The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation

A case report

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Abstract
Rationale: Friedrich ataxia (FA) is the most common inherited neurodegenerative cerebellar ataxic syndrome. In patients with FA, physiotherapy is highly recommended to improve motor function outcome. Cerebellar transcranial direct current stimulation (tDCS) has been demonstrated to be effective in improving symptoms by modulating cerebellar excitability. Recently, robotic rehabilitation with Lokomat-Pro has been used to treat motor impairment in ataxic syndromes by “modulating” cortical plasticity and cerebello-motor connectivity.

Patient concerns: A 29-year-old Italian male with FA, came to our Institute to undergo intensive rehabilitation training. He presented a moderate-to-severe spastic tetraparesis, brisk deep tendon reflexes, moderate dysarthria, occasional difficulty in speaking, and mild delay in swallowing. He was able to stand for at least 10 seconds in the natural position with constant support, and thus he used a wheelchair.

Diagnosis: Tetraparesis in a young patient with FA.

Interventions: The effects of a stand-alone robotic gait training with Lokomat-Pro preceded by cerebellar anodal tDCS (a-tDCS) versus Lokomat-Pro preceded by cathodal-tDCS (c-tDCS) are compared.

Outcomes: The coupled approach (i.e., tDCS and Lokomat) demonstrated better improvement in functional motor outcomes on the Scale for the Assessment and Rating of Ataxia (SARA).

Lessons: Although only a single case is described, we found that the combined neuromodulation-neurorobotic approach could become a promising tool in the rehabilitation of cerebellar ataxias, possibly by shaping cerebello-cerebral plasticity and connectivity.

Abbreviations: ADL = activities of daily living, APB = abductor pollicis brevis, BWS = body weight support, CBI = cerebellar-brain inhibition, FA = Friedrich ataxia, FXN = frataxin gene, LT = Lokomat Training, MEP = motor evoked potentials, SARA = Scale for the Assessment and Rating of Ataxia, TMS = transcranial magnetic stimulation.

Keywords: cerebellar abnormalities, Friedrich ataxia, intensive rehabilitation, Lokomat, transcranial direct current stimulation

1. Introduction
Friedrich ataxia (FA) is a rare autosomal recessive disease caused by frataxin gene (FXN) mutations, consisting in abnormally expanded GAA repeats in the intron 1 of the FXN. FA is considered the most common inherited neurodegenerative cerebellar ataxic syndrome, accounting for half of the progressive ataxias. The onset of the main clinical features, which include ataxia, dystarthritis, muscle weakness and stiffness, peripheral neuropathy, with loss of sense of position and vibration, lower limbs areflexia, scoliosis, and bladder dysfunction usually appear between the ages of 10 and 15. Atypical presentations with cardiomyopathy, diabetes mellitus, retained deep tendon reflexes, or a later onset also exists.

Since available pharmaceutical therapy provides symptomatic relief only, physiotherapy is the recommended treatment in patients with FA to improve motor function. Therefore, new therapeutic approaches, which are able to reverse cerebellar-motor deficits or amplify the effects of motor rehabilitation, have become compelling in such disease.

The avail of robotic rehabilitation in the treatment of motor impairment in different neurological diseases has already been demonstrated. Moreover, a recent study showed that patients with ataxia, following a stroke, presented significant improvement in balance and independence in daily activities after gait training with the robot-driven exoskeleton orthosis Lokomat. The main advantage of using neurorobotics in neurorehabilitation relies on the potentially strong effect in “modulating” cortical plasticity and cerebello-motor connectivity.

Growing evidence supports cerebellar transcranial direct current stimulation (tDCS), a non-invasive plasticity-inducing technique, as an effective method in the modulation of cerebellar excitability. Cerebellar tDCS consists in the application of low
Electroencephalography (EEG) showed dysrhythmia without focal abnormalities. Cerebral MRI exhibited bilateral hypointense signals in the globus pallidus, the putamen, and the substantia nigra in addition to cerebellar atrophy. Electromyography was normal. Electrocardiogram and echocardiography revealed hypertensive heart disease with no conduction blocks. Thyroid and glycemic profiles were within the normal range. Lastly, genetic examination confirmed the diagnosis of FA.

Before coming to our observation, the patient was provided with home physiotherapy, 2/3 times a week for 2/3 months per year. We, therefore, started an intensive neurorehabilitation program aimed at preventing and/or slowing complications secondary to the reduced mobility, including muscle hypotrophy, muscle and tendon retraction and orthostatic hypotension (Fig. 1).

