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Pilates exercise improves the clinical and immunological profiles of patients with human T-cell lymphotropic virus 1 associated myelopathy: A pilot study

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ABSTRACT

Background: HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is an infectious chronic-inflammatory disease, which can lead to lower limb motions.
Methods: The study evaluated the effects of serial Pilates exercises on the clinical and immunological profiles of patients with HAM/TSP. Eight patients with ages ranging from 39 to 70 years old (2 males and 6 females), 2 wheelchair users and 6 with compromised gait, were evaluated. The patients were submitted to 20 Pilates sessions for 10 weeks. Data were collected at 3 time points (beginning of the study, after Pilates sessions and after 10 weeks without Pilates) and consisted of evaluations of the pain level, spasticity, motor strength, balance, mobility, functional capacity, quality of life and quantification of IFN-γ, IL-10 and IL-9 cytokines levels.
Results: After the Pilates sessions, significant improvements in pain level, static and dynamic balance, trunk control, mobility and quality of life were observed, with simultaneous and significant reductions in the serum levels of the cytokines IFN-γ and IL-10. However, after 10 weeks without Pilates, there were significant changes in terms of increasing pain and regression of mobility, with no changes in strength, spasticity, functional capacity in any of the periods of the study.
Conclusions: The results suggest that Pilates may be a promising auxiliary physical therapy for patients with HAM/TSP.

1. Introduction

HTLV-1-associated myelopathy/tropical spastic paraparesis is a neurological syndrome associated with human T-cell lymphotropic virus 1 (HTLV-1), characterized by chronic inflammation and demyelination of the central nervous system (CNS), mainly the lower thoracic spinal cord (Gessain and Gout, 1992; Iwasaki, 1990; Bangham, 2018). Neurological symptoms affect only from 3 to 5% of those infected and appear insidiously, with weakness and progressive stiffness of the lower limbs, which may be accompanied by lower back pain, urinary incontinence and leg paresthesia (Osame et al., 1986; Varandas et al., 2018).

During the development of HAM/TSP, both HTLV-1-infected T lymphocytes and activated cytotoxic T lymphocytes (CTLs) migrate to the central nervous system, causing infection of local cells, which subsequently undergo demyelination through direct action of the activated CTLs and expression of pro-inflammatory mediators (Bangham, 2000, 2018; Nagai and Jacobson, 2001; Oh and Jacobson, 2008; Matsuura et al., 2015). The detection of large numbers of $CD8^{+}$ CTLs in patients' lesions and the significant increase in the number of these cells with disease progression reinforce this theory (Nagai and Jacobson, 2001; Oh and Jacobson, 2008; Greten et al., 1998). Some authors suggest that the central nervous system lesions are also caused by the high concentrations of cytokines and toxic metalloproteinases secreted by lymphocytes chronically activated by the HTLV-1 Tax protein (Biddison et al., 1997; Champs et al., 2019).

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The clinical manifestation of HAM/TSP is marked by a scissor gait that can progress to a more severe condition in which the patient loses strength and develops spasticity in the lower limbs, associated with back pain and autonomic dysfunction (Gessain and Gout, 1992; Román and Osame, 1988; Ribas and Melo, 2002; Zaninovic, 1998).

Weakness and spasticity of the lower limbs are among the most limiting factors that impair gait functionality. For this reason, physical therapy is believed to decrease the neurological sequelae and improve patient quality of life (Lannes et al., 2006; Costa et al., 2018). One of the physical therapy methods used is Pilates exercises, which is recognized in both general orthopedic rehabilitation and therapeutic strategies for neurological disorders and chronic pain (Davis, 2006; Mostagi et al., 2015; Baillie et al., 2019; de Oliveira et al., 2019). The principles of Pilates are based on the breath awareness movement, motor control, concentration, harmonic motion or fluidity of movement, center of force and precision (Sacco et al., 2005; Ferreira et al., 2007; Netto et al., 2008; Mattos, 2011).

