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Transcranial Direct Current Stimulation Treatment in an Adolescent with Autism and Drug-Resistant Catatonia

Dear Editor:

Catatonia is a syndrome characterized by alterations in motor, vocal and behavioral signs, generally occurring in the context of various medical and neuropsychiatric conditions [1]. Recent evidence suggests an increased recognition of catatonia as a comorbid syndrome of Autism Spectrum Disorder (ASD), with a prevalence ranging between 12% and 17% [2]. Although the nature of the association between these two conditions is still unclear, the co-occurrence of catatonic symptoms and ASD may be due to shared abnormalities in neuronal circuitries. Indeed, alteration in several areas of the prefrontal cortex was documented to play a critical role in catatonia [3] as well as in ASD [4].

The medical treatment for catatonia in ASD recommends the use of benzodiazepines, whereas electroconvulsive therapy (ECT) is indicated when patients are unresponsive or insufficiently responsive to benzodiazepines [1,5]. Although ECT is an established treatment for severe catatonic regression, its use in children or adolescents is still a controversial issue [6]. Recently, a new therapeutic approach, aimed at modulating the cortical activity by non-invasive brain stimulation techniques, has been proposed. In adults, successful treatment of catatonic symptoms by repetitive transcranial magnetic stimulation (rTMS) [7,8] and transcranial direct current stimulation (tDCS) [9] over the frontal regions has been reported. Given growing evidence supporting the safety and tolerability of tDCS in children and adolescents, tDCS was administered over the dorsolateral prefrontal cortex to an adolescent with ASD and drug-resistant catatonia.

Case report

F is a 14-year-old girl with a diagnosis of ASD with catatonia and a mild intellectual disability (nonverbal IQ: 58). F functioned well at home, at school, and in the community by age 11; then, after the exposure to a stressful life event, she manifested a prominent behavior and affective regression. Specifically, she started to show progressive slowing movements, episodes of stupor, loss of speech, echopraxia, and inability to start movements without external prompts.

At the age of 12 y, F was hospitalized and completed all physical and medical examinations according to the clinical practice guideline for catatonia, including electroencephalogram (EEG), magnetic resonance imaging (MRI) and complete blood count, which failed to show any abnormality. However, clinical evaluation diagnosed F with catatonia.

She was treated with increasing doses of lorazepam up to 20 mg/day, associated with an intensive psychological intervention for 3 months; however, her clinical condition continued to worsen. Due

