Sistema Socio Sanitario
Presidio Ospedaliero di Brescia
Regione Lombardia
ASST Spedali Civili
Università degli Studi di Brescia

CLINICA NEUROLOGICA - UNIVERSITA' DEGLI STUDI DI BRESCIA
UO Neurologia 2 - AZIENDA SOCIO SANITARIA TERRITORIALE degli SPEDALI CIVILI DI BRESCIA
Direttore: Prof. Alessandro Padovani

Title of the study: "Cerebello-Spinal tDCS as Rehabilitative Intervention in Neurodegenerative Ataxia"

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EXPERIMENTAL CLINICAL PROTOCOL

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DIVISION WHERE THE RESEARCH IS PERFORMED: Clinica Neurologica, Università di Brescia, Spedali Civili di Brescia

MAIN EXPERIMENTATOR: Prof. Barbara Borroni

INTRODUCTION AND RATIONAL: Transcranial stimulation with direct currents or transcranial direct current stimulation, tDCS is a neurophysiological method of non-invasive modulation of the central nervous system excitability, which is having an increasing diffusion and an increasingly numerous spectrum of potentials
therapeutic applications such as, for example, post-stroke rehabilitation, depression and pain, already consolidated. This method, being non-invasive, low-cost and simple to carry out, has the potential to be widely used both as a research tool and as a support tool for rehabilitation treatment, as in the case of Spinocerebellar Ataxias, a group of neurodegenerative pathologies based on genetics, characterized by slowly progressive ataxia of walking, posture and limbs, associated with dysarthria and / or alteration of oculomotion, for which no treatments are currently available. This method also finds application in Cerebellar Ataxias of neurodegenerative origin, such as in Multisystem Atrophy (MSA), in Friedreich Ataxia and in other Central Nervous System pathologies with selective involvement of cerebellar structures. Indeed, a positive effect of tDCS has been demonstrated in modulating cerebellar excitability in humans (Galea 2009) with a favorable effect of cerebellar anodic stimulation by tDCS on motor learning and walking (Jayaram 2012). Based on these premises, the treatment of patients with Cerebellar Ataxias of neurodegenerative origin is proposed (for example SCA, MSA, Friedreich's Ataxia).
Transcranial magnetic stimulation (TMS) techniques have been widely used in the study of neurodegenerative diseases, particularly in Parkinson's disease and dementia due to Alzheimer's disease. Over the years, numerous transcranial magnetic stimulation protocols have been developed to obtain information on neurophysiological parameters

with the aim of investigating both the pathogenesis and the evolution of some neurodegenerative pathologies.
The study of the cerebellar-brain inhibition (CBI) allows us to investigate the physiological inhibitory activity of the cerebellar cortex on motor circuits. This stimulation protocol is evaluated through the simultaneous magnetic stimulation of the cerebellar cortex and of the motor cortex with two separate coils (Carrillo 2014; Koch 2014). Some studies have in fact highlighted an alteration of cerebello-motor connectivity, assessed by CBI protocol, in patients suffering from cerebellar ataxias of degenerative origin (Ugawa 1994; Ugawa 1997; Conde 2013; Bonnì 2014).

OBJECTIVES: The aim of the study is to evaluate the long-term effects on cognitive performance, quality of life and motor performance, in particular coordination and balance, of tDCS applied at the level of the cerebellar cortex and at the spinal level in patients suffering from cerebellar ataxias of degenerative origin to identify a possible rehabilitation protocol. The effect of tDCS on cerebello-motor connectivity will also be evaluated by CBI TMS protocol.

PROCEDURES: Patients already enrolled at the Neurological Clinic recognized as suffering from cerebellar ataxia of degenerative origin according to the current clinical criteria will be enrolled, with a disorder of motor coordination, walking or a mild to moderate balance, which are due to regular clinical controls. Patients will be divided into two groups. The first group will undergo stimulation protocol by means of tDCS, while the second group will be subjected to placebo (sham) treatment. Each session will consist of the application of ten sessions of tDCS at 2mA, at the level of the cerebellar cortex and at the spinal level (2 cm caudally at T11) for the duration of 20 min each. The effects will be evaluated before stimulation with tDCS, two weeks after treatment and three months. In particular, the effects on cognitive performance, quality of life and performance of motor coordination and balance will be evaluated by using dedicated scales. Finally, the effects on neurophysiological parameters of CBI will be evaluated by TMS.

INCLUSION / EXCLUSION CRITERIA: Patients with spino-cerebellar ataxia, Friedreich's ataxia, multisystem atrophy, sporadic ataxia in adult onset will be included. Patients affected by: i) cerebrovascular diseases, hydrocephalus, expansive intracranial processes ii) significant medical problems (eg diabetes and arterial hypertension poorly controlled; cancer in the past 5 years) will be excluded iii) major depressive disorders, bipolar disorders, schizophrenia, abuse of substances, mental retardation according to DSM-IV criteria) implanted metal objects or history of epilepsy. Patients should not suspend any ongoing therapy.

