Research Article

The Effects of Low-Frequency High-Intensity Pulsed Electromagnetic Fields (Diamagnetic Therapy) in the Treatment of Rare Diseases: A Case Series Preliminary Study

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Abstract

Rare and orphan diseases are a group of disabilities that limit the life quality in young and adult patients, affecting the socio-economic burden for the families and the community. Despite the continuous attempts in research, no standardized and effective therapies are nowadays available. Orthosis supports and rehabilitation remain the unique possibilities to alleviate these challenging conditions. Among the emerging therapeutic odds, Pulsed Electromagnetic Fields (PEMFs) express anti-inflammatory and regenerative effects on musculoskeletal and parenchymal tissues. They have also shown intriguing properties to stimulate the central and peripheral nervous system either as Transcranial Magnetic Stimulation (TMS) and Low Frequency - High-Intensity -Pulsed electromagnetic Field (LF-HI-PEMFs) or Diamagnetic Therapy (Diamagneto-therapy). This last modulates brain plasticity and is effective in pain, reducing muscles contractures and tissue oedema. Our experience refers to the use of Diamagnetic Therapy to rare and orphan diseases and reports promising functional and behavioural results, opening the possibility of therapeutic applications integrated with conventional rehabilitative methods.

Introduction

Rare and orphan diseases are a group of pathologies that affect, by definition, small numbers of patients. The classification criteria are different in the various countries as there is no unified categorization globally accepted. According to the United States Rare Diseases Act (2002), a rare disease is a condition that affects about 1: 1500 person while the European Commission defines a rare disease as any disease that affects less than 1: 2000 people and some definitions rely on the existence of proper treatments [1]. Currently, despite their low prevalence, almost 8000 existing rare diseases are esteemed to affect about 350 million patients, with a worldwide impact on healthcare and the socio-economic systems in terms of direct and indirect costs.

Recent progress in molecular biology, next-generation sequencing-based technologies, and genetics have enhanced the therapeutic choices: small-molecule drugs, protein-based therapeutics, antisense oligonucleotides, small interfering RNAs, gene and cell therapies [2] aim to trigger reparative molecular
mechanisms. Nevertheless, there is still a lack of appropriate diagnostic tools and treatments that need more specific knowledge [3]. Thus, despite the growing interest in this field, the high costs related to the rarity of the diseases and their obscure pathogenesis slow the progress in specific therapeutic tools [1].

Given the frequent involvement of the nervous system, one of the recent therapeutic attempts is biophysical stimulation, whose target is to modify the excitability and plasticity of a specific brain or peripheral area. Repetitive Transcranial magnetic stimulation (rTMS) is a non-invasive painless technique for electromagnetic stimulation of the brain and the nervous system. Appropriate guidelines for the therapeutic use of rTMS derive from experimental evidence in pain, movement disorders, stroke, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, and other conditions [4]. On its own, the electromagnetic stimulation induced by Pulsed Electromagnetic Fields (PEMFs) retains biological effects worldwide recognized to be effective in the treatment of pain and inflammation as well as in regenerative medicine, drugs delivery, and Immuno-therapy [5]. PEMFs have been successfully applied also in musculoskeletal diseases [6] to modulate the activity of various neurotransmitters and the cortical plasticity in the brain [7,8].

Due to the recurrent ineffectiveness of conventional treatments, based on previous experiences, we employed a novel technology of PEMF to treat a series of 13 patients suffering from disabling neuro-motor and behavioral conditions related to a rare disease. We used a treatment based on Low Frequency - High-Intensity Pulsed Electromagnetic Fields (LF-HI-PEMFs) named Diamagnetotherapy (Diamagnetic Therapy), with a positive result.

**Methods**

From May 2019 to April 2021, at the Cell Regeneration Medical Organization in Bogotá (Colombia), a series of 13 variously aged and suffering from different neuro-muscular rare diseases were treated with Diamagnetic Therapy. The pathologies included 2 muscular dystrophies, 1 neuroaxonal dystrophy, 6 spastic cerebral palsies, 1 hemorrhagic stroke, 1 left focal seizure, 1 Dystonia 28, 1 Glass syndrome, 1 dysgenesis of the corpus callosum, 1 hypoplasia of the cerebellar bridge, and 1 dysgenesis of the dorsum-lumbar spine.

