European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

ROLE OF FOCUSED TRANSCUTANEOUS NEUROMODULATION IN THE ASSESSMENT AND TREATMENT OF MYOFASCIAL PAIN SYNDROME: A PILOT STUDY

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ABSTRACT

Myofascial pain syndrome (MPS) is an extremely widespread and insidious pathology characterized by strong musculoskeletal pain that is associated with the presence of myofascial trigger points. Its etiopathogenesis is very complex and, among the main symptoms of the disorder, there is pain and the modification of the postural and biomechanical settings of the affected patients. Multiple therapeutic approaches have been successfully proposed over time for MPS, at a pharmacological, manual, instrumental, and physical level. Among the most interesting instrumental approaches, there is neuromodulation (NM), which in most cases is invasively performed through percutaneous modality. Therefore, to bypass the invasiveness of percutaneous NM, we performed a study to evaluate the short-term effectiveness of a new treatment modality using Focused Transcutaneous Neuromodulation (FTNM) which is designed to be less invasive and more tolerable than percutaneous NM, for patients suffering from MPS. 27 patients (average age of 56 ± 15.1 years) were selected and underwent a single session of FTNM applied according to the Bio-Physico-Metric approach, consisting in the research and treatment of the most dysfunctional myofascial trigger points (MTrPs) in the patient's body through a bioimpedance investigation. Patients were assessed with the Numeric Pain Rating Scale (NPRS) and the evaluation of the Postural Biometric Index (PBI), calculated by a specific baropodometric device, before (T0) and after (T1) the treatment session. At the end of the study, it was possible to observe a significant improvement both in pain (-37.3%) and in the degree of postural dysfunction (-25.1%). Therefore, we can state that FTNM applied with Bio-Physico-Metric modality is a promising and effective therapeutic approach in controlling the symptoms associated with MPS.

KEYWORDS: *myofascial pain syndrome, chronic pain, trigger point, electrotherapy, transcutaneous electrical stimulation, rehabilitation*

Received: 01 August, 2024
Accepted: 14 October, 2024

2974-6345 (2024)

INTRODUCTION

Myofascial pain syndrome (MPS) is one of the most common and frequent causes of pain, reaching peak prevalence levels in the general population of up to 85% (1). In fact, it is estimated that up to 95% of the general population has received a diagnosis of MPS at least once in their life in the presence of musculoskeletal pain (1). This syndrome is capable of causing a multitude of musculoskeletal problems of various kinds, particularly in terms of neck pain and low back pain, but also at the level of the pelvis and limbs. In general, MPS is characterized by the presence of diffuse, local, and radiating musculoskeletal pain, associated with the presence of Myofascial Trigger Points (MTrPs) (1,2). According to the universally accepted definition given by Simons and Travel, a MTrP can be defined as "a hyperirritable spot in skeletal muscle that is associated with a hypersensitive palpable nodule in a taut band. The spot is painful on manual compression and can give rise to characteristic referred pain, referred tenderness, motor dysfunction, and autonomic phenomena" (3). Although the genesis and chronicity processes of MPS are still unclear and much debated in the literature, it is widely probable that the pain perception of affected patients is characterized by phenomena of centralization of pain due to localized structural changes due to MTrPs and aberrations in the mechanism of nervous input-output at the peripheral nervous level (4). In particular, in the presence of MTrPs causing MPS, it is possible to witness a dysregulation of the reflex central nervous control mechanisms with respect to the responses to visceral and somatic afferents that characterize the patient with MPS (5). Since these somatic and visceral reflex control mechanisms are very responsive to external stimuli of both aberrant and rebalancing types, it is possible to identify MTrPs, intended as the maximum structural expression of these somatic alterations, as an ideal therapeutic target in patients affected by MPS (6-9).

It should be emphasized that MTrPs, which are characterized by locoregionality and well-defined referred pain patterns, differ from the so-called tender points, which are areas of soft tissue that are not exclusively muscular and are characterized by widespread tension and typical of generalized syndromes such as fibromyalgia (10).

A valid approach to identify and adequately treat MTrPs would appear to be the Bio-Physico-Metric one (11,12). This approach is based on the identification of the so-called key MTrPs, i.e. those trigger points that are able to determine the appearance of pain and functional limitation both in their anatomical location and in areas distant from them, according to a hierarchical development scheme of satellite MTrPs (11,12). The key MTrPs can be identified by impedance measurement, palpation, and investigation (using specific questionnaires) and their deactivation can contribute to quickly and lastingly rebalancing the patient's musculoskeletal health status (11,12).

Once the MTrPs responsible for the patient's pathological condition have been identified, especially in the presence of MPS, these can be stimulated in different ways to try to bring the muscle tissue back to a state of balance. The therapeutic approach to MTrPs can be based on manual therapy, instrumental treatments, and pharmacological approaches (4).

Among the most interesting instrumental approaches for MTrPs and musculoskeletal pain in general is certainly neuromodulation (NM). NM is a therapy based on the use of a focused current aimed at inducing neuro-metabolic stimulation to the target area that can modulate the information flow at the level of the affected neuronal circuit (13). In particular, the application of NM seems to exploit a phenomenon of modulation of synaptic activity at the nervous level, producing a controlled release of neurochemical substances capable of inducing a series of therapeutic activities at the nervous level (13). This mechanism would seem to lead to evident effects, especially in the control of perceived local and radiated pain, through mechanisms connected to the gate control theory (14,15) and the modulation of pain perception at the level of the central nervous system (14,16). Although these mechanisms have not yet been fully clarified to date, NM in all its forms (percutaneous, transcutaneous, implantological, etc.) appears to be one of the most interesting and effective non-pharmacological therapeutic techniques for the modulation of pain, particularly in the presence of MPS, MTrPs, and musculoskeletal dysfunctions in general (17-19).

Therefore, considering the widespread use of NM techniques for musculoskeletal pain control in the rehabilitation field, we decided to study the effectiveness of Focused Transcutaneous Neuromodulation (FTNM) applied with a Bio-Physical-Metric approach on MPS patients.