Borges et al. observed that Pilates exercises alleviate lower back pain and quality of life of patients with HAM/TSP (Borges et al., 2014). In addition to these benefits, Pilates also improves the balance, mobility and muscle strength of wheelchair patients with multiple sclerosis (Van Der Linden et al., 2014; Guclu-Gunduz et al., 2014).

It is possible to speculate on the role of Pilates in improving the immunological response. The method may decrease fat masses by increasing lean body mass (Fourie et al., 2013). In addition, an increase of adipose tissue is directly linked to a predisposition to inflammation through the increased release of adipokines (proinflammatory cytokines) by adipocytes (Lucas et al., 2009). With this pilot study we aim to evaluate the effects of Pilates exercises on the clinical and immunological profiles of patients with HAM/TSP.

2. Method

2.1. Participants and data collection

A group of 13 HTLV-1 infected persons with a clinical diagnosis of HAM/TSP were initially included in the study. The group represented all patients with clinical diagnosis of HAM/TSP who were registered and attended at the Laboratory of Functional Rehabilitation Studies (LAERF) at the Federal University of Pará (UFPA). The inclusion criteria selected individuals of both sexes, aged over 18 years old, with confirmed HTLV-1 infection and clinical diagnosis of HAM/TSP. Individuals who were under 18 years old or who had any disease that prevented treatment by Pilates exercises or presenting any disease that could influence the patients' symptoms and unrelated to HAM/TSP, such as bone tuberculosis and the occurrence of pain caused by disc herniation or fibromyalgia, were excluded. Due to health and/or personal problems five patients discontinued the intervention. The following flow chart (Fig. 1), according to the guidelines of the CONSORT statement, illustrates the included and excluded subjects during the research process.

Information was collected through physical examination and blood collection at three points: evaluations #1 (1st Ev – at the beginning of the study), #2 (2nd Ev - after 10 weeks of Pilates treatment) and #3 (3rd Ev - after 10 weeks without Pilates treatment).

The data for the immunological evaluation were collected at two points: evaluation #1 and #2. Patients were under medication for spasticity for the whole period of the study (Baclofeno®, Novartis Biosciences S.A., Taboão da Serra, São Paulo state, Brazil).

Blood samples were obtained with a vacuum collection system, in 5-mL tubes containing EDTA as anticoagulant, to obtain plasma and cells and were sent to the Laboratory of Virology of the Institute of Biological Sciences - ICB of the Federal University of Pará - UFPA to perform pro- and anti-inflammatory cytokines quantification tests. Plasma and leukocyte (peripheral blood mononuclear cell - PBMC) aliquots were stored at -70 °C until use.

A form from the LAERF was used during the physical therapy consultation, which included the identification of the clinical manifestations and functional disability resulting from HAM/TSP, along with the evolution of the symptoms and the treatments already performed.

2.2. Pilates procedure

This study was submitted to and approved by the Research Ethics Committee of the Health Sciences Institute of the Federal University of Pará (#1.455.649) and Brazilian Registry of Clinical Trials (REBEC) of the Health Ministry of Brazil (#RBR-2ctm5q). The individuals who agreed to participate in the study signed an Informed Consent Form (ICF) in accordance with the Declaration of Helsinki.

The protocol consisted of a Pilates physical intervention, performed twice a week, for ten weeks, with the duration of approximately 50 min, reaching 20 sessions in a mean period of 2.5 months.

The wheelchair and gait patient groups performed exercises to strengthen the pelvic floor and core muscles, always associated with breathing, stabilization of the spine and hip. Patients with walking capacity, active stretching of the anterior and posterior chain (spine stretch), stretching of the lumbar square (mermaid) and the rotating spinal muscles (the opining) was performed, always with spinal mobility and rotational movements. It also included strengthening exercise of the abdominal muscle (hundred, the roll up, the roll down, down stretch), the extensors of the spine (the planks, lost in space), the lower limbs (one leg circle, prances, calf raises, legs footwork, the shoulder bridge), the upper limbs (supine arms springs), but always with the intention of stabilizing the trunk, and balance training with one of the lower limbs on a stable surface (solo) and the other on an unstable base (ball or roll). The difference between the walking and wheelchair patients' exercises was that some exercises were adapted to become active assisted, and the bipedation balance exercise for those with gait was replaced by a ball-controlled trunk control exercise. Each exercise was performed with its variations (facilitation or progression of movement) in a slow and controlled manner, which consisted of 2 sets of 8 repetitions.