They attended an individualized treatment of Diamagnetotherapy applying the CTU Mega 20® Plus Diamagnetic Pump machine (Periso SA – Pazzallo- Switzerland), in addition to the standard of care. Depending on the symptoms and features of the disease, the health personnel used different therapeutic protocols. This technology delivers a High Intensity – Low-Frequency Electromagnetic Field (2.2T – <50 Hz) and supplies a wide range of amplitudes of the Magnetic Field and variable electromagnetic frequencies able to match the electromagnetic properties of the body tissues, stimulating them at the cellular level [8]. The choice of the area of treatment depended on the etiopathogenesis of the disease. In pathologies of the Central Nervous System (CNS) a direct transcranial stimulation has been applied, if the Peripheral Nervous System and muscles were involved (PNS), we treated the peripheral region concerned. The main target of the treatments, as occurs for conventional technologies employing PEMF, was to stimulate the metabolic activity of the cells. Additionally, the CTU Mega 20 Plus machine offers the possibility to move diamagnetic substances such as water, ions, and proteins of the Extracellular Matrix (ECM), promoting the transmembrane flow at the cellular level. Furthermore, activates muscular apparatus, the electrical conduction of slow and fast nerve fibers, thanks to the possibility to variate, selectively, the electromagnetic frequencies and the amplitudes of the Magnetic Field, according to the proper of the biological tissues [8].

Table 1 summarizes the main characteristics of the treatment provided for each patient according to the diagnosis, the protocol and the area of treatment, the number of sessions.
| Patient   | Diagnosis                        | Treated Area             | Diamagnetic Treatment                                                                 | Sessions Number |
|-----------|----------------------------------|--------------------------|---------------------------------------------------------------------------------------|-----------------|
| Patient 1 | Limb girdle muscular dystrophy   | Gluteal-lumbar           | Pain Control                                                                           | 10              |
|           |                                  |                          | Slow Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 2 | Limb girdle muscular dystrophy   | Gluteal-lumbar           | Pain Control                                                                           | 7               |
|           |                                  |                          | Slow Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 3 | Neuroaxonal dystrophy            | Transcranial: frontoparietal region | Pain Control                                                                           | 19              |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Cell Membrane stimulation                                                              |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 4 | Spastic cerebral palsy           | Transcranial: temporal region | Pain Control                                                                           | 10              |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Cell Membrane stimulation                                                              |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 5 | Spastic cerebral palsy           | Transcranial: temporoparietal region | Pain Control                                                                           | 6               |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Cell Membrane stimulation                                                              |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 6 | Spastic cerebral palsy           | Transcranial: temporoparietal region | Pain Control                                                                           | 11              |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Cell Membrane stimulation                                                              |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 7 | Spastic cerebral palsy           | Transcranial: occipital region | Pain Control                                                                           | 6               |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Cell Membrane stimulation                                                              |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
| Patient 8 | Hemorrhagic stroke               | Transcranial: occipital region | Pain Control                                                                           | 10              |
|           |                                  |                          | Fast Nerve Fibers stimulation                                                         |                 |
|           |                                  |                          | Liquids Movement                                                                       |                 |
### Table 1: Summary of the patients treated with diagnosis, stimulated area, protocol of therapy, number of sessions.

| Patient | Pathology                   | Clinical Outcome                                                                 |
|---------|-----------------------------|-----------------------------------------------------------------------------------|
| Patient 1 | Limb girdle muscular dystrophy | Improvement in lower limbs muscle strength, less falls, possible bi-podalic standing. |
| Patient 2 | Limb girdle muscular dystrophy | Decrease in upper limbs strength.                                                   |

**Results**

Given the complexity and the diversity of these pathologies, standardized assessments of cumulative functional scores are not available to evaluate the response to treatments. Moreover, they are heterogeneous, require multiple rehabilitative therapies, and have unpredictable evolution. Then, the results of this study provide only a qualitative analysis of the clinical progression. These data are summarized in the table below (Table 2) as absence/presence of improvement compared to the starting conditions: motor and relationship difficulties typical for these diseases. Almost all subjects enjoyed motor and relational improvements. Only two patients reported, respectively, the decrease in upper limbs strength in a case of limb-girdle muscular dystrophy and only a weak improvement after the treatment of cervical spine in Dysgenesis of the anterior dorsum-lumbar spine.
Patient 3: Neuroaxonal dystrophy

- Improvement of the spontaneous motor activity and better control of hand movements. More reactive to external stimuli: smile, eye movements, more attentive to lights and sound.