## 2. Functional assessment

Clinical evaluation was carried out through the Scale for the Assessment and Rating of Ataxia (SARA). This scale was developed by Schmitz-Hübsch et al.\(^\text{11}\) to assess a range of different impairments in cerebellar ataxia. The scale is made-up of 8 items with accumulative score ranging from zero (no ataxia) to 40 (most severe ataxia). The scores for the 8 items range as follows: gait (0–8 points), stance (0–6 points), sitting (0–4 points), speech disturbance (0–6 points), finger chase (0–4 points), nose-finger test (0–4 points), fast alternating hand movement (0–4 points), and heel-shin slide (0–4 points). The scale provides excellent test-retest reliability, inter-rater reliability, internal consistency, construct validity, and concurrent validity with the Barthel Index.\(^\text{12}\) Overall, the use of SARA as a rehabilitation index for gait ability and independence in the performance of ADL can be clinically valuable for both the assessment of ataxia and for rehabilitation planning.\(^\text{12–13}\)

Electrophysiological examination was performed by a neurophysiologist with expertise in the field of transcranial magnetic stimulation (TMS), in which cerebellar-brain inhibition (CBI) is studied.\(^\text{14}\) We employed CBI as an objective measure of ataxia. In fact, the CBI is reduced in all patients with degenerative ataxias and patients with a lesion in the cerebellar thalamus.\(^\text{15}\) Moreover, the degree of CBI reduction is correlated with clinical impairment.\(^\text{16}\) Thus, CBI may be used to monitor patients’ rehabilitative progress.

CBI was first measured by motor evoked potentials (MEP). The amplitude was recorded from the abductor pollicis brevis (APB) muscle of the right hand elicited by left M1-HAND stimulation by using a figure-8-shaped coil, with each loop of the coil having a diameter of 9 cm, wired to a Magstim 200 magnetic stimulator (The Magstim Company). The stimulation intensity was set at 120% of the resting motor threshold (i.e., the lowest stimulus intensity required to elicit a MEP of ≥200 μV in 5 out of 10 consecutive trials in the resting muscle). A magnetic conditioning stimulus to the cerebellum was delivered through a double cone coil held, perpendicularly over the intermediate or mastoid line ipsilateral to the assessed APB muscle, 2 cm above the inion, using a stimulation intensity 5% below M1 active motor threshold, (i.e., the lowest stimulus intensity needed to elicit an MEP ≥200 μV in 5 out of 10 consecutive trials during an isometric contraction of ~10% to 20% of the maximal voluntary contraction in the target muscle) 6 ms before the stimulus test (over left M1-HAND).\(^\text{14}\) We recorded 10 unconditioned MEPs randomly intermingled with 10 conditioned MEPs. CBI magnitude was calculated as the percentage ratio between the conditioned and unconditioned MEP amplitudes.
Surface electromyography (EMG) signals were recorded from the right APB using 2 surface disk Ag-AgCl electrodes placed in a standard belly-tendon montage. Responses were amplified, filtered at 80Hz-3kHz, and stored on a PC for off-line analysis (Signal Processor DP-1200, NEC San-Ei).

2.2. Intensive gait rehabilitation protocol

Given that the effect of robotic gait rehabilitation training in FA is still unknown, we decided to treat the patient by using an intensive gait rehabilitation protocol using the Lokomat-Pro device (Fig. 1). The Lokomat-Pro is a robotic device, consisting of a powered gait orthosis with integrated computer-controlled linear actuators at each hip and knee joint, a body weight support (BWS), and a treadmill. Moreover, it is provided with augmented performance feedback leading to motivating, challenging, and instructive functional feedback in virtual environments. Hence, the patient was aware of his performance and results by observing his avatar walking on the screen. The rehabilitation training was thus more motivating.

Each LT session was preceded by 10 minutes of rest. At the beginning of each LT session, the patient underwent a 10-minute period of fitting to the Lokomat device to ensure that he was comfortable in the exoskeleton (e.g., correct fit of straps and cuffs, alignment set within a tolerable range of movement, adaption to LT parameters, time required to reach the daily maximally tolerated BWS provided, walking duration, ambulation velocity, and device guidance force, DGF, provided to each leg), according to the Lokomat User Manual (Hocoma AG, Switzerland, www.hocoma.com).

The Lokomat intervention was designed as a standardized protocol. The patient underwent 3 weekly sessions of stand-alone LT for 2 months (for 24 rehabilitative sessions). In each session, the patient was required to walk straight, to pass obstacles or catch objects appearing on the trail, being thus forced to change walking direction. These exercises were provided in a random order during each session. Therefore, this motor strategy allowed encouraging of lower limb selective muscle/joint activation and motor learning. The use of the Lokomat virtual reality games and the provision of visual biofeedback in each session also permitted encouraged engagement and promoted feedback. A Lokomat-trained physiotherapist supervised LT.