The physical therapy evaluations examined (i) the level of pain through the Visual Analogue Scale (VAS), (ii) muscle tone (using the Modified Ashworth Scale), (iii) muscle strength of the lower limbs (Motor Force Scale) and (iv) trunk balance (Modified Trunk Impairment Scale (TIS) for wheelchair users. The patients who presented gait, the Balance and Gait Assessment Scales (Tinetti and Timed Up and Go) were applied. In addition, the Functional Independence Measure (FIM) and quality of life were assessed by the Quality of Life Questionnaire (SF-36). Manual therapeutic resources were used to improve the strength, muscle tone, trunk balance and functional capacity of the patient, in addition to the use of devices such as Reformer, Cadillac, Chair and Ladder Barrel and accessories such as Swiss Balls of several sizes, elastic bands of various strengths, a circle flex and a proprioception disc for stretching and for strengthening of the lower limbs and trunk.

VAS quantifies the intensity of pain and ranges from 0 (no pain) to 10 (maximum pain), as described in the literature (Franca and Senna-Fernandes, 2004) the Modified Ashworth scale, quantifies muscle tone during a passive limb solicitation, using a scale ranging from 0 (normal tonus) to 5 (lower limb parts rigid in flexion or

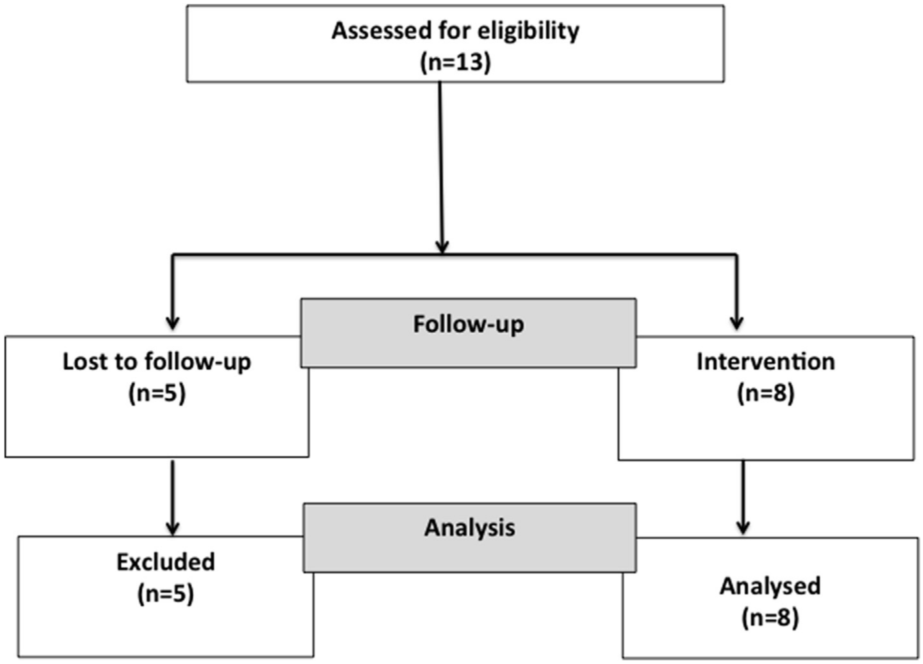

Fig. 1. Flowchart of the included and excluded subjects during the research process.

extension (Teixeira and Fonnoff, 2004), and the Motor Force scale (Jambeiro et al., 2008), ranging from 0 (total incapacity of movement - paralysis) to 5 (full normality). Spasticity and muscle strength were assessed by movements of the hip (flexion, extension, adduction, abduction, internal and external rotation), knees (flexion and extension) and ankle (plantar flexion and dorsiflexion).