Patient 4: Spastic Cerebral Palsy

- Increase of hand movements, better cephalic control, and disappearance of primary reflexes.

Patient 5: Spastic Cerebral Palsy

- More language skills, increase of movements and attention.

Patient 6: Spastic Cerebral Palsy

- Increase of motor activity, more sociable, more fluent language, and better memory.

Patient 7: Spastic Cerebral Palsy

- Increase of motor activity, starting to crawl.

Patient 8: Hemorrhagic stroke

- Better ocular response to external stimuli, more reactive to external light, colors, and objects. Increase of motor activity.

Patient 9: Dystonia

- Decrease of abdominal pain and of the tremor in lower jaw.

Patient 10: Glass syndrome

- Increase in motor activity and more attention. Possibility to introduce integrative treatments (occupational, music and hippo-therapy).

Patient 11: Dysgenesis of the Corpus Callosum

- Increase of motor activity and languages.

Patient 12: Hypoplasia of the cerebellar bridge

- General increase on motor activity

Patient 13: Dysgenesis of the anterior dorsolumbar spine

- Small, general improvement after the treatment of Cervical Spine

Table 2: Diagnosis and general clinical results for each patient at the end of the treatment.

**Discussion**

Rare diseases are severe life-threatening chronic syndromes usually beginning in childhood. The rarity, lack of validated and standardized procedures for care and rehabilitation, the limited clinical expertise, and the low number of specialist hospitals significantly complicate their management. Moreover, the pathophysiology, the natural course, and the epidemiological data are scarce and sometimes totally unavailable. These factors delay appropriate diagnose, adequate treatment, and prevention [2].

Over recent years, emerging therapeutic perspectives in molecular biology, genetic and biophysics, aim to stimulate neuroplasticity and neuromodulation in the nervous system, considering this frequent involvement. Among these technologies, biophysical stimulation induced by variable PEMFs has shown interesting perspectives in treating various pathological conditions in force of their regenerative and anti-inflammatory properties, also in the nervous system [5,6,8]. For its part, repetitive Transcranial -Magnetic stimulation (rTMS) affects cortical excitability outlasting the stimulation period and acting both in motor and non-motor brain areas, with local and nonlocal effects on cerebral activity. The TMS is a highly effective, painless way to generate suprathreshold current in the brain. The peak magnetic field strength is like that of the static field in a Magnetic Resonance Imaging (MRI) scanner (1–2 T), allowing the impulse to penetrate the brain without attenuation by the scalp or skull and generate a current according to the electromagnetic induction phenomenon.

As for Trans-Electrical Stimulation (TES), TMS stimulates axons rather than the neuron’s body since the latter have a much longer electrical time constant and higher threshold [9,10]. Furthermore, clinical studies show inhibitory and facilitatory effects to modulate nervous excitability and synaptic plasticity [11].

PEMFs exert multilevel electrochemical interactions with cell membranes and inhibit the IL-6 transcription activated by the pro-inflammatory factor IL-1α [12]. This control of inflammation mediated by the A2A and A3 Adenosine Receptors [13] would prevent and treat degenerative changes occurring in various tissues thanks to the well-known regenerative effects of PEMF [14] by the trigger of metabolic responses according to the Intensity and the Magnetic Field Gradient (T/sec) [15]. The electromagnetic induction provided by the device employed in the present study (CTU Mega 20® Plus Diamagnetic Pump Machine – Periso SA
Rare diseases are challenging to treat and are characterized by various degrees of neurologic involvement, showing impairment of motor control, coordination, language, and cognitive status [19]. Severity is often difficult to detect. In isolated agenesis of the Corpus Callosum (AAS), prenatal diagnosis detects chromosomal abnormalities, anomalies at prenatal or post-natal MRI, or the clinical evaluation. On the other hand, animal models of Corpus Callosum Dysgenesis have shown reactive heterotopic connectivity [20]. This experimental model is in accord with the belief that resting-state functional brain networks supporting cognitive control are at least partially preserved in individuals with CCD [21]. In Neuroaxonal Dystrophy, palliative treatments (i.e., botulinum toxin injections) locally reduce spasticity and dystonia, relieve pain and momentarily facilitate rehabilitation and nursing [22]. It confirms the theoretical possibility to use complementary treatments in these diseases. On the other hand, we must consider that, in addition to genetic factors, chronic inflammation would play a proper role [23].

