Efficacity of tDCS in catatonic patients with Phelan McDermid syndrome, a case series

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To the Editor:

Phelan-McDermid syndrome (PMS) is a rare disorder characterized by deletion or mutation of the *SHANK3* gene located in the chromosomal region 22q13.33. It is associated with catatonia in 53% of cases [1]. In neurodevelopmental disorders like PMS, under-diagnosis and lack of prompt management lead to chronicity of the catatonic episode [2], a factor associated with poor therapeutic response to the two standard treatments: lorazepam and electroconvulsive therapy (ECT). Despite Expert Therapeutic Recommendations (https://pmsf.org/), effective and well-tolerated cares for chronic catatonia in PMS are still lacking. Furthermore, in PMS, benzodiazepines such as lorazepam, while reducing catatonic symptoms, may increase impulsivity, psychomotor arousal, confusion and insomnia limiting the use of this treatment [3]. ECT is also sometimes not available or contraindicated. Transcranial direct current stimulation (tDCS), an easy-to-apply noninvasive brain stimulation technique, has been shown to be effective and safe in neurodevelopmental disorders [4] and in twelve cases of catatonic patients [5]. In this letter, we present the efficacy and safety of tDCS in four cases of catatonia occurring on PMS.

The four cases are described in Table 1. The catatonic episode was diagnosed by two different clinicians according to the DSM-5 criteria. Severity was assessed by the Bush and Francis Catatonia Rating Scale (BFCRS). All participants received the same tDCS protocol that we previously reported as effective for schizophrenia and bipolar patients with catatonia [5], i.e. anode over the left dorsolateral prefrontal cortex (DLPFC, midway between F3 and FP1) and cathode over the left temporo-parietal junction (TPJ,

Table 1
Cases description. Chronic = more than 6 months. ASD = autism spectrum disorder. ID = intellectual disability.

Case/year	Age/Gender	Evolution/ Malignant features	Genetic profile	Other psychiatric diseases	Lorazepam /day	Others treatments	tDCS protocol	BFCRS (/69) before/mid/after/ discharge	BFCRS reduction mid/ after/delay
1/2020	21/M	Chronic/No	De novo mutation intron/exon junction	ASD, ID, bipolar disorder	15mg	lithium 1000mg melatonine 6mg	10 sessions 2/day	21/NA/16/10	NA/24%/52%
2/2020	23/F	Chronic/No	Del 22q13.33 55,9Kb	Dysphasia, bipolar disorder	18mg	lithium 1000mg	14 sessions 1/day	35/24/16/7	33%/54%/80%
3/2021	15/F	Chronic/No	De novo nonsens mut	ASD, ID	1mg	melatonine 3mg	20 sessions 2/day	16/10/5/NA	50%/69%/NA
4/2021	33/M	Chronic/No	Del 22q13.33 1,76Mb	ASD, ID, bipolar disorder	0mg	none	30 sessions 2/day	24/14/13/8	7%/46%/67%

Abbreviations: PMS, Phelan-McDermid syndrome; tDCS, transcranial direct current stimulation; ECT, Electroconvulsive therapy; DLPFC, Dorsolateral prefrontal cortex; TJP, Temporo-Parietal Junction; BFCRS, Bush Francis Catatonia Rating Scale.

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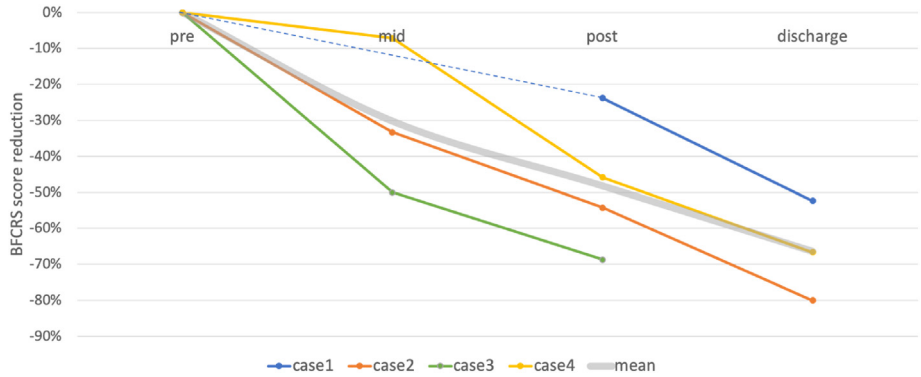

