/jerks per second. At the same time, non- parametric tests are sometimes not sensitive enough to pick up small effects. In the interest of comprehensiveness, we thus decided to report ﬁndings from both ANOVA/Friedman and paired sample *t*-tests/ Wilcoxon tests. We also compared the pre-tDCS data on day one (base- line) to the post-tDCS data on day ﬁve using *t*- and Wilcoxon tests, assuming that the treatment effect should be strongest between these measurement points.

1. Results

[Fig. 2](#_bookmark6)C shows the average frequency of epileptic spikes and jerks in the right hand and left shoulder during treatment. According to *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 *t*s(15) ≤ 0.613, all *p*s ≥ 0.549; all χ2s(1) ≤ 0.091, all *p*s ≥ 0.763) as well as jerks in the right hand and left shoulder (all *F*s(2,30) ≤ 1.74, all *p*s ≥ 0.192; all *Z*s ≥ 0.642, all *p*s ≥ 0.521). The mean spikes and jerks across all raters for pre-tDCS on day one (baseline) ver- sus 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

*p*s ≥ 0.215; all *Z*s ≤ 1.34, all *p*s ≥ 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.

1. Discussion

Neither spike nor jerk frequency changed over the course of ﬁve tDCS sessions (between before, during, and after tDCS) or when com- paring 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 epilepsia partialis continua in POLG-related mitochondrial disease. Hence, our results are inconsistent with those of Ng et al. [[6](#_bookmark7)], 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](#_bookmark7)] 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 avail- ability. Moreover, while the patients appeared to have similar seizure frequency their genotypes were different; the patient reported by Ng and colleagues was homozygous for the c.1399GNA whereas our pa- tient was homozygous for the c.2243GNC genotype. Both patients were also on multiple, but different anticonvulsant regimens, raising the possibility that competing mechanisms modulated response to tDCS. Lastly, our case was severe, so by the time we started the interven- tion the seizures may have become refractory to both medication and tDCS treatment. We cannot rule out that cathodal stimulation else- where (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. Simi- larly, 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](#_bookmark7)]. Similarly, it remains unclear whether transcranial magnetic stimulation (TMS), another type of non-invasive brain stimulation, is an effective treatment of epilepsy [[16–18](#_bookmark7)], although there are some positive ﬁndings for epilepsia partialis continua [[19](#_bookmark9)]. 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](#_bookmark7)], ﬁnding novel treatments is highly relevant. To our knowl- edge, this is only the second documented attempt to use tDCS in mito-

chondrial disease. With one positive and one negative result, it is too early to say whether tDCS will ﬁnd a place in the treatment of mitochon- drial epilepsy, but during the early stages of any new treatment, *all* ﬁnd- ings, 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

awareness of reporting bias and replication issues in the scientiﬁc com- munity and with it a growing recognition of the relevance of negative ﬁndings. We hope that our ﬁndings contribute to a growing body of lit- erature 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.

Acknowledgments

We express our deepest gratitude to the patient and would like to give our heartfelt condolences to the bereaved family. The present research was funded by a grant from the Bergen Research Foundation (BFS2016REK03) to Marco Hirnstein and the Haukeland University Hospital.

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:](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0005) [397–406.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0005)
2. [Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. Epilepsia 2012;53:](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0010) [92–7.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0010)
3. [Tzoulis C, Tran GT, Coxhead J, Bertelsen B, Lilleng PK, Balafkan N, et al. Molecular](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0015) [pathogenesis of polymerase gamma-related neurodegeneration. Ann Neurol 2014;](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0015) [76:66–81.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0015)
4. [Hikmat O, Eichele T, Tzoulis C, Bindoff LA. Understanding the epilepsy in POLG re-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0020) [lated disease. Int J Mol Sci 2017;18:1845.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0020)
5. [Parikh S, Cohen BH, Gupta A, Lachhwani DK, Wyllie E, Kotagal P. Metabolic testing in](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0025) [the pediatric epilepsy unit. Pediatr Neurol 2008;38:191–5.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0025)
6. [Ng YS, van Ruiten H, Lai HM, Scott R, Ramesh V, Horridge K, et al. The adjunctive ap-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0030) [plication of transcranial direct current stimulation in the management of de novo re-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0030) [fractory epilepsia partialis continua in adolescent-onset POLG-related mitochondrial](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0030) [disease. Epilepsia open 2018;3:103–8.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0030)
7. [Torgrimsen E, Stensland B, Ljøstad U, Mygland Å. Epilepsi – anfallsklassiﬁsering og](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf9000)

[akuttbehandling til pasienter med epileptiske anfall. In. 22.09.2017 ed.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf9000) [helsebiblioteket.no: Folkehelseinstituttet; 2017. p. 6.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf9000)

1. [Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0035) [weak transcranial direct current stimulation. J Physiol 2000;527:633–9.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0035)
2. [Horvath JC, Forte JD, Carter O. Quantitative review ﬁnds no evidence of cognitive ef-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0040) [fects in healthy populations from single-session transcranial direct current stimula-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0040) [tion (tDCS). Brain Stimul 2015;8:535–50.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0040)
3. [Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0045) [Neuroscientist 2011;17:37–53.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0045)
4. [Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0050) [direct current stimulation: evidence based update 2016. Brain Stimul 2016;9:641–61.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0050)
5. [San-juan D, Morales-Quezada L, Garduño AJO, Alonso-Vanegas M, González-Aragón](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0055) [MF, López DAE, et al. Transcranial direct current stimulation in epilepsy. Brain Stimul](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0055) [2015;8:455–64.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0055)
6. [Lin Y, Wang Y. Neurostimulation as a promising epilepsy therapy. Epilepsia open](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0060) [2017;2:371–87.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0060)
7. [Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0065) [Evidence-based guidelines on the therapeutic use of transcranial direct current stim-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0065) [ulation (tDCS). Clin Neurophysiol 2017;128:56–92.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0065)
8. [San-Juan D, Sarmiento CI, González KM, Barraza O, Manuel J. Successful treatment of](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0070) [a drug-resistant epilepsy by long-term transcranial direct current stimulation: a case](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0070) [report. Front Neurol 2018;9:65.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0070)
9. 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.](mailto:lynn.marquardt@uib.no) [org/10.1002/14651858.CD011025.pub2](mailto:lynn.marquardt@uib.no).
10. [Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0080) [Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0080) [stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0080)
11. [Fisher R, Zhou J, Fogarty A, Joshi A, Markert M, Deutsch GK, et al. Repetitive transcra-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0085) [nial magnetic stimulation directed to a seizure focus localized by high-density EEG:](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0085) [a case report. Epilepsy Beh Case Rep 2018;10:47–53.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0085)
12. [Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. Repet-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0090) [itive transcranial magnetic stimulation in the treatment of epilepsia partialis con-](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0090) [tinua. Epilepsy Behav 2009;14:253–7.](http://refhub.elsevier.com/S2589-9864(19)30113-3/rf0090)