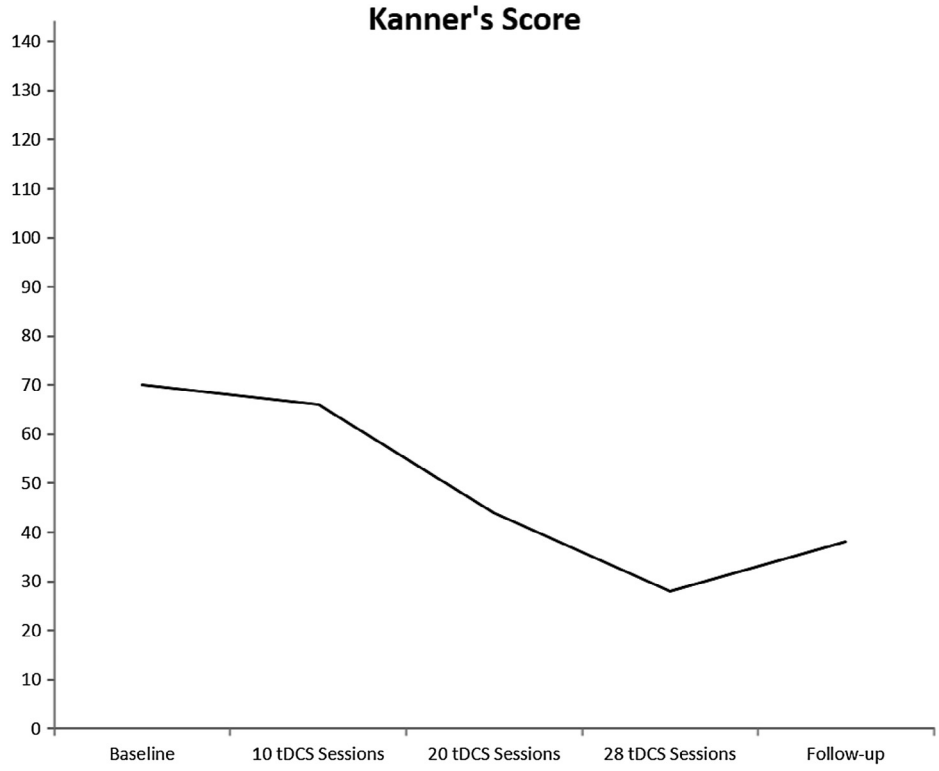

Figure 1. Time course of catatonic symptoms, as assessed by the total score of the Kanner Catatonia Rating Scale, before starting the tDCS treatment, after 10, 20 and 28 tDCS sessions and after 1-month follow-up.

to concerns related to safety of ECT, we switched to another pharmacological treatment. She started treatment with Aripiprazole (up to 25 mg/day) without any improvement; subsequently was treated with Sertraline (up to 20 mg/day) and Olanzapine (5 mg/day) and after 10 months with Lorazepam (up to 20 mg/day) together with Aripiprazole (up to 20 mg/day) and Sertraline (up to 50 mg/day) for 4 months. Given no improvement was observed, a new pharmacological treatment was proposed including Valproic Acid (up to 200 mg/day), Aripiprazole (up to 20 mg/day) and Carbamazepine (up to 600 mg/day) for 5 months. Finally, she was treated with Carbolithium (up to 600 mg/day), Quetiapine (up to 400 mg/day) and Promazine (up to 20 mg/day).

Considering the severity of her condition and after the failure of other therapies, new strategies were considered to try to obtain a clinical response, such as tDCS.

Written informed consent was obtained by the girl's parents. The intervention protocol consisted in 28 consecutive daily tDCS sessions (excluding the weekend). The cathode was positioned over the right dorsolateral prefrontal cortex and the anode over the left. A direct current of 1 mA for 20 min was applied, delivered via a pair of identical, rectangular, scalp electrodes (5×5 cm) covered with conductive rubber and saline soaked synthetic sponges. Catatonic symptoms were assessed before tDCS treatment, after 10, 20 and 28 tDCS sessions and 1 month after the end of treatment, through the Kanner Catatonia Rating Scale [10], a tool for detecting the main symptoms of catatonia in ASD.

As shown in Fig. 1, a reduction of catatonic symptoms was documented over the treatment period and at the end of treatment she showed about a 30% of symptoms reduction (total score reduced from 70 to 28). In details, symptoms as excitement, grimacing, stereotypy, rigidity, impulsivity and refusal to eat and to drink fully recovered after 28 sessions of tDCS; a mild improvement was observed for symptoms of mutism, staring, negativism and combativeness, although a slightly worsening of posturing was detected (see Table 1). She progressively improved in grasp reflex, motor planning (became able to cross lines) and waxy flexibility. Moreover, she started eating, and after 28 sessions of tDCS she was able to feed herself. The improvement was stable at 1-month follow-up evaluation.

Discussion

This is the first study documenting tDCS intervention for the treatment of catatonia in an adolescent with ASD. Shiozawa et al. [9] first used anodal tDCS over the left dorsolateral prefrontal cortex to treat a 65-year-old woman with long-term schizophrenia and catatonia. The Shiozawa et al.'s patient improved during the course of 10 daily tDCS sessions, with a direct current of 2 mA for 20 min, and fully recovered up to 4 months follow-up. The mechanism underlying this improvement has been explained as the effect of tDCS on the induction of prefrontal cortex activity, thus modulating top-down dysfunction and reversing some of the catatonic symptoms [9].