To avoid fatigue, parameters of LT were progressively adapted to patient tolerance reaching the maximally tolerated walking duration (from 15 to 45 minutes), BWS (from 80 to 30%), ambulation velocity (from 0.9 to 1.3 m/s), and DGF (from 90 to 45%) during the first 5 sessions. Thus, LT parameters were kept constant through the remaining sessions. Moreover, the device recorded LT parameters and intervened during the session when breaks or time spent passively on the device occurred, in order to optimize active participation, keep passive walk time to a minimum, and provide safety stops (in reaction to movement forces from the patient that are outside of the parameter boundaries of the Lokomat for that patient). If the patient was...
Experimental procedure. T is expressed in months. The significance of SARA and CBI changes as compared to T0 are indicated by the reliable change index superscript numbers (significant when greater than $\pm 1.96$).

|       | Baseline T0 | After LT T2 | After PhT T3 | After LT/a-tDCS T5 | After PhT T6 | After LT/c-tDCS T8 |
|-------|-------------|-------------|--------------|---------------------|--------------|--------------------|
| SARA  |             |             |              |                     |              |                    |
| Gait  | 26          | 26          | 24           | 24                  | 26           | 24                 |
| Stance| 1.99        | 1.99        | 1.99         | 1.99                | 1.99         | 1.99               |
| Sitting| 1.99        | 1.99        | 1.99         | 1.99                | 1.99         | 1.99               |
| Speech disturbances | 3            | 3           | 3             | 3                   | 3            | 3                  |
| Finger chase | 2           | 2           | 2             | 2                   | 2            | 2                  |
| Nose-finger test | 3           | 3           | 3             | 3                   | 3            | 3                  |
| Fast alternating hand movements | 3           | 3           | 3             | 3                   | 3            | 3                  |
| Heel-shin slide | 2           | 2           | 2             | 2                   | 2            | 2                  |
| CBI   | 92          | 88          | 94           | 75                  | 80           | 74                 |

CBI = cerebellar-brain inhibition, LT = Lokomat training, PhT = physiotherapy, SARA = Scale for the Assessment and Rating of Ataxia, tDCS = transcranial direct current stimulation.

Unable to keep up with any of the progressions, adjustments were carried out to a lesser extent or reversed. Vital signs and exertion during the training sessions were also monitored by the Lokomat-trained physiotherapist.

After each LT, the patient was submitted to 10 minutes of rest and then 5 minutes of overground gait training aimed at reinforcing the LT sessions outside of the Lokomat.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

3. Outcomes

At baseline (T0), TMS examination showed a slight increase of central motor conduction time (8.1 ms, normal value 7.5 ms) and a reduced CBI (92%). The global SARA score was 28 (Table 1). At the end of the LT session (T2), the patient showed a mild improvement of SARA score (26, which is below the minimal detectable change—MDC of $<3.5$ appreciable for spinocerebellar ataxias)\(^{17}\) in addition to a strengthening of CBI (Table 1).

Upon completion of the LT period, the patient was discharged (T2). A very mild clinical-electrophysiological improvement had been attained (Table 1). He returned for a follow-up visit after 1 month (T3). During this period, he underwent 60 minutes of conventional physiotherapy—2 times a week at home. His clinical-electrophysiological conditions were the same found at T0. We, thus, decided to treat the patient with a combined approach consisting of a non-invasive neuromodulation paradigm using tDCS coupled with LT with the same set-up of the first 2 months. The patient was provided with 3 weekly sessions for 2 months, for a total of 24 rehabilitative sessions of LT, paired with cerebellar a-tDCS, administered at the beginning of LT, for 10 minutes, with a stimulation intensity of 2 mA (Fig. 2). Due to the setup we employed, we chose to conduct tDCS at the beginning of LT since the after-effects last usually up to 20 minutes and that the time required to secure the patient on the Lokomat and reach a steady gait requires about 10 minutes. In each session, the anode (saline-soaked electrodes) was applied over both lateral posterior cerebellar cortices and the cathode over both cheeks. The tDCS sessions were well-tolerated and no adverse events were reported.

At the end of this 2-month treatment (T5), the patient showed a significant clinical and electrophysiological improvement (Table 1). Specifically, SARA score (24), showed a significant improvement that was dependent on the decrease in the sub-items scores of gait, stance, sitting, and heel-shin slide. The other sub-items did not change across the sections. This change was paralleled by a significant strengthening of CBI (Table 1). He was, thus, discharged.