In chronic inflammation, Reactive Oxygen Species (ROS) are in balance with the antioxidant processes in the cell. When oxidative stress prevails, inflammation misses its protective role, and ROS overproduction may lead to an exaggerated inflammatory response. In this case, the release of neurotoxic factors causes the loss of neuronal structure and function, with motor and cognitive impairment [24,25]. Considering that, at least in part, chronic inflammation contributes to neurodegeneration, starting from current data from the literature; we hypothesized to support the conventional treatments in rare diseases employing a novel therapy based on the effects of LF-HI- PEMFs or Diamagnetic Therapy. As already explained, this technology exploits the repulsive behaviour of diamagnetic materials once exposed to a High-Intensity Magnetic Field and the therapeutic effects arise from the consequent molecular acceleration induced on diamagnetic substances like water ions and proteins [8]. Like the low-intensity Magnetic Fields applications, this technology offers the possibility to treat inflammation, including neuroinflammation, but in a more selective manner stimulating the proper functions of the various tissues. For this reason, a rationale to employ this non-invasive technology, at least in support of conventional treatments, exists and is sustained by incoming clinical experiences [8,26].

Our results (Table 2) show a functional improvement in muscle applications like in Limb-Girdle Muscular Dystrophy, with a significant reduction in the number of falls and better ability to maintain the bipedalism standing. One patient reported a decrease in upper limbs strength, even if the treatment interested the gluteal and lumbar region, but this could be due to a proper progression of the disease affecting the upper limb. A general improvement in spontaneous motor activities concerned three cases of Spastic Cerebral Palsy, including better reactivity in hand movements, the maintenance of cephalic control, the disappearance of primary reflexes, and better cognitive skills. Finally, a better reactivity to external stimuli and the ongoing activity of the hand resulted in Neuro Axonal Dystrophy, and improvement of spontaneous gesture involved a case of Corpus Callosum Dysgenesis. In the case of Glass Syndrome, the motor improvement was sufficient to allow the integrated treatment with the rehabilitative program.

We recognize the weakness of this study, having not a control group necessary to validate and enforce these results. Nevertheless, the impossibility of enrolling more subjects, the characteristics of the disease from a subjective and functional point of view, practical and ethical concerns justify this choice.

**Conclusions**

Diamagnetic therapy was demonstrated to be safe, improving several clinical aspects in rare diseases, mainly from the social point of view. We know that these diseases do not change easily but worsen over time. Nevertheless, we may consider that those, though limited improvements, can positively change the quality of life in such patients and their families. Further studies are needed to assess further improvements and integration with other treatments.

**References**

1. Jia J, Shi T (2017) Towards efficiency in rare disease research: what is distinctive and important? Sci China Life Sci 60: 686-691.
2. Tambuyzer E, Vandendriessche B, Austin CP, Brooks PJ, Larsson K, et al. (2020) Therapies for rare diseases: therapeutic modalities, progress, and challenges ahead. Nat Rev Drug Discov 19: 93-111.
3. Angelis A, Tordrup D, Kanavos P (2015) Socio-economic burden of rare diseases: A systematic review of the cost of illness evidence. Health Policy 119: 964-979.
4. Roth Y, Padberg F, Zangen A (2007) Transcranial Magnetic Stimulation of Deep Brain Regions: Principles and Methods. In: Marcolin MA, Padberg F, curator. Advances in Biological Psychiatry. Basel: KARGER. 204-224.
5. Saliev T, Begimbetova D, Masoud A, Matkarimov B (2019) Biological effects of non-ionizing electromagnetic fields: Two sides of a coin. Prog Biophys Mol Biol 141: 25-36.
6. Paolucci T, Pezzi L, Centra AM, Giannandrea N, Bellomo RG, et al. (2020) Electromagnetic Field Therapy: A Rehabilitative Perspective in the Management of Musculoskeletal Pain - A Systematic Review. J Pain Res 13: 1385-1400.
7. Del Seppia C, Ghione S, Luschi P, Ossenkopp KP, Choleris E, et al. (2007) Pain perception and electromagnetic fields. Neurosci Biobehav Rev 31: 619-642.