The Tinetti scale assesses the risk of falling through the analysis of balance and gait, with scores ranging from <19 (high risk) to >24 (low risk) (Mata et al., 2008); the Timed Up and Go test quantifies the functional mobility by measuring the time to perform the test, in a time period from <10 s (normal) to ≥30 s (impaired) (Podsiadlo and Richardson, 1991); and the trunk impairment scale which, assesses the quantitative aspects of trunk function for wheelchair users regarding the vertical perception of the trunk, the impairment of verticality in the sitting position and the impairment of abdominal muscle strength (Lima et al., 2008).

The FIM has shown to be a reliable, valid, accurate, practical and easy way to evaluate the patients through interviews and observation during clinical care regarding the level of functional dependence, considering self-care, sphincter control, mobility, locomotion, communication and social cognition (Ciconelli et al., 1999); the SF-36 assesses the individuals' perception of their own health status and considers the most representative health aspects (pain, functional capacity, vitality, mental health, general health status, social aspects and limitations due to their physical and emotional aspects (Riberto et al., 2004).

2.3. Quantification of serum cytokines

The serum levels of cytokines IL-9, IL-10 and IFN-γ were quantified at the Laboratory of Virology at ICB/UFPA using the Human Th1/Th2/Th17 Magnetic 8-Plex Panel kit (Novex-Life Technologies, Foster City, California, USA) and reading in the LUMINEX 200 system, following the manufacturer's protocols.

2.4. Statistical analysis

Comparison of the clinical evaluations measured by the VAS, Modified Ashworth Scale, Motor Force Scale, Tinetti and Timed Up and Go test, FIM and SF-36 questionnaire, along with the cytokine quantifications, was performed through the Wilcoxon and paired Student's T-tests using the BioEstat 5.3v program (Ayres et al., 2011).

3. Results

Initially, 13 HAM/TSP patients were included in the study, but only 8 completed treatment due to health and/or personal problems. Of these, 2 patients were wheelchair users, and 6 walked (with or without assistance). The patients showed a mean age of 54.28 years old; 75% ($n = 6$) were females, and 25% ($n = 2$) males. The patients' complaints during the initial evaluation included gait alteration, weakness in the lower limbs and low back pain.

Significant differences were obtained in reduction of the patients' pain at the end of the Pilates sessions and an increase of the pain after 10 weeks without Pilates treatment (Fig. 2A). The patients reported a significant increase in lower back pain, but still below that observed at the beginning of the study. The two wheelchair patients showed a trunk balance increase of 1° after the Pilates sessions in both the perception of trunk verticality and the impairment of verticality in the sitting position compared with the initial evaluation; however, the same degree was maintained after 10 weeks without Pilates. Only one patient showed an increase, of 1°, after the Pilates sessions in regard of the impairment of abdominal muscle strength, and there was no change in the third evaluation after 10 weeks without Pilates (data not shown).

Patients showed significant differences in static and dynamic balance at the end of the Pilates treatment compared with the initial evaluation, but there was no significant difference after 10