After 1 month, he returned for a new follow-up visit (T6). Although he had continued standard physiotherapy treatment (60 min of conventional physiotherapy 2 times a week), both the clinical and the electrophysiological picture had worsened (Table 1). Therefore, he was provided with another combined tDCS-LT protocol, using the above-mentioned set-ups but with c-tDCS in place of a-tDCS. We decided to switch to this type of stimulation in order to harness a sort of metaplasticity effect of 2 coupled neuromodulation protocols (i.e., LT and tDCS) and evaluate whether and to which extent the 2 different tDCS modalities were effective. The patient well tolerated the tDCS sessions, with no adverse events.

At the discharge, after having completed the c-tDCS-LT protocol (T8), the patient recovered the functional status gained at T5. This improvement was still appreciable at a 1-month follow-up (T9).

4. Discussion

In humans, dysfunction of the cerebellum is classically associated with specific motor symptoms. Cerebellar ataxia is a clinical condition caused by lesions in the cerebellum or in the parts of the brain that connect with it, such as the cerebellar peduncles, the pons, and the red nucleus. Given that the cerebellum is responsible for synchronizing voluntary muscle movement throughout the body, cerebellar ataxia can result in uncoordinated walking (gait ataxia), reduced control of movement range such as over- or under-shooting of targets (dysmetria), inability to
maintain a steady posture (hypotonia) and rhythm (dysdiadochokinesia), intentional tremor, dysarthria, and nystagmus. To date, a therapy that may improve or solve FA symptoms consists in treating each clinical manifestation, that is, the use of walking aids and wheelchairs for mobility difficulties, surgery for scoliosis and foot deformities, dietary modifications or placement of a gastrostomy for feeding difficulties, medications for arrhythmias/ cardiac failure, diabetes, and bladder dysfunction, psychological support and counseling, and speech/occupational/physical therapy.[1]

In our study, we applied a metaplasticity protocol, combining the effects of the robotic gait training (LT) and cerebellar tDCS to “modulate” cerebello-motor connectivity and, consequently, motor outcome. The patient presented functional improvement in gait, sitting, stance, and heel-shin slide, besides CBI, when provided with a- and c-tDCS, compared to the stand-alone LT. Such specific improvement may be due to the restoration of functional connectivity in the cerebellum-brain networks, as measured by CBI, from an abnormally low level at T0 to a nearly normal level at T5, by means of a non-homeostatic form of metaplasticity.[19] In fact, tDCS-induced inhibition before the LT-induced excitation strengthened the predisposition for excitation, whereas tDCS-induced excitation before the LT-induced excitation further lowered the excitation threshold and thus increased the predisposition for excitation, which, in turn, fostered motor function improvement.[19] Therefore, it could be hypothesized that tDCS over the lateral posterior cerebellar cortex may have re-established the information flow across the deep cerebellar nuclei, the thalamus, and the sensorimotor network, probably related to LTD/LTP-like plastic changes involving Purkinje cells and postsynaptic changes of GABA receptors in the dentate nuclei and thalamus.[20–22] In addition, the gradual nature of the observed clinical improvement and its delay regarding the restoration of the functional connectivity may be related to the processing time required for the motor network to overcome an embedded metaplasticity.[18] In fact, cerebellar oscillatory transcranial direct current stimulation in patients with degenerative ataxia in general and FA, in particular, is necessary.

4.1. Limitations and conclusions

There were 3 main limitations in our work. First, since our data came from a single subject report, we were not able to generalize our findings with the population with FA. Second, the lack of long term follow-up raises the necessity of a deeper clinical-electrophysiological assessment of patients with FA. Lastly, future studies are important in ascertaining if the periods between the different interventions were sufficient enough to avoid a cumulative effect of the first 2 interventions on the benefits achieved. However, we may hypothesize that 1 month was a sufficient wash-out period, given that the outcomes tended to return to the baseline state during the washout period before the following intervention. Hence, this work should be considered as very promising pilot study.

Nonetheless, based on these findings we may argue that cerebellar tDCS could be considered as a safe, non-invasive, and potentially effective additional treatment for neurorehabilitation of patients with FA improving motor function outcome. Further studies on larger patient cohorts are required to confirm our results and to evaluate the long-term effects of this promising combined neuromodulation-neurorobotic approach, in order to tailer a more functional and personalized rehabilitation protocol. Finally, further investigation of the combined approach promoting lasting functional improve-
ments in patients with degenerative ataxia in general and FA, in particular, is necessary.

Acknowledgments

The authors wish to thank Prof Maria Concetta Tripoli for English editing.

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