MATERIALS AND METHODS

The present research pilot study was carried out at the Ce.Fi.R.R. Gemelli Molise Point (Termoli, Italy) from January to March of 2023.

The rehabilitation protocol to which the patients were subjected is safe, as all the procedures applied to patients comply with the safety regulations in force in the country where the study was carried out; the protocol is accessible to all patients who do not highlight specific contraindications to the initial clinical evaluation that is necessary for all patients who access

the facility where the study was carried out. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained at enrolment from participants who were willing and able. By virtue of all these considerations and the lack of incontrovertible national legislation regarding the need for submission of retrospective and/or non-pharmacological studies to an ethics committee, the normal ethics committee clearance was not required (20,21).

A total of 27 patients (14 women and 13 men, Caucasian ethnicity, average age of 56 ± 15.1 years) suffering from MPS and other visceral symptoms were recruited within the Ce.Fi.R.R. Gemelli Molise Point. The presence for at least 6 months of frequent symptoms of back pain and the presence of knotty and painful muscle areas upon palpation in the lower back area allowed physiatrists in charge of the initial clinical evaluation of each patient to diagnose the presence of chronic MPS associated to MTrPs. It should be emphasized that although MPS typically presents itself as an acute pathology that resolves within a few weeks of the onset of the trauma, in some cases this pathology takes on the characteristics of a chronic health problem, with a duration of symptoms that ranges from a minimum of 6 months up to several years and a severity of the pathology proportional to its persistence over time (22).

Furthermore, it should be highlighted that some studies have shown a rather linear correlation between the presence of MPS and the onset of chronic low back pain (23,24). This relationship, which would appear to be independent of any structural alterations visible at the vertebral level and through MRI, could depend on mechanical and painful-irradiative factors due to the MTrPs present in the lower back muscles, with a direct proportional relationship between the number of muscles involved and the severity of the pathology (23,24).

The inclusion criteria included an age between 30 and 80 years and the presence of MPS. The exclusion criteria included all the typical contraindications for treatment with electrotherapies (cancer, pregnancy, electronic implants, serious vascular and cardiac diseases, epilepsy), as well as severe neurological impairments and clear sensory alterations.

The patients considered for the study underwent evaluations before (T0) and after (T1) a single treatment session with FTNM through:

- The Numeric Pain Rating Scale (NPRS): NPRS is one of the most common tools for measuring subjectively perceived pain by patients. It is a derivate of the Visual-Analogue Scale (VAS) divided into ten levels, usually distributed equidistant on a 10 cm long strip, which corresponds to the level of pain perceived by the patient at the time of the evaluation, and where 0 is the total absence of pain and 10 is the maximum level of pain imaginable and/or ever experienced (25). This scale is reliable, effective, and easy to apply even in the presence of dysfunctions of the musculoskeletal system such as MPS (25). In the case of the present study, patients were asked to express a value from 0 to 10 corresponding to the maximum level of pain perceived at the level of the lower back in the most insidious point for them (then identified as the location of the MTrPs being treated, variable from subject to subject among those in the observed sample and responsible for their MPS);
- Postural Biometric Index (PBI): PBI is an index calculated by Milletrix 3.0 platform software (Diasu Health Technologies, Rome, Italy) on the basis of a stabilometric evaluation carried out using the same device (26). This index takes into account the parameters of center of pressure, symmetry of bipodalic load, symmetry of retro-forefoot load, angle of centers of pressure, podalic angle, location of maximum pressure point, symmetry of support surface, and center of gravity deviation-center of pressure (26). These parameters are then calculated to obtain an index that quantifies the patient's postural state, which can often be altered in the presence of MPS (26). The PBI value is considered healthy from 0 to 10 and dysfunctional if >10.

Patients in the studied population underwent a single treatment session of FTNM applied through a device called Monos (AD SWISS MEDTECH SA, Gravesano, Switzerland, granted in use by A CIRCLE S.p.A., San Pietro in Casale, Italy). Following the principles of the Bio-Physical-Metric approach, the Monos instrument was first used in skin impedance evaluation mode, at a fixed frequency of 60 Hz. Through this mode, it was possible to investigate various points of a standard dermatomal map in search of the Key MTrPs within approximately 10 minutes, to stimulate in the lower back area, starting from the point that the patient had identified as most painful at the NPRS assessment. After identifying the focal points of the treatment, the Monos instrument was used at a frequency oscillating between 15 and 60 Hz along the dermatomal course of the areas hosting key MTrPs. The therapeutic portion of the Monos treatment took approximately 20 minutes for each patient.

At the end of the study data collection, statistical analysis was carried out using the Wilcoxon Signed Rank test for dependent samples, performed through the Statistics Kingdom online calculator (https://www.statskingdom.com, Melbourne, Australia).

RESULTS

The analysis of the results of the NPRS values highlighted a significant improvement in the painful symptoms experienced by the studied patients ($p < 0.01$), with an average percentage reduction in pain equal to -37.3% (Fig.1).