In the present case, compared to Shiozawa et al.'s study, the current was delivered at half intensity (1 mA) and the number of sessions was increased (28 instead of 10 sessions). Even with the outlined differences, our treatment protocol, being effective in reducing a 30% of F's catatonic symptoms up to 1-month follow-up, is in line with the previous findings by Shiozawa et al. [9], supporting the role of the increased activity of the left dorsolateral prefrontal cortex (by tDCS) in improving catatonic symptoms. It is important to underline that tDCS was associated with a stable dose of Promazine (20 mg/day), Quetiapine (400 mg/day) and Carbolithium (600 mg/day), and that the effects observed might reflect an association between tDCS and this medication.

Considering the improvements in F's conditions, tDCS could represent an innovative future direction for the treatment of catatonia in ASD developmental population, although randomized, controlled trials are needed to confirm its efficacy.

Table 1
Specific catatonic symptoms as assessed by the Kanner Catatonia Rating Scale. Asterisks indicate symptoms that fully recovered during the treatment course.

Symptom	Baseline	10 tDCS sessions	20 tDCS sessions	28 tDCS sessions	1 month follow-up
Excitement	6	2	2	0*	0*
Immobility	6	6	6	6	6
Stupor	2	4	2	2	4
Mutism	8	8	6	6	8
Staring	6	8	2	2	4
Posturing	4	4	6	6	6
Grimacing	6	6	2	0*	2
Stereotypy	6	4	0*	0*	0*
Mannerism	2	0	2	2	2
Rigidity	6	0*	0*	0*	0*
Flaccidity	0	0	0	0	0
Negativism	8	6	6	2	2
Refusal to eat	2	6	2	0*	0*
Refusal to drink	2	4	2	0*	0*
Impulsivity	2	2	0	0*	2
Nudism	0	2	4	0	0
Incontinence	0	0	0	0	0
Combativeness	4	4	2	2	2

F. Costanzo
D. Menghini
L. Casula
A. Amendola
L. Mazzone
G. Valeri
S. Vicari*

Department of Neuroscience, Child Neuropsychiatric Unit, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, I-00165 Rome, Italy

* Corresponding author. Department of Neuroscience, Child Neuropsychiatry Unit, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, I-00165, Rome, Italy.
Tel.: +39 06 68592735-4; fax:+39 06 68592450
E-mail address: stefano.vicari@opbg.net (S. Vicari)

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Trigeminal Nerve Stimulation (TNS) for the Treatment of Irritable Bowel Syndrome in an Elderly Patient with Major Depressive Disorder: A Case Study

Dear Editor:

Irritable Bowel Syndrome (IBS) is a functional somatic disorder with demonstrated high prevalence of depression and anxiety disorders [1]. When present, psychiatric disorders are associated with decreased heath-related quality-of-life with greater gastrointestinal symptom burdens [2]. The use of trigeminal nerve stimulation (TNS) has already been presented with interesting results for major depressive disorder (MDD) [3]. So far, studies on TNS for irritable bowel syndrome have not yet been reported.

In this report, we describe an 83-year-old female patient diagnosed with IBS according to Roma III Diagnostic Criteria for Functional Gastrointestinal Disorders for 1 year and who successfully underwent an at-home TNS intervention protocol, with amelioration of her gastrointestinal symptoms. “Ms. M.” experienced depressive and anxiety symptoms for 8 months prior to TNS treatment, commonly comorbid to IBS. Patient reported abdominal discomfort associated with important looseness of bowels and diarrhea, with three daily episodes of fecal incontinence. Her depression and anxiety symptoms included sadness, loss of interest in daily activities, insomnia, slowness of thought, apprehensiveness about minor matters, tensional headache and anxiety. Patient had received fluoxetine 40 mg/daily for 4 months, without clinical response. Dose escalation had not been possible due to tolerability limits from side effects. Her medical presentation was also notable for comorbid arterial hypertension, type II diabetes, diabetic peripheral neuropathy, osteoarthritis in both knees, and metabolic syndrome with obesity. Considering the severity of her symptoms and lack of clinical improvement with pharmacotherapy, experimental TNS was proposed. However, due to walking difficulties as a consequence of her clinical comorbidities, it was not feasible for the patient to attend the in-office TNS sessions on a 2-week daily basis, as previously employed in treatment paradigms [3–6]. Following previous safety results, with no life threatening, serious, or chronic adverse effect described so far [3], and other work with TNS administered in the home [7], at-home TNS was performed after the adequate training of the patient and a caregiver and written informed consent was provided (IRB approved).