STUDY DESIGN: this is a randomized, double-blind, non-pharmacologic, placebo-controlled clinical trial, since neither patients nor those who will administer the evaluation tests will be aware of the type of treatment carried out, real-tDCS or sham (anodic tDCS: placebo tDCS = 1: 1) with cerebellar tDCS 5 days a week for 2 consecutive weeks in 40 patients with neurodegenerative ataxia.
A randomized stratification by type of pathology will be implemented, so as to balance the patients with the same pathology between the two groups (real and sham). Subsequently, a randomization in blocks will be implemented, in order to balance the quantitative asymmetry of the patients assigned to the two groups, guaranteeing a similar number of patients enrolled in the two groups, even if the trial should be interrupted early.
Patients with spinocerebellar ataxia, Friedreich's ataxia, multisystem atrophy, sporadic ataxia in adult onset will be included. Each patient will undergo a clinical evaluation (cognitive performance, quality of life and performance of motor coordination and balance), evaluation of CBI connectivity by transcranial magnetic stimulation at baseline (T0), after 2 weeks of treatment with tDCS (T1) and follow -up to 3 months (T2).
An open phase will follow and all patients will receive an anodic tDCS stimulation at the cerebellar and cathodic levels at the spinal level (5 days / week for 2 weeks) and will receive the same standardized evaluation after the 2-week treatment (T3), at the follow- up to 3 months (T4) and 6-month follow-up (T5).

END POINTS:
Primary Outcome Measures:
1. Change in the International Cooperative Ataxia Rating Scale (ICARS) Score (Baseline – 2 Weeks).
2. Change in the Scale for the Assessment and Rating of Ataxia (SARA) Score (Baseline – 2 Weeks).
3. Change in the Cerebellar cognitive affective syndrome (CCAS) Scale (Baseline – 2 Weeks).

Secondary Outcome Measures:
4. Change in the International Cooperative Ataxia Rating Scale (ICARS) Score (Baseline - 2 weeks - 3 month - 6 months - 9 months).
5. Change in the Scale for the Assessment and Rating of Ataxia (SARA) Score (Baseline - 2 weeks - 3 month - 6 months - 9 months).
6. Change in the Cerebellar cognitive affective syndrome (CCAS) Scale (Baseline - 2 weeks - 3 month - 6 months - 9 months).

7. Change in Cerebellar Brain Inhibition (CBI) Measurements (Baseline - 2 weeks - 3 month - 6 months - 9 months).
8. Change in the Short-Form Health Survey 36 (SF36) Score (Baseline - 2 weeks - 3 month - 6 months - 9 months).

STATISTICAL PLAN: we will use parametric analyzes (t tests) to compare the demographic variables (age and education) of the two groups at the baseline. A $P < 0.05$ will be considered significant. To evaluate the effect of the stimulation protocol by means of tDCS on cognitive performances, of motor coordination and balance and quality of life, at T 2-3-4-5 we will use a mixed-model ANOVA.
We performed a "power analysis" to estimate the sample size, based on some previously published studies (Benussi A, Brain Stimul, 2017) using methods similar to those applied in the study in question. The "effect size" f (V) was calculated by direct method. Taking into account the aforementioned studies an effect size equal to a partial η^2 of 0.037, equal to an "effect size" f (V) of 0.195 and, considering alpha = 0.05 and the power (1-β) = 0.80, the expected sample size is 54 subjects using a repeated measures ANOVA study. The proposed sample size of 60 subjects should be adequate to achieve the main objective of the study.

ETHICAL CONSIDERATIONS (RISK-BENEFIT): tDCS is a non-invasive, low-cost and easy-to-implement method which is having an increasing diffusion and an increasingly numerous spectrum of potential therapeutic applications such as, for example, post-stroke rehabilitation, depression and pain, already consolidated. Recently its efficacy in modulating cerebellar excitability in humans (Galea 2009) has been demonstrated with favorable effect of cerebellar anodic stimulation by tDCS on motor learning and walking (Jayaram 2012).
We therefore hypothesize that tDCS may have a positive effect on the performance of motor coordination and balance in patients with Spinocerebellar Atrophy, a group of neurodegenerative pathologies characterized by slowly progressive ataxia of walking, posture and limbs, associated with dysarthria and / or alteration of oculomotor , for which currently no treatments are available.
Literature data show that the application of the method according to the current safety guidelines (Iyer, 2005; Nitsche, 2003; Wassermann 2005) has little relevant side effects, including mild tingling sensation during or after stimulation , moderate fatigue, slight sensation of itching at the electrode application points, slight burning or pain, headache, nervousness, nausea, appearance of vesicles at the electrode application points in more rare cases.

Regarding the TMS method, it is a non-invasive brain stimulation that allows the study of neurophysiological parameters that can provide information on the pathophysiological mechanisms involved in neurodegenerative diseases.
Literature data show that the application of the method according to the current safety guidelines has little relevant side effects: a certain number of subjects participating in TMS experiments (up to 20%) suffer headaches or back pain, due to probably due to excessive muscle tension and a rigid position of the head and / or neck during the application of the TMS. These effects are temporary and in most cases do not require any treatment.
Since the TMS produces a magnetic field, people with fixed electrical stimulators (for example, cardiac stimulators, nerve stimulators, auditory implants) that would not work or would be damaged by the magnetic field cannot participate in the study. Examination is also excluded for people with particular metallic foreign bodies (such as splinters, some prostheses, screws and nails) that could move if placed inside the magnetic field. Since the effects of TMS on the developing fetus are not known, pregnant women cannot participate in the study.

DETECTION OF ADVERSE EVENTS: The Principal Investigator will promptly communicate to the Provincial Ethics Committee of the Province of Brescia any adverse event induced by the method.

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