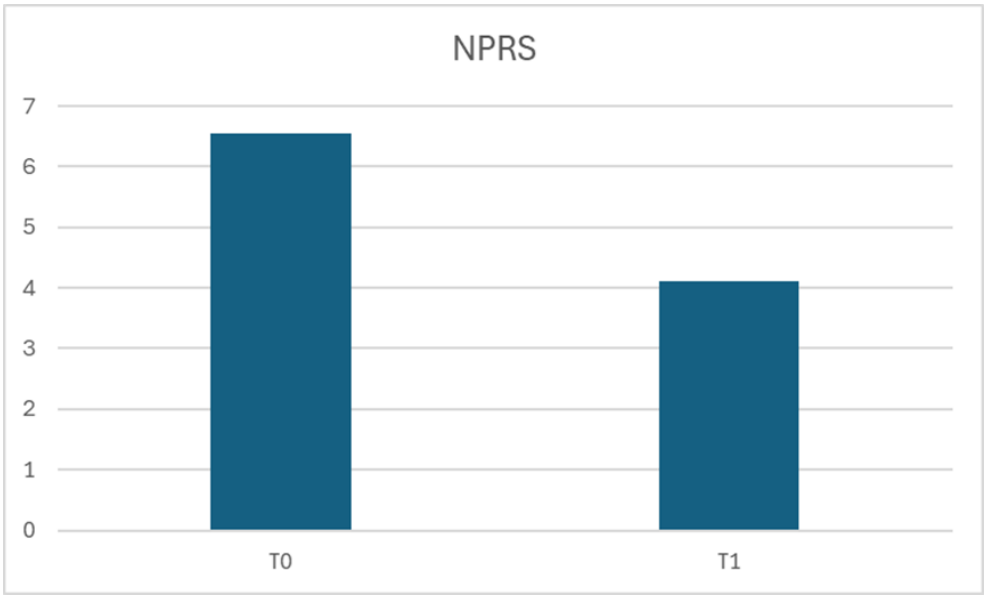

Fig. 1. *Change in NPRS values between T0 and T1.*

Similarly, the analysis of the results of the PBI values highlighted a significant improvement in the postural structure of the studied patients ($p < 0.01$), with an average percentage reduction in pain equal to -25.1% (Figure 2). The final average value, equal to a score of 10.29, although remaining above the maximum threshold of postural normality, equal to 10 according to the PBI system applied, markedly approached the ideal range (from 0 to 10 points).

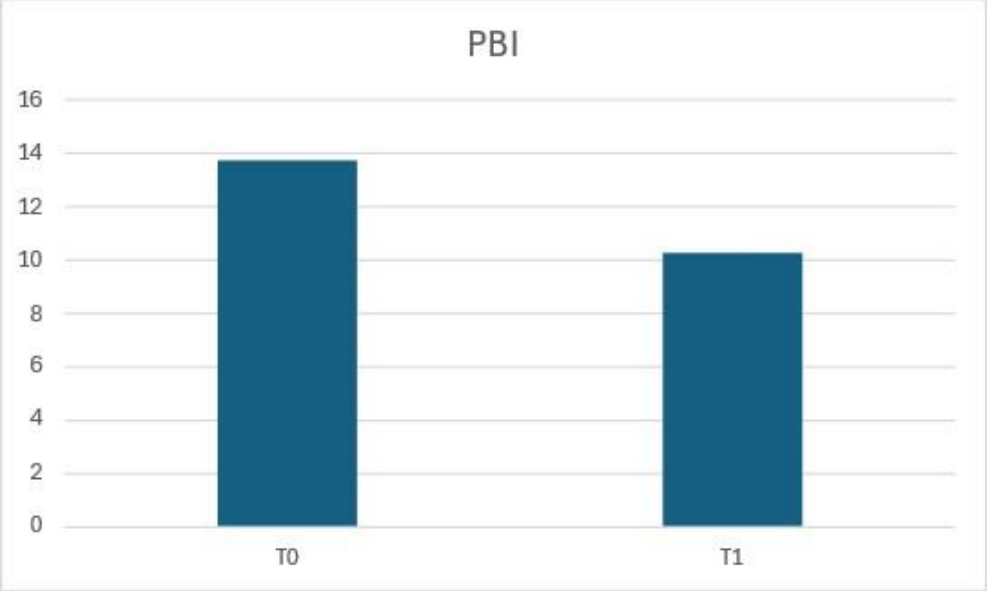

Fig. 2. *Change in PBI values between T0 and T1.*

DISCUSSION

At the end of the study, it was possible to note how MPS patients subjected to a single session of FTNM applied with a Bio-Physical-Metric approach obtained a significant improvement in both subjectively perceived musculoskeletal pain assessed using the NPRS (-37. %) and the value of the postural-biomechanical setting assessed by PBI (-25.1%).

MPS is a complex and very frequent disorder of the musculoskeletal system which is characterized by the presence of widespread pain and MTrPs (27). The causes are typically multifactorial (27), including functional aspects (reduced or

increased muscle use), traumatic, ergonomic (incorrect posture and biomechanics), structural (osteoarthritis, scoliosis, etc.) and systemic (hypothyroidism, Vitamin D deficiency and/or or Iron, etc.), as well as psycho-emotional causes (28).

A key role in the management of the pathology seems to lie in the deactivation of MTrPs through modalities ranging from local injection to manual and electrotherapeutic applications (29,30). In particular, the management of these MTrPs should focus on both central and peripheral nervous desensitization to the abnormal nociceptive stimuli that are perceived by the patient (30).

One of the most effective and promising therapeutic strategies in the management of musculoskeletal pain from MTrPs is that of NM, consisting of electrical stimulation, typically with a percutaneous electro-needle, of a portion of musculoskeletal tissue where MTrPs and myofascial pain are present (18,31). Given the therapeutic efficacy highlighted by percutaneous NM in multiple studies (18,31,32), it is not surprising that a very similar technique at a conceptual level such as FTNM was effective in modulating the pain of the patients studied. Furthermore, in addition to the effectiveness of the treatment studied, it should be underlined that its transcutaneous application, without resorting to piercing the patient's tissues, guarantees less invasive treatment, resulting in greater compliance on the part of the patients.

It must also be considered that MPS is a pathology that is widespread throughout the patient's body, often mainly affecting the tonic-postural muscles, especially at the level of hips and spine (33). It is no coincidence that the postural and biomechanical alterations that affect the back (both in the cervical and lumbar spine), the hips, and the shoulder joint are often identified among both the causative and perpetuating factors of MPS (34-36). It is also no coincidence that various therapeutic interventions based on exercise, manual therapy, or electrotherapy, have proven useful in improving the posture of patients suffering from MPS and myofascial dysfunctions in general, highlighting a proportionality between the improvement of posture and that of painful symptoms (37,38). In our case, the intervention using FTNM according to the Bio-Physical-Metric approach to the treatment of MTrPs proved useful in improving the posture of the treated patients, confirming the trend observed in the literature.

