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Case report

Relationship of herpes simplex encephalitis and transcranial direct current stimulation–a case report

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ABSTRACT

We report a rare case of relapsing herpes simplex encephalitis in a-37-year-old patient which was previously confirmed by positive polymerase chain reaction, herpes simplex virus (HSV) type1 IgG antibodies in cerebrospinal fluid and characterized on MRI. During the first admission, he was treated with continuous acyclovir treatment for one month with clinical improvement except for residual aphasia, for which he received a course of outpatient transcranial direct current stimulation (tDCS). A constant current of 1.2 mA was applied for 20 min twice daily. After the 4th day the patient was found to be irritable and uncooperative by staff and family members. A subsequent MRI showed significant deterioration of the lesion on comparison to the first MRI which led to discontinuation of tDCS.The relatively rapid exacerbation of HSV in only a few days is unusual. Our aim is to discuss if tDCS is related to HSV relapse and in doing so highlight possible mechanisms.

1. Why is this case important?

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that delivers weak polarizing direct currents (1–2 mA) to the cortex using two electrodes placed on the scalp. During recent years, tDCS has been used for various neurologic disorders such as stroke, chronic pain, Parkinson's disease and depression [1–11]. Common side effects, though infrequent include mild tingling, fatigue, pruritus, headache, nausea and insomnia [12]. While it is well-known that herpes simplex virus reactivation may be triggered by trauma [13] (i.e., surgery and UV – radiation), to date there has been no reported association between exposure to tDCS and exacerbation of herpes simplex encephalitis (HSE).

2. Case description

A 37-year-old male with insignificant past medical history was admitted to Department of Neurology with behavioral abnormalities, confusion and amnesia for 23 days along with right arm hemiparesis, aphasia and generalized cognitive blunting for 6 days. The patient was afebrile albeit uncooperative with no nuchal rigidity. Deep tendon reflexes were normal and Babinski's sign was negative bilaterally.

His cerebrospinal fluid (CSF) demonstrated a transparent color with an opening pressure of 180 mm H_2O, leukocytes at 13/uL (lymphocytes, 80%), protein at 60 mg/dl and normal glucose concentration. CSF samples were sent for quantitative real-time polymerase chain reaction (PCR) assay [14] (ABI7500, American) which showed presence of herpes simplex virus type 1 (HSV-1) DNA (2.1×10^2 copies/mL of CSF). The CSF was positive for IgG antibodies, with no IgM antibodies seen against HSV-1 on double-antibody sandwich enzyme-linked immunosorbent assays [15] (Trinity Biotech, American). IgG antibodies against HSV-1 in serum were also positive [the ISR(immune status ratio) in CSF and serum were 6.16 and 5.52, respectively]. Brain MRI without contrast (see Fig. 1) showed abnormalities consistent with HSE. Electroencephalography (EEG) on admission showed moderate slowing

Abbreviations: HSE, herpes simplex encephalitis; HSV-1, herpes simplex virus type 1; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; tDCS, transcranial direct current stimulation; EEG, Electroencephalography; ISR, immune status ratio.

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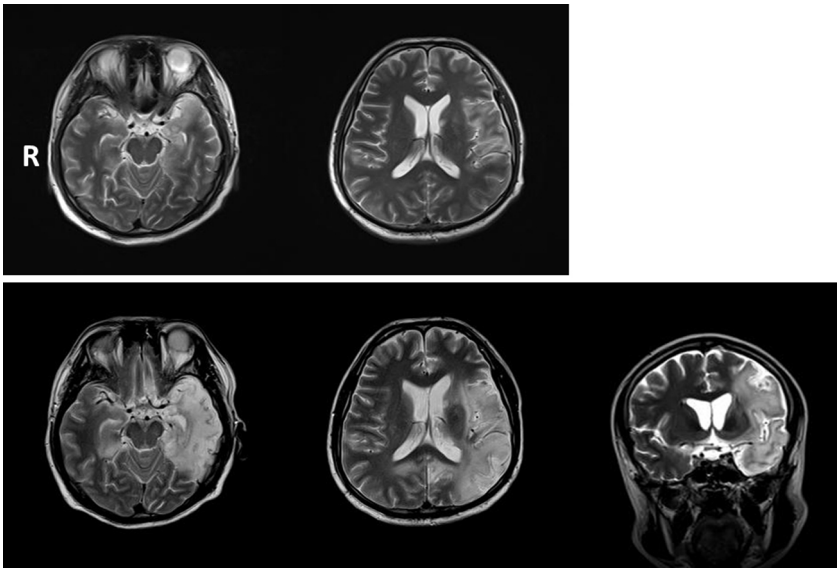

Fig. 1. Progression of HSE on T2-weighted brain MRI. Top: the lesions were mainly in left temporal lobes, frontal lobes and parietal lobes. Bottom: the lesions spread from left temporal lobes, frontal lobes, parietal lobes to left insular lobes and occipital lobes and the signals of the lesions were much higher than that of the lesions in the first MRI.