Fig. 1. BFCRS score reduction with tDCS course. Case 1 did not have a mid-treatment measure so a dotted line was added for understanding.

midway between T3 and P3). Stimulation was performed using a DC-stimulator plus (Neuroconn) with two 7 × 5 cm sponge electrodes soaked in a 0.9% saline solution. The stimulation level was set at 2 mA for 20 minutes. The sessions were conducted twice daily (separated by at least 3 hours), except for one patient who received only one session per day (case 2) (see Table 1). The present study was authorized by the local ethics committee under reference number D22-R003.

All four cases improved at each step of the tDCS course. After the last session of tDCS, the mean BFCRS reduction score was 48%, (range: 24%–69%). However, patients continued to improve after tDCS and at discharge the mean BFCRS reduction score was 66% (range: 52%–80%) (see Fig. 1). With a one-tailed Wilcoxon test, we found a statistical difference between the pre- and post-cure BFCRS scores ($W = 15$, p-value $= 0.027$) and between the pre- and discharge BFCRS score ($W = 12$, p-value $= 0.029$). Tolerance was optimal. The only adverse events described were tingling and fatigue, and vomiting which was observed in one patient after one session.

In contrast to the pediatric catatonia rating scale, the BFCRS does not attribute points to regression symptoms that frequently occur in catatonia associated with genetic syndrome, underestimating the severity. This explains why the improvement reported by family and medical teams in the patients' environments was even greater than that measured by the BFCRS. Two out of 4 cases had a clear improvement of sphincter disorders at the end of the tDCS course. In all cases, tDCS resulted in an improvement of spontaneous speech. In one case, the patient was able to speak again after months of mutism, while in another case it improved his elocution and in a third one her vocabulary. The improvement in verbal language observed in some of these patients are similar to the improvement of post-stroke aphasia induced by tDCS treatment [6]. tDCS also resulted in tranquilization in all cases, with a strong reduction of impulsivity where lorazepam failed to improve in these particular patients with chronic catatonia [3].

Haploinsufficiency of *SHANK3* appears to be associated with the risk of catatonic syndrome [1]. *SHANK3* encodes a scaffolding protein of the postsynaptic density of glutamatergic excitatory synapses and its deficiency induces NMDA receptor (NMDAR) hypofunctionality [7]. Several authors argue for hypofunctionality of the glutamatergic system in catatonia [8]; while this system seems to have a crucial role in the neuroplasticity induced by tDCS [9]. In the case of catatonia associated with PMS, the action of tDCS on the glutamatergic system and in particular on NMDARs could be particularly important for the resolution of the episode. Moreover, we observe in this case series a persistent effect over time after treatment with tDCS. The hypothesis is that tDCS leads to long-lasting long term potentiation (LTP) inducing metaplasticity lasting for weeks [10]. However, two out of 4 cases (cases 1 and 2) showed a relapse of catatonia after several months, which argue for the interest of repetitive tDCS seances as it happens with some cases responsive to ECT.

With the observational design, we cannot exclude the placebo effect or confounding factors such as drugs, even though patients have very few treatments and no change during the duration of the whole protocol. The two patients receiving lithium during the tDCS course had a very good therapeutic response. Indeed, lithium is most likely to enhance tDCS efficacy as it does with rTMS [11] even though more studies are needed to evaluate the effect of lithium on tDCS. Two patients (cases 3 and 4) received low or no dose of benzodiazepine, mainly because of paradoxical agitation. Case 3, with the lowest dose of lorazepam per day, had the best BFCRS score reduction at the end of tDCS treatment. We can hypothesize that the poorer response of patients with higher doses of lorazepam is due to the well-known reduced efficacy of tDCS under benzodiazepines [12]. Our results suggest that the optimal treatment is about 20 sessions combined with lithium and benzodiazepine discontinuation on the morning of the tDCS sessions.

Despite the need for further studies to confirm the results, tDCS seems to be a good and safe therapeutic strategy for chronic catatonia in patients with PMS.

Declaration of competing interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgment

The present study was authorized by the local ethics committee under reference number D22-R003.

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