Although the results obtained are positive and encouraging, it is appropriate to underline some weak points of our study. First of all, the sample appears to be relatively small compared to the general diffusion of MPS. Furthermore, it is also possible to highlight a certain variability in the age of the patients enrolled. In addition, it must be considered that the study was carried out without a control group (either no-treatment or sham) and that the treatment was performed for a single session, in the absence of follow-up.

Despite this, the results obtained were positive and encouraging, considering both the efficacy seen in treatment and its broad tolerability by the patients studied. Furthermore, given the transcutaneous and minimally invasive nature of the NM treatment applied, no side effects associated with the treatment were detected.

CONCLUSIONS

The treatment of MTrPs according to the Bio-Physico-Metric approach through FTNM is effective in significantly improving, in the short term, pain and postural dysfunction in patients suffering from MPS. These results are important and encouraging as they allow us to identify a new rapid, relatively economical, and minimally invasive therapeutic approach to the treatment of a complex pathology such as MPS.

By virtue of the positivity of the results obtained, it would be desirable in the future to investigate the effectiveness of the therapeutic approach we tested in a more in-depth and extensive manner, through controlled and randomized studies on a large sample and for an extended period of time.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

MULTIPLE SCLEROSIS AND BIO-PHYSICO-METRIC APPROACH: EFFECTS OF FOCUSED MECHANO-ACOUSTIC VIBRATIONS

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ABSTRACT

Multiple sclerosis (MS) is a complex disease involving the nervous system with severe musculoskeletal manifestations in terms of postural-biomechanic functionality and stability, paired with a worsening of the visual system. Among the most interesting therapies for neuromuscular stimulation of the human body is vibration therapy, in particular in the form of Focused Mechano-Acoustic Vibrations (FMAVs), whose therapeutic efficacy, however, is still not fully understood in the field of neurodegenerative diseases such as MS. Therefore, in this observational pilot study we evaluated the evolution of clinical parameters such as fatigue, measured by the Fatigue Severity Scale (FSS), and postural stability, measured by a Stabilometric Analysis (SA), in a sample of 12 MS patients who underwent 3 weekly sessions for 4 weeks of FMAVs. At the end of the study, we observed a significant improvement in the FSS value in response to FMAVs treatment, although the results in terms of SA were mixed. In conclusion, FMAVs appear to be a promising and safe treatment for MS patients, but further and more in-depth studies on the topic are needed to clarify their role in the field of rehabilitation.

KEYWORDS: *Vibrations, neurodegenerative disease, multiple sclerosis, muscle spasticity, physical therapy modalities, rehabilitation, gait analysis, fatigue*

INTRODUCTION

Different experiences over the years have shown that when a mechanical vibration (100-200 Hz) is applied to a relaxed muscle, it causes a tonic contraction of the vibrating muscle which can be recorded by EMG and the resulting tonic vibration reflex (TVR) is framed as an autogenous reflex and this obviously strongly affects the spinal reflexes (1). Most of these effects have been found to arise from vibration-induced activation of spindle Ia afferents (presynaptic inhibition) demonstrated by the presynaptic inhibition of the T reflex and the H reflex (2-4).

These considerations are relevant for people affected by Multiple Sclerosis (MS), who can manifest various combinations of disabilities, such as physical dysfunction (motor weakness, spasticity, sensory dysfunction, vision loss,

Received: 04 December, 2024
Accepted: 30 December, 2024

2974-6345 (2024)

ataxia, etc.), fatigue, pain, incontinence, and cognitive deficits (memory, attention, executive dysfunction). MS has various presentation patterns (5), which include:

- "Relapsing-remitting" MS (80% of all MS cases), presenting with exacerbations and remissions, potentially evolving into a "secondary-progressive" form of MS with progressive disability that occurs between acute “attacks” of the disease;
- "Primary-progressive" MS (15% of all MS cases), in which progressive disability can manifest itself from the onset onwards;
- "Progressive-relapsing" MS (5% of all MS cases), in which the disease gradually worsens and then manifests itself with discretely severe “attacks”.

MS can be accompanied by psychosocial, behavioral, and working capacity alterations. These have a multidimensional impact on the activity (function) and participation of a person in the activities of daily, social and working life, with a significant impact from a social cost point of view (6).

A consultation of MS rehabilitation studies on balance, weakness, cardiovascular fitness, ataxia, fatigue, bladder dysfunction, spasticity, pain, cognitive impairment, depression and pseudobulbar affections concluded that fatigue affects approximately two thirds of people with MS (7).

MS-related fatigue is a complex and subjective symptom characterized by a lack of energy or an overwhelming sense of physical and / or mental fatigue. Fatigue is associated with a poorer quality of life (even when controlling the severity of the disease) and is one of the main reasons for retirement from work in MS patients (8).

Fatigue management has been identified as a priority for the quality of life of MS patients. In routine clinical care, drug treatments tend to be the first choice, with behavioral interventions and exercises considered as alternative or additional treatment options (9). In many cases, patients are never offered these non-pharmacological treatment options, and this is concerning as current evidences suggest that drug interventions to date are largely ineffective, while exercise and behavioral interventions have greater effects (9). Evidence for the end-of-treatment effects of different types of exercise interventions suggests that there is no single optimal exercise modality to strengthen muscle function in MS, but rather the choice of the type of exercise may depend on the specific combination of symptoms of MS, by the level of disability of the patient and his/her needs and preferences (9).

The mechanisms by which exercise improves fatigue will therefore differ for different types of personalization of the rehabilitation treatment (10).

Also, the results of the various experiences for balance work are moderate, so this rehabilitation practice should be used with some caution and applied according to the differences in the nature of the interventions. Balance exercise interventions include hippotherapy, vestibular rehabilitation and eye movement and balance exercises (11-13). However, since in this category there are only end-of-treatment effects, it is uncertain if these effects will last over time.

Furthermore, it must be considered that postural and biomechanical adjustments can be largely influenced by vision, and this is even more true in MS patients.