(2–6.5 Hz) in the left fronto-temporal region without epileptic discharges. Based on clinical suspicion of HSE the patient received intravenous acyclovir therapy (10 mg/kg, three times daily) for almost one month. Treatment with prednisolone was started on day 2 after admission (40 mg/day initially, tapered over 4 weeks).

The patient was clinically stabilized on day 6 and underwent a second EEG exam on day 12 which showed mild slowing (3–7 Hz) in the left fronto-temporal region without epileptic discharges. After 30 days of acyclovir treatment, the neurological picture improved and the patient was discharged on no medications with moderate cognitive and behavioral impairments manifesting as aphasia.

On the first day of discharge, after receiving informed consent he received outpatient speech-language therapy and tDCS directed to improve aphasia in the rehabilitation clinic. Direct current was applied using a saline-soaked pair of surface sponge electrodes (4.5 cm × 5.5 cm) consisting of anode and cathode and delivered by a battery-driven, constant current stimulator (IS200, Chengdu, China). A constant current of 1.2 mA was applied for 20 min, twice daily. The anode was placed over the left posterior perisylvian region and cathode over the right forehead. On day 5 of discharge, the patient was found to be irritable and uncooperative which led to discontinuation of tDCS. He was re-admitted on day 6 of discharge and was afebrile. Repeat MRI (day 2 of readmission) (see Fig. 1) showed high signal intensities in the right temporal lobe and worsening of the previously seen left lesion.

A CSF examination on day 2 of readmission showed: transparent color, opening pressure 150 mm H_2O, leukocytes at 9/uL (lymphocytes, 85%), protein at 56 mg/dL and normal glucose concentration with 8 red blood cells/mm^3, negative oligoclonal bands, elevated IgG index (2.02), positive HSV-1 PCR (1.8×10^4 copies/ml of CSF). IgG antibodies against HSV-1 in CSF and serum were also postitive (the ISR were 6.32 and 5.35, respectively). Suspecting HSE relapse, he received intravenous therapy with acyclovir (10 mg/kg, three times daily) for another 22 days. He was clinically stabilized on day 5 of readmission. A third MRI (day 10 of readmission) revealed unchanged lesions compared to the second MRI. Two repeat EEGs (4–8 h every time, including sphenoidal electrodes) showed no epileptic discharges. He was discharged on day 22 of the second hospitalization with an ability to partially cooperate with activities of daily living.

However, three months after second discharge the patient presented to the clinic with seizures. An EEG showed epileptic discharges and he was diagnosed with symptomatic epilepsy and treated appropriately with anti-epileptic medications. Other sequelae included aphasia and moderate cognitive dysfunction. He did not show any relapse during the one-year follow-up. To date, there has been no reported association between tDCS and HSE relapse.

3. Discussion

We report a rare case of HSE exacerbation in an adult patient with diagnosis being supported with positive PCR and IgG antibodies for HSV-1 and characteristic MRI images. After clinical improvement with acyclovir the patient experienced a relapse after 4 days of tDCS, with repeat MRI showing significant deterioration of lesions. We hypothesize four mechanisms linking tDCS with HSE exacerbation.

1. A low probability of Immune-mediated relapse- the MRI lesions were predominantly cortical with minor sub-cortical white matter involvement. CSF analysis showed pleocytosis and blood cells indicating necrotic intracerebral hemorrhagic lesions. After readmission, the patient demonstrated clinical improvement on antiviral therapy, making an immune mediated relapse less likely.
2. Reactivation of virus- although the patient was afebrile he demonstrated clinical symptomology that emanated from typical lesions on brain MRI, positive PCR and increased blood cells in CSF with an overall improvement on acyclovir treatment. This reinforces the mechanism of viral reactivation by an external source (tDCS) as the most likely mechanism. In most cases, viral reactivation stems from short treatment period and inadequate acyclovir dosage, both of which do not apply to our case [16–19]. This makes the scenario of the possibility of innate HSV-specific immune-deficiency less likely [20]. The possibility of prednisone suppressing host immunity leading to viral reactivation is also small for the following reasons: (1) during the first hospitalization (after 15 days of prednisone therapy), both leukocytes and lymphocyte ratio in blood were increased whereas in the second admission the ratio had normalized. In addition, antibodies (IgG,