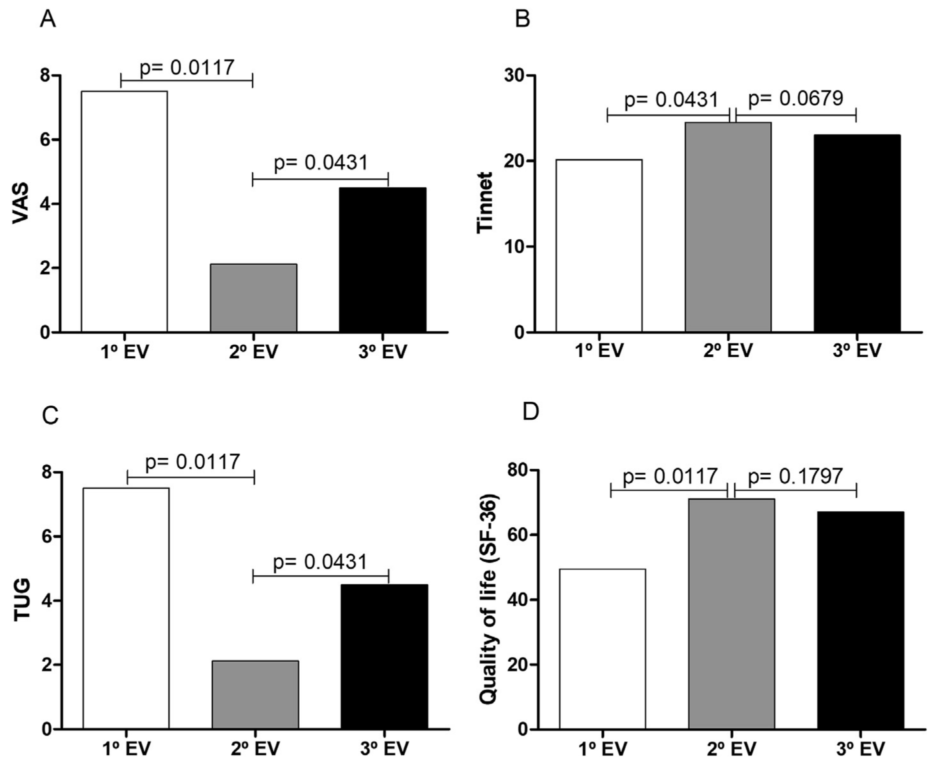

Fig. 2. (A) Evaluation of pain at the beginning of the study (1st Ev), 10 weeks after Pilates treatment (2nd Ev) and 10 weeks after the period without Pilates treatment (3rd Ev) through the Visual Analog Scale. (B) Evaluation of static and dynamic balance in walking patients at 1st Ev, 2nd Ev and 3rd Ev through the Tinetti Scale. (C) Evaluation of the mobility in walking patients at 1st Ev, 2nd Ev and 3rd Ev through the Timed Up and Go test. (D) Evaluation of the quality of life (pain), at 1st Ev, 2nd Ev and 3rd Ev through the Quality of Life Questionnaire SF-36. Wilcoxon test.

weeks without Pilates treatment (see Fig. 1B). At the end of the Pilates treatment, there was a significant reduction in the time to perform the mobility test and an increase in that time after 10 weeks without Pilates treatment (Fig. 2C). The quality of life evaluation showed an improvement at the end of the Pilates treatment, with a significant difference in the patients' pain; however, no difference was observed after 10 weeks without Pilates treatment (Fig. 2D). The analyses of the other quality of life items (functional capacity, limitations by physical aspects, limitations by emotional aspects, vitality, mental health, general health status and social aspects), spasticity, strength and functional capacity did not show significant changes at any time (data not shown).

IL-10 was measured in seven patients; IFN-γ and IL-9 were measured in five of them, because of the technical restriction of the assay detection which was deficient to detect below a certain limit. Serum levels of IFN-γ and IL-10 were significantly decreased at the end of the Pilates sessions, but not that of IL-9, as compared with the initial evaluation (Fig. 3). The comparison of the cytokine profiles with the pain level at the end of the Pilates sessions significant decrease was observed in pain level and IFN-γ and IL-10, but no difference was seen for IL-9, compared with the initial evaluation (Fig. 4).

4. Discussion

Among HAM/TSP patients, the most common symptoms are the change in gait pattern, urinary symptoms and pain, and these aspects are directly related to the impairment of their quality of life. However, the regular practice of physical activity significantly improves this clinical manifestation (Martins et al., 2012).

In this pilot study, the evaluation of the pain level in the lower back region of patients with HAM/TSP showed a significant improvement after Pilates treatment, possibly because of the strengthening of the abdominal muscles, mainly the deeper ones, such as the transversus abdominis, multifidus, diaphragm and pelvic floor, along with improvements in lumbo-pelvic motor control. Low back pain affected approximately 75.5% of patients with HAM/TSP, a symptom aggravated by physical movement and exertion (Tavares et al., 2010). However, strengthening the muscles of the abdominal region, such as the transversus abdominis (Moon et al., 2015; Herrington and Davies, 2005; Lim et al., 2016; Giacomini et al., 2016), multifidus (Lim et al., 2016), rectus abdominis (Dorado et al., 2012), internal oblique (Moon et al., 2015; Herrington and Davies, 2005; Lim et al., 2016; Giacomini et al., 2016), external oblique diaphragm (Giacomini et al., 2016) and pelvic floor (Lim et al., 2016), lead to improvement of the lumbo-pelvic motor control and, improvement of lower back pain (Herrington and Davies, 2005).