Looking at the association between eye diseases and MS, it must be highlighted that in the typical MS optic neuritis the inflammatory recruitment from the vascular bed to the perivascular space, then to the parenchyma of the central nervous system, is the result of chemokine activity. In fact, a key role is played by the chemokine ligand CXCL-10 and its receptor CXCR3 (14) on a predisposing genetic substrate (altered mode of immune response), peculiarly in carriers of histocompatibility antigens HLA-A3, B7, DRW2. The distribution of genetic factors plays an important role in the topographical clustering of phenotypes.

In MS, the initial plaques of demyelination are generally not particularly extensive, and present only in the white matter of the brain or of the medulla and optic nerves, causing a so called retrobulbar optic neuritis (RON). In the advanced stages, plurifocal lesions are associated with pyramidal, cerebellar and sensory syndrome. RON takes on particular importance as it can constitute the first isolated, acute, generally unilateral and transient manifestation of MS, and precede in time - up to 10 to 20 years - other subsequent symptoms, with a probability of 34% in males and 74% % in females (15).

Spontaneous retrobulbar pain or pain caused by movements of the bulb would be related to contractions of the oculomotor muscles, which would cause stretching of the optic nerve inflamed meninges, inside the orbital cone or the fibrous/osteo-fibrous ring of Zinn (16) and to the fascial wrapping of the medial rectus and superior rectus (17). Moreover, temporal pallor with shading of the margin of the optic disc is a late sign of Wallerian-like degeneration. The functional deficit translates into centro-cecal scotoma, due to involvement of the papillo-macular bundle, with functional visual damage, reduction in amplitude and increase in latency of the VEPs, dyschromatopsia of the red-green axis, which is superimposed by the yellow-blue axis in the presence of papillary oedema (18). The conduction delay derives from the modification of ionic concentrations along the axons and from the slowing of the axonal flow with a reduction of the

chemical mediators of the synapses and exhaustion of the response. This translates into difficulty in systemic motor control with fatigue gradually worsening as the systemic damage progresses.

Usually, in the initial stages, the scotoma regresses spontaneously, although a reduction in contrast sensitivity with a general sensation of visual blurring is often evident due to the involvement of the papillo-macular bundle; in subsequent phases it may then be associated with pars planitis, with general signs of motor difficulties and fatigue, attention and memory disorders, detectable with psychometric tests. Diplopia due to nuclear lesions of the III, IV, VI cranial nerve, and nystagmus complete the typical MS Charcot's symptomatic triad (18); also, venous engorgement with whitish sleeves, expression of periphlebitis with lymphoplasmacytic infiltration at two-three papillary diameter away from the optic disc, can appear, until leading the patient into the territory of low vision.

Low vision is an irreversible pathological condition characterized by reduced central visual acuity (typical of demyelinating pathologies), which is also essential for orientation and independent walking (19), inducing decisive consequences on postural behavior (20). The tonic-postural system consists of peripheral receptors (afferent and efferent nerve pathways) and peripheral and central nervous system. The impairment of the visual entrance causes an imbalance that spreads over the whole muscular chains, in an ascending or descending and also spiral manner. The imbalance, the bascules and the rotation are projected to the foot sole and can be recorded with specific 3D digitalized baropodometric platforms.

The evaluation with a visually central impaired patient, as for MS, shows a hypercharge on the side of the dominant eye (21), whilst in peripheral defects there is a contralateral overload compared to the dominant one (22).

Concerning the muscular stimulation aspects of rehabilitation, we know that if a vibratory stimulation is applied to a spastic muscle, it influences its tone (1); at the same time when the stimulation is applied to the antagonist muscle, it may cause a reciprocal inhibition of the spastic muscles: neurophysiologically, this phenomenon would be linked to presynaptic inhibition (23,24).

For example, in patients with spasticity, the reduction in the soleus muscle activity and H reflex is less pronounced during the application of a vibration to the Achilles tendon and this suggests the need to use specific vibration techniques and methodologies adapted to the specific case and pathology (25-27).

In general, to date, the literature tends to be very scarce and uncertain in relation to the effects of vibration therapy for neurological pathologies, including MS (28,29).

The aim of this study is to explore the effectiveness of new technologies, based on the application Focused Mechano-Acoustic Vibrations (FMAVs), to interact with the posture and muscle function of MS patients and to affect their quality of life and disability.

MATERIALS AND METHODS

This research is a pilot retrospective analytical observational study carried out at the "San Stef.Ar. Molise" Rehabilitation Center of Campobasso, Italy, accredited by the National Health System, in cooperation with the Ce.Fi.R.R. (Center for Physiotherapy, Rehabilitation and Re-Education) staff from March to September 2022.

The study was developed following the Good Clinical Practice (GCP) guidelines. It was conducted within the ethical principles outlined in the Declaration of Helsinki, and with the procedures defined by the ISO 9001-2015 standards for “Research and experimentation”. Written informed consent was obtained at baseline from all participants. All the procedures applied comply with the national safety regulations and the protocol is accessible to anyone who does not highlight specific contraindications (pregnancy, epilepsy, electrical implants, infections and tuberculosis) to the prescribed treatment. The protocol does not constitute an experimental practice, as applies the same procedures used at the study facility for all patients who do not present the listed contraindications. Furthermore, the Ce.Fi.R.R., as the institution in charge for carrying out the study through part of its staff, is certified for the realization of "Clinical observational studies in the rehabilitation field" (Certificate from the Italian Accreditation Body "Accredia" n. IT15/0304), in accordance with the ISO 9001:2015 standards. Due to these considerations, the lack of incontrovertible national legislation regarding the need for the submission of retrospective and/or non-pharmacological observational studies to an Ethics Committee (30) and the routine nature of the data collection performed (31), a formal Ethics Committee clearance was not required. This is intended as a pilot study, to validate or improve the study protocol.

A total of 12 patients (7 women and 5 men; Caucasian ethnicity; average age of 51 years) were enrolled within the study facility.

All patients had a diagnosis of MS and were able to maintain an upright position for at least 30 seconds. The therapeutic protocol was prescribed by a medical doctor after careful evaluation of the general health status of the patient

and the possibility and convenience of intervening on his/her MS in a minimally invasive way through a complementary rehabilitation approach based on FMAVs.