Ten consecutive daily TNS sessions were performed with the help of the trained caregiver. Electric stimulation was performed at 120 Hz with a pulse wave duration of 250 μs, a duty cycle of 30 s on:30 s off, for 30 minutes per day. We used square auto-adhesive rubber electrodes of 25 cm^2 placed over supraorbital trigeminal branches (V1) bilaterally following our previously tested protocol [8]. To assess depressive symptoms we used the Yesavage Geriatric Depression Scale (GDS) and the 17-item Hamilton Depression Rating Scale (HDRS). For anxiety symptoms we used the Hamilton Anxiety Rating Scale (HAM-A). We also assessed cognitive functions with the Montreal Cognitive Assessment (MOCA). Cognitive functions were unaltered (21 both at baseline and at final outcome) as assessed by MOCA. Depressive and anxiety symptoms substantially improved during the 10-day treatment course and remained stable after 2-month follow-up (60 days after last day of TNS), and the patient reported significant global clinical gains (see Fig. 1). With regard to her symptoms of IBS, by the end of treatment, the patient reported two episodes of abdominal discomfort with looseness of bowels and diarrhea in the first 30 days of follow-up, with no episode of fecal incontinence. No episodes of fecal incontinence or abdominal discomfort were reported at all in second month of follow up.

The rationale behind stimulating the supraorbital branch of the trigeminal nerve is the so called “bottom up” mechanism in which the stimulation of brain stem centers would lead to modulation of activity in central brain structures, such as the amygdala and the hippocampus, with further propagation to the prefrontal cortex [4]. In fact, neuroanatomical alterations have been observed in IBS patients, with decreased gray matter density in medial prefrontal cortex, ventrolateral prefrontal cortex, and left dorsolateral prefrontal cortex [5], structures also related to depression and anxiety [6]. Shiozawa et al. (2015) have previously reported a randomized, sham-controlled trial with 40 patients with moderate or severe depressive symptoms who underwent TNS [6]. The authors reported a statistically significant difference between depressive symptoms at baseline and at the last day of stimulation ($p = 0.01$) and 1-month follow-up ($p = 0.009$) in that study. Safety issues have been previously evaluated with no severe adverse effects related to the technique [4]. Data on the use of TNS for anxiety symptoms are limited. Two previous cases of TNS for posttraumatic stress disorder and generalized anxiety disorder have been reported with

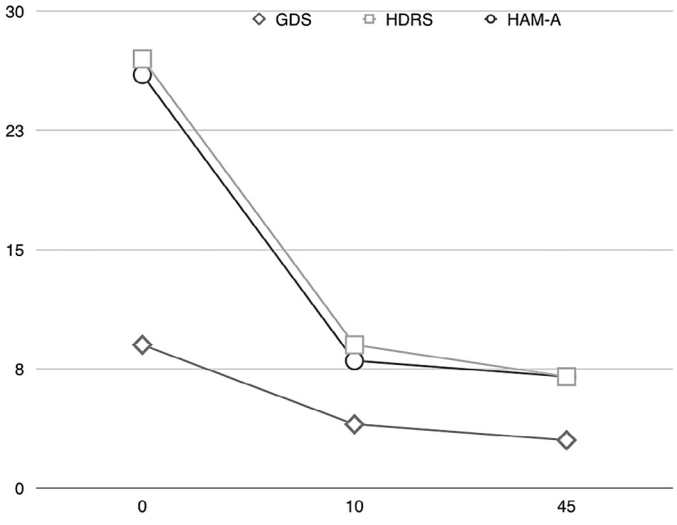

Figure 1. Geriatric Depression Scale, the Hamilton Depression Rating Scale with 17 items and Hamilton Anxiety Rating Scale at baseline, end of treatment and 1-month follow-up.

The present work was performed at the Interdisciplinary Center for Clinical Neuromodulation, Santa Casa School of Medical Sciences, São Paulo, Brazil.