A study with 22 HAM/TSP patients found that pain and quality of life were improved after 30 sessions of the Pilates method (Borges et al., 2014). In our study, 10 weeks after the end of the Pilates sessions, the patients complained a significant increase in lower back pain, but still below that observed at the beginning of the study. This change may have occurred due to Pilates be a method that strengthens the deep abdominal muscles. However, the return of the pain may have been because of the need for more than 20 sessions to maintain the strengthening of the abdominal muscles.

Although this result did not show a prolonged effect on pain reduction, an increase in the activation and thickness of the deep abdominal muscles (transversus abdominis and the internal oblique) was observed among people who practiced Pilates and resistance exercises in relation to sedentary individuals (Moon et al., 2015). Therefore, we believe that a longer evaluation period could

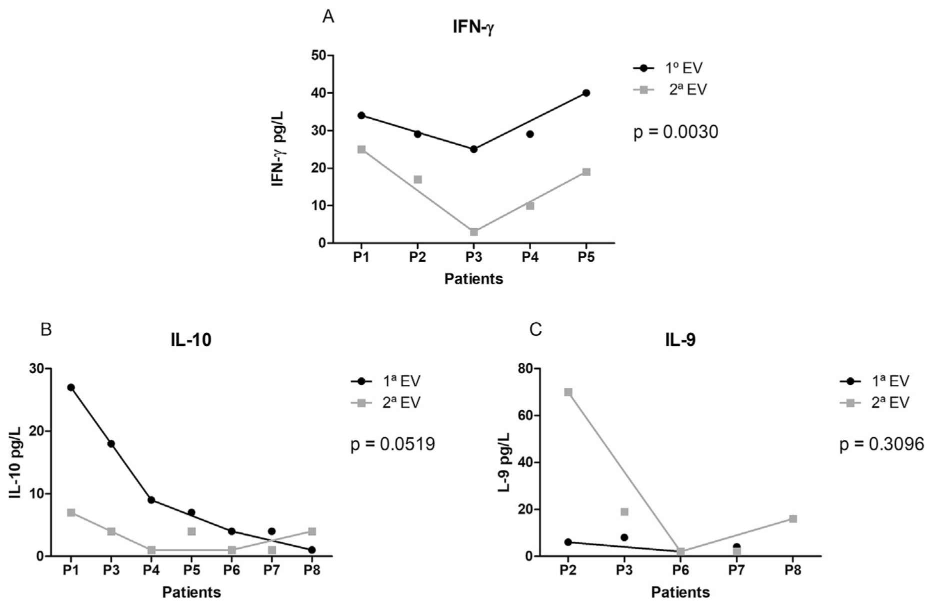

Fig. 3. Quantitative analysis of serum cytokine levels at 1st Ev and 2nd Ev: (A) IFN-γ, (B) IL-10 and (C) IL-9. Paired Student's t-test (IFN-γ, IL-9), Wilcoxon test (IL-10).

improve the understanding of the role of the Pilates sessions.

Regarding the trunk impairment, there was improvement in the two wheelchair patients concerning the perception of trunk verticality, and only one improved in vertical impairment in the sitting position and the abdominal muscle strength, possibly due to improvements in abdominal strength, posture and trunk control, similar result was found in wheelchair patient with multiple sclerosis, after 12 weeks of the Pilates method (Van Der Linden et al., 2014).

In the evaluation of the static and dynamic balance of patients who were able to walk, a significant improvement occurred after Pilates and was maintained after 10 weeks without Pilates, suggesting improvements in muscle strength, motor control and posture. Similar results were observed in the static and dynamic balance in patients with multiple sclerosis, stroke and multiple sclerosis after the Pilates excercises (Lim et al., 2016; Tarakci et al., 2013; Kalron et al., 2016).