To assess the musculoskeletal health status of patients before (T0) and after (T1) the therapeutic protocol, a routine evaluation of the patients was carried out using the following diagnostic tools:

- Fatigue Severity Scale (FSS): it is a 9-items scale evaluating symptoms of chronic fatigue based on the answers given by the patient to questions regarding both physical, cognitive and psychosocial fatigue (32). The total score is derived from the sum of the points assigned to answers given for each item, with each answer presenting an assigned value from 1 (no fatigue perception) to 7 (severe fatigue perception). The maximum total score is therefore 63 points, indicating a situation of extreme fatigue for the patient (32). It is considered a reliable tool to assess general fatigue in the presence of MS (32);
- Stabilometric Analysis (SA): it consists in recording the parameters of Ellipse Area (mm2), Antero-Posterior Oscillations (mm) and Lateral-Lateral Oscillations (mm) through a platform equipped with sensors on which the patient stands to register his stability (33). The device used for the observed patients was Argoplus (Fremslife S.r.l., Genova, Italy); the measuring device is composed of a large support surface, placed on the ground through four vertical load measurement sensors placed under the edges of the support surface. The instantaneous load signals are sampled at 100 Hz and combined in order to calculate the position of the COP (Center of Pressure) with a precision better than 0.1 mm in the entire supported weight range (10-200 Kg). The support surface, in honeycomb panel, has a natural resonance frequency under alternating load of over 200 Hz to ensure that all the components of the Sway are effectively transferred to the load sensors and therefore to the processing of all the harmonics of the COP oscillation in the frequency band up to 10 Hz. This assessment has proven useful in assessing the body-stabilization abilities of MS patients (33).

The observed patients underwent a protocol consisting in the application of FMAVs 3 times a week for 4 weeks, for a total of 12 sessions lasting approximately 25 minutes each. The treatments were performed on an outpatient basis in the study venue. FMAVs therapy was administered through the Vibration Sound System (ViSS) (Vissman Europe S.r.l., Rome, Italy), using vibrating plastic cups connected to the air generator of the device. The transducers were symmetrically positioned on multiple body areas of the trunk and lower limbs in which typically palpable Myofascial Trigger Points (MTrPs) might be located, in particular at the level of upper trapezius, dorsal paraspinal muscles, lumbar paraspinal muscle, rectus femoris, vastus medialis, vastus lateralis, hamstrings, gastrocnemius and tibialis anterior. During each session, the stimulation frequency was set at 120 Hz for the first 15 minutes followed by a frequency of 180 Hz applied for the remaining 10 minutes. The FMAVs treatments were administered to the patients through a device called Vibration Sound System One (Vissman S.r.l., Rome, Italy).

Given the relatively small size and demographic variability of the observed group of patients, the data collected at time T0 and T1 were processed through the application of a non-parametric Wilcoxon signed-rank test. Data analysis was performed through the Statistics Kingdom open online calculator software (https://www.statskingdom.com, Melbourne, Australia). The observed changes were considered significant for p values < 0.05.

RESULTS

At the end of the therapeutic protocol, mixed changes were observed both for FSS and SA values.

In particular, the FSS variable showed a significant reduction ($p = 0.04$) between T0 and T1, equal to an average percentage variation of -14%, going from a mean value of 49.4 ± 10.4 to 42.5 ± 11.3 (Fig.1).

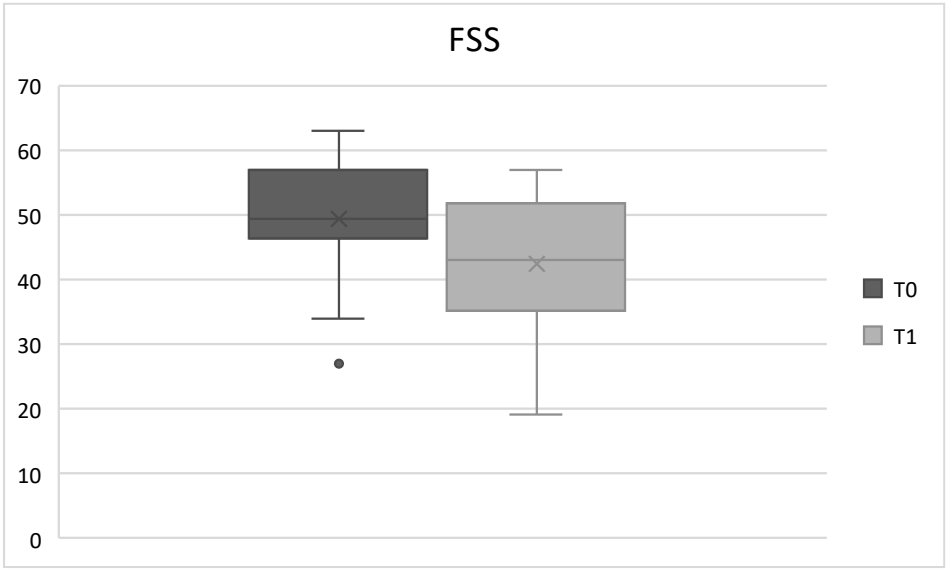

Fig. 1. *Box plots of MFIS values at times T0 and T1.*

Nevertheless, mixed results were observed in relation to the SA parameters. In fact, mainly non-significant variations of the considered values were observed, with the exception of a slight significant increase in Closed-Eyes Ellipse Area at Closed Eyes (+31.2%, p = 0.04) and Closed-Eyes Lateral-Lateral Oscillations (+16.9%, p = 0.02), as highlighted in Table I.