8. Premi E, Benussi A, La Gatta A, Visconti S, Costa A, et al. (2018) Modulation of long-term potentiation-like cortical plasticity in the healthy brain with low frequency-pulsed electromagnetic fields. BMC Neurosci 19: 34.

9. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, et al. (2015) Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots, and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 126: 1071-1107.

10. Pell GS, Roth Y, Zangen A (2011) Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. Prog Neurobiol 93: 59-98.

11. Levkovitz Y, Roth Y, Harel EV, Braw Y, Sheer A, et al. (2007) A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin Neurophysiol 118: 2730-2744.

12. Tang X, Alliston T, Coughlin D, Miller S, Zhang N, et al. (2018) Dynamic imaging demonstrates that pulsed electromagnetic fields (PEMF) suppress IL-6 transcription in bovine nucleus pulposus cells. Orthop Res 35: 778-787.

13. Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, et al. (2013) Pulsed Electromagnetic Fields Increased the Anti-Inflammatory Effect of A1 and A2 Adenosine Receptors in Human T/C-28a2 Chondrocytes and hFOB 1.19 Osteoblasts. PLoS One 8: e5561.

14. Viganò M, Sansone V, d’Agostino MC, Romeo P, Orfei CP, et al. (2016) Mesenchymal stem cells as a therapeutic target of biophysical stimulation for the treatment of musculoskeletal disorders. J Orthop Surg Res 11: 163.

15. Zablotskii V, Polyakova T, Lunov O, Dejneka A (2016) How a HighGradient Magnetic Field Could Affect Cell Life. Scientific Reports 6: 37407.

16. Izzo M, Napolitano L, Coscia V, La Gatta A (2010) The role of diamagnetic pump (CTU mega 18) in the physical treatment of limbs lymphoedema. A clinical study. European Journal of Lymphology 21: 24-29.

17. Obando AFT, Velasco JM, Romeo P (2020) Variable Low-Frequency-High Intensity-Pulsed Electromagnetic Fields in the Treatment of Low Back Pain: A Case Series Report and a Review of the Literature. J Orthop Res Ther 5: 1174.

18. Obando AFT (2020) Effects of High-Intensity Pulsed Electromagnetic Fields (HI-PEMF) in Interstitial Lung Fibrosis due to the Anti-Synthetase Syndrome Associated with Sjögren’s Syndrome. A Case Report. EC Pulmonol Respir Med 9.

19. D’Antonio F, Pagani G, Familiari A, Khalil A, Sagies TL, et al. (2016) Outcomes Associated With Isolated Agenesis of the Corpus Callosum: A Meta-analysis. Pediatrics 138: e20160445.

20. Edwards TJ, Fenlon LR, Dean RJ, Bunt J, Sherr EH, et al. (2020) Altered structural connectivity networks in a mouse model of complete and partial dysgenesis of the corpus callosum. Neuroimage 217: 116868.

21. Hearne LJ, Dean RJ, Robinson GA, Richards LJ, Mattingley JB, et al. (2019) Increased cognitive complexity reveals abnormal brain network activity in individuals with corpus callosum dysgenesis. Neuroimage Clin 21: 101595.

22. Dangel T, Kmiec T, Januszaniec A, Wazny B (2020) Palliative care in 9 children with neurodegeneration with brain iron accumulation. Neurol Sci 41: 653-660.

23. Li L, Fong CY, Tay CG, Tae SK, Suzuki S, et al. (2020) Infantile neuroaxonal dystrophy in a pair of Malaysian siblings with progressive cerebellar atrophy: Description of an expanded phenotype with novel PLA2G6 variants. J Clin Neurosci 71: 289-292.

24. Chen WW, Zhang X, Huang WJ (2016) Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep 13: 3391-3396.

25. Hinarejos I, Machuca C, Sancho P, Espino C (2020) Mitochondrial Dysfunction, Oxidative Stress and Neuroinflammation in Neurodegeneration with Brain Iron Accumulation (NBIA). Antioxidants 9: 1020.

26. Izzo M, Napolitano L, Coscia V, La Gatta A, Mariani F, et al. (2010) The role of Diamagnetic Pump (CTU mega 18) in the physical treatment of Limbs Lymphoedema. A Clinical Study. The European Journal of Lymphology 21: 61.