There was a significant improvement in mobility of subjects after treatment with Pilates, possibly due to improvements in pain and dynamic balance (Dorado et al., 2012). However, after 10 weeks without Pilates, there was a significant worsening. This may be associated with the increase in lower back pain reported during this period; probability due to the gait capacity is affected by: pain in the lower back region, strength, age (mean age of 40 years), duration of disease, asymmetry at the onset of symptoms and spasticity (Franzoi and Araújo, 2007).

The quality of life showed a significant improvement after the Pilates treatment when using the SF-36 questionnaire in the evaluation of pain, showing a probable relationship between the improvement of life quality and the decrease in pain, but no significant changes were observed after 10 weeks without Pilates, demonstrating that it was not affected, despite the increase in the pain level as measured by the VAS. Pilates exercises have shown to improve patient quality by decreasing nonspecific chronic low back pain and increasing functional capacity and vitality (Natour et al., 2015). Spasticity, strength and functional capacity did not change at any time, demonstrating that although HAM/TSP is a progressive disease, Pilates therapy may contribute to the management of the progression of the disease.

Plasma levels of IFN-γ showed a significant decrease after Pilates exercises when compared to the initial evaluation, possibly as a direct effect of physical activity in the production of proinflammatory cytokines such as IFN-γ.

Patients with a predisposition to acute myocardial infarction who underwent a cycle of 6 months of physical activity showed a decrease in the level of proinflammatory cytokines (IFN-γ and TNF-α), and increase of IL-10, followed by tumor necrosis factor (TGF-β) and IL-4 (Noz et al., 2019; Smith et al., 1999). The decrease of IFN-γ, through physical activity, may contribute to delaying the progression of the disease as there is a direct association of high levels of IFN-γ with the need for gait assistance (Dias et al., 2016).

In the present study IL-10 levels was decreased after Pilates, probably due to a homeostatic response followed by the reduction of IFN-γ. Although the present study did not included information on proviral load, it has been shown that asymptomatic patients with low viral load appeared to have a regulatory mechanism with the balance of IL-10 and IFN-γ levels, whereas symptomatic patients with high proviral load and HAM/TSP showed an IFN-γ concentration higher than the IL-10 concentration (Espíndola et al., 2015), indicating that this imbalance in the immunological response may contribute to disease progression.

IL-9 levels did not show significant change after Pilates. The decrease of IFN-γ was associated with the increase in IL-9 in the presence of IL-2, TGF-β and IL-4 (Schmitt et al., 1994). It was observed that IL-9 increase concomitant with a decrease in IL-5, IL-7 and IFN-γ plasma levels in patients with chronic heart failure, showing that when the increase is accompanied by a high IL-10 level and the consequent tissue inflammation (Cappuzzello et al., 2011).

The comparison of cytokine levels with the levels of pain following the Pilates exercises showed significant decrease in pain and cytokines IFN-γ and IL-10 levels; but not to cytokine IL-9. Thus, suggesting that the improvement of the symptoms may be associated with reducing tissue inflammation and, consequently, decrease of lower back pain, once CNS injury is caused by the release of proinflammatory cytokines, such as IFN-γ and TNF-α, which cause damage and dysfunction death of the CNS (Selmaj et al., 1991; Araújo and Silva, 2006; Gonçalves et al., 2008).

The main limitation of the present study was the loss of patients during the research, for reasons such as the absence of