Table. I. *Stabilometric Analysis variations between times T0 and T1.*

	Ellipse Area (mm^2)		Antero-Posterior Oscillations (mm)		Lateral-Lateral Oscillations (mm)	
	Open-Eyes	Closed-Eyes	Open-Eyes	Closed-Eyes	Open-Eyes	Closed-Eyes
Mean	616.6	543.2	1070.1	1404.3	36.1	35.9
S.D.	644.4	373.5	948.3	1155.4	13.7	14.8
p	n.s.	0.04	n.s.	n.s.	n.s.	0.02
Δ%	-11.9	+31.2	-0.6	+11.1	+3.5	+16.9

DISCUSSION

To date, the literature regarding vibrations as a therapeutic approach in MS patients is scarce. Our study pointed out a positive correlation between FMAVs application and improvement of perceived fatigue, measured with FSS, in MS patients. However, mixed results were observed in the relationship between FMAVs application and postural stability measured with SA in the same MS patients.

It is known that vibrations, administered with different modalities and physical parameters, are able to produce a multitude of mechanical and endocrine-metabolic effects at the musculoskeletal level (34). In particular, in the context of localized FMAVs vibrations, it would seem that frequencies between 100 Hz and 200 Hz, such as those applied in our study, are endowed with myorelaxing properties compared to the hyper-tonifying proper-ties of FMAVs vibrations in the order of 300 Hz (34); this difference might be attributable to the different stimulation frequency threshold of mechanoreceptors that are found in various kind of tissue, in particular those of the skin such as Meissner and Pacinian corpuscles (34), as well as to the different changes in muscle morphology induced by different stimulation frequencies (34). However, the influence of these pathways on the perception of fatigue by subjects undergoing vibration therapy remains unclear. Typically, the application of localized vibrations or Whole-Body Vibrations (WBVs) is associated with an increase in fatigue in the human muscular system, which however tends to manifest it-self more intensely at low frequencies, in the order of 10-50 Hz (35,36), probably by virtue of a greater synchronization of the low frequencies with

respect to the activation threshold of the Tonic Vibration Reflex (26).On the contrary, localized vibrations at higher frequencies, starting from approximately 100 Hz and above, would seem to be associated with an improvement in the perception of fatigue (36,37), probably by virtue of mechanisms linked to peripheral proprioception (38) and central perception of fatigue (39), mechanisms which however require further clarification. Furthermore, it is also hypothesized that localized vibrations at higher frequencies are able to improve the efficiency of joint control in stimulated subjects (40). It should be considered that other studies in the past have already highlighted how the application of localized vibrations, even of the FMAVs type, at frequencies from 120 Hz to 300 Hz would seem to be able to reduce muscle soreness (41) and perceived fatigue at a central level (42) in the human body. In light of what has been expressed so far, it is possible that the 120 Hz and 180 Hz FMAVs to which the observed MS patients were subjected actually contributed to the significant 14% reduction in the FSS score detected by the analysis of the available data.

The same factors considered in relation to the observed improvement in fatigue could have also influenced the mixed results obtained regarding the stability of patients subjected to SA. In particular, we observed how MS patients treated with the FMAVs protocol in general did not undergo particularly significant variations in postural stability in terms of oscillations and area of the ellipse in relation to the Center of Pressure. In fact, a slight increase in the reference values of SA was observed. The literature would seem to suggest that muscles respond to vibratory stimulation with plastic adaptations, which are expressed in a maximum potentiation obtained at frequencies around 300 Hz when such stimuli are applied in the form of FMAVs (43).Since the patients we observed were treated with FMAVs at frequencies between 120 Hz and 180 Hz, which are known to be associated with myorelaxant effects (23), it is possible that the stimulation frequency did not significantly influence the postural stability of MS patients. As the patients we observed were treated with FMAVs at frequencies between 120 Hz and 180 Hz, notoriously associated with myorelaxant effects (34), it is possible that the stimulation frequency did not significantly influence the postural stability of MS patients, since the applied frequencies denote a markedly more analgesic and hypotonifying activity compared to higher frequencies capable of directly strengthening the treated muscles and therefore increasing the postural stability of the treated subjects. Furthermore, since the observed patients were treated with 25 minutes of continuous application of FMAVs, it cannot be excluded that the relatively prolonged exposure time produced a rebound phenomenon of the activation of Tonic Vibration Reflex mechanisms, which apparently undergo reduction of EMG activity, motor unit firing rates, and contraction force when the involved receptors are overstimulated and irritated for a long time (44). In any case, the postural effects of the treatment seem to be amplified when the visual sensory input is removed in the patient by closing his eyes, confirming that eyes play an important role in the postural control (22) even in the case of MS patients and can in turn influence and be influenced by the peripheral muscle stimulation of a FMAVs-type treatment, raising questions about this physiological interrelationship that would merit future investigation.

Although the observed results are encouraging and interesting, some limitations of this study must necessarily be taken into account. Among the limitations of the study, it is necessary to consider the small sample size. Furthermore, the selected sample referred only to MS patients who could maintain an upright position. In fact, a choice of allocation could exaggerate the estimate of the treatment effect, on average. Furthermore, the absence of a control group and a follow up, due to the observational design, would constitute an ulterior limitation with respect to the reliability of the observed variations. Nonetheless, among the many tools that could be used in MS symptoms assessment, the scales and systems here applied are widely adopted in several studies, allowing for comparison of results across different cohorts.

About the safety of the protocol, potentially, the use of vibration cups could expose patients to an increased risk of muscle reaction (contractures and/or instability), but in our study and in our routine clinical experience this never happened, suggesting a high level of safety and minimal invasiveness of FMAVs, which was generally detected in many reviews and complex clinical contexts (45-47). A medium-term follow-up could be useful to verify the effectiveness of the vibratory treatment over time, as well as to establish how often to program any recall cycles.

One of the key strengths that must be considered is the uniqueness of the study which, to the best of our knowledge, reported for the effect of FMAVs in MS, both from the point of view of fatigue and posture.

CONCLUSIONS

In conclusion, the vibratory stimulation was well tolerated by MS patients, proved to be safe and effective, easy to use, without risk for the patient and particularly effective for reducing MS-related fatigue, which is a fundamental point to increase the autonomy of the patient and may result in a notable reduction in the support of caregivers and consequently a saving in social expenses for health.