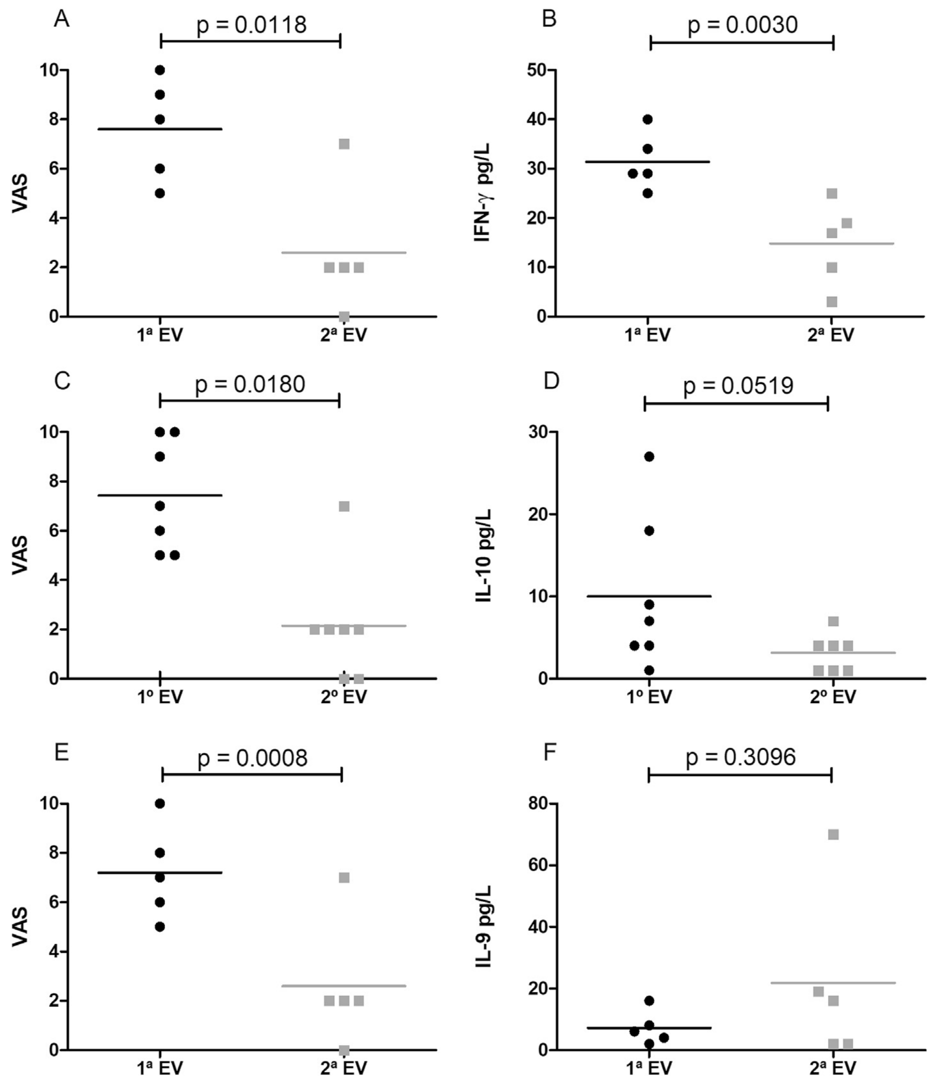

Fig. 4. Analysis of cytokine serum levels in relation to the level of pain, using the Visual Analogue Scale, at 1st Ev and 2nd Ev: (A) VAS, (B) IFN-γ, (C) VAS, (D) IL-10, (E) VAS and (F) IL-9. Paired Student's t-test (VAS, IFN-γ, IL-9), Wilcoxon test (IL-10).

transportation and/or a chaperone and the presence of personal and health problems, which hindered the displacement to the place where Pilates exercises were performed. However, the results presented here suggest that Pilates is beneficial to patients with HAM/TSP, emphasizing the importance of implementing complementary therapeutic methods and that Pilates may be another auxiliary treatment to be introduced into physical therapy programs for patients with this debilitating neurodegenerative disease which, so far, has no cure. However, further studies are needed to confirm the information herein observed.

5. Conclusion

The results suggest that the practice of Pilates exercises may be a promising auxiliary treatment for HAM/TSP, favoring: the decrease in pain, improvements in the quality of life, trunk balance in wheelchair users, mobility and static and dynamic balance of patients with impaired gait. Furthermore, it provided strength maintenance, reduced the progression of lower limb spasticity, maintained functional capacity, as well as, seems to result in changes in the serum levels of the cytokines IFN-γ and IL-10, probably as a form of homeostatic response, indicating a decrease in inflammation.

Finally, considering that the present investigation was a pilot study, the number of HAM/TSP carriers investigated may not have been the optimal one, particularly because the prevalence of infection is not high, so we suggest that a continuous evaluation with a larger sample size is important to confirm the results.

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Declaration of competing interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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