FMAVs can influence the musculoskeletal system of the patient affected by MS, inducing changes in postural attitude and related adaptation capacities in terms of stability and relationship with visual inputs. However, the effects on the

postural system determined by different vibration frequencies and times of exposure to the treatment require further study to better clarify the specific application parameters for each pathological condition.

Although there is positive evidence for the effects of FMAVs in MS patients, our experience suggests the need for further randomized studies on larger samples to determine the best frequency and the best amplitude and duration of exposure to FMAVs in order to better improve function in patients with neuromuscular alterations in MS.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

We sincerely thank Marco Licameli, Physiotherapist at the Gemelli Molise Hospital of Campobasso, for supporting the operational staff during some procedures of the study.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

Letter to the Editor

SOMATOMEDIN (INSULIN-LIKE GROWTH FACTOR) IS IMPORTANT FOR DEVELOPMENT, MATURATION, AND BRAIN FUNCTION

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KEYWORDS: *Somatomedin, insulin-like growth factor, IGF-1, IGF-2, growth hormone, brain, CNS*

INTRODUCTION

The name somatomedin (SM) is composed of *somato*, meaning "factor with a target inside the body", and *medina*, the intermediary of the somatotropic hormone. SM is a molecule present in the serum and an intermediary of somatotropin which acts on tissues and first appeared in the scientific literature in 1972 (1). Growth hormone (GH) does not directly affect tissues; instead, it acts through SM, which is synthesized in the liver and released into the bloodstream (2). Since these factors, in addition to causing tissue growth, are mitogenic, they have been called insulin-like growth factors (IGFs) (3).

Somatomedin (SM) is a molecule present in the serum that acts in cooperation with growth hormone (GH). SM, also called insulin-like growth factor (IGF) (4), is synthesized by the liver, circulates in the bloodstream, and acts on tissues as a mitogen. In the serum, there are two SMs that act as transporters that bind to its receptor on the target cell, producing an effect on somatostatins. SM is composed of IGFs-1 and 2, SM-A, and multiplication-stimulating factor (MSF), which mediate the GH on skeletal tissues. Experiments have shown that in hyposectomized rats, GH alone does not act as a mitogen. Instead, it becomes active in combination with SM. IGFs-1 and 2 have a chemical formula similar to insulin and biological effects on the growth of children. SM is a mediator of GH and promotes cell differentiation and multiplication in both muscle and cartilage.

DISCUSSION

SM is a small GH-dependent peptide that is composed of insulin-like growth factors (IGFs)-1 and 2, SMs-A and C, and multiplication-stimulating factor (MSF), that mediates the GH on skeletal tissues (5). Two SMs are present in the serum, and they have a high molecular weight (150 and 60 Kd) (6). The complex of these two transporter proteins, and their effect on the biological activity of somatostatins, creates a complicated physiological control that includes the delivery of SM to its receptor which is located on the target cell.

In experiments, it was seen that cartilage mucopolysaccharides can be stimulated with the addition of serum in hyposectomized rats that were pretreated with GH (7). Treatment with GH alone does not cause tissue stimulation (8); Rather, the stimulating factor results from SMs-A and C (9). IGF-1 and IGF-2 have a formula which is similar to insulin and they are composed of A domains homologous to the A chain of insulin, B domains homologous to the B chain, C

Received: 10 October, 2024
Accepted: 04 December, 2024

2974-6345 (2024)

domains homologous to the C chain of proinsulin and D domains extending from the C terminals of A Chains (10). SM-C is identified as IGF-1 because they have the same amino acid chain.

SM is associated with protein macromolecules and can be extracted from human plasma where it circulates. Its molecular structure is similar to that of insulin and SM plays a key role in the growth of children (11). SM is a mediator of GH and promotes cell differentiation and multiplication in both muscle and cartilage (12). Therefore, SM plays a role in the activity of chondrocytes by promoting the synthesis of cartilage and osteoblasts (13). In GH-deficient individuals such as children, plasma concentrations of SM are low. SM secretion is inhibited by cortisol, and this could explain its negative effects on body structure (14). SM is produced by various tissues and organs, including the liver, under the stimulus of GH or the somatotropic hormone produced by the pituitary gland (15). Even after childhood, SM continues to affect the tissues into adulthood (16). IGF-1 levels in the blood begin to increase in childhood, until reaching a maximum peak level around 40 years of age and then gradually decreasing after that age (17). SM has anabolic activity and is a cellular growth factor, although the dynamic effects on cells have not yet been clarified.

IGF-1 is a powerful hormone produced by liver cells and chondrocytes that regulates cartilage synthesis. After generation, IGF-1 is released into the circulation, where it binds to the transport proteins IGF-binding proteins (IGF-BP), which increases its plasma half-life (18). IGF-1 (also known as SM) is a hormone that is molecularly similar to insulin and plays a very important role in the growth processes of children, maintaining its effects even into adulthood (19). GH has been found in human brain tissue and IGF-2 has also been detected in cerebrospinal fluid (CSF). The mammalian brain expresses the SM receptors IGF-1R and IGF-2R (20). GH is generated in human brain tissue and carries out its biological action in collaboration with IGF-1. These hormones mentioned above are very important for brain function and development and increase the ratio between neurons and glia (21). For children with impaired brain development, treatments with human GH (hGH) improve growth recovery and intelligence quotient (22). Therefore, GHs and SMs are very important in the development, maturation, and function of the brain in childhood.

The genetic deficiency of SM results in functional brain damage with reduced capacity of its receptors and can cause growth delays (23). Inflammatory processes influence the hypothalamic-GH-IGF-1 axis, causing resistance to GH and a decrease in IGF-1 (24). The binding of IGF to its receptor activates a biochemical cascade that includes phosphatidylinositol 3-kinase (PI3K), mTOR and MAPK involved in cell growth and differentiation, producing biological effects which are also shared by insulin signaling pathways (25)

Both IGF-1 and IGF-2 act on the IGF-1R which is ubiquitous in all tissues (26). It has been reported that the chemical structure of IGF-1R is similar to that of the insulin receptor (27). The extracellular region of IGF-1R is composed of alpha and beta subunits which act as a ligand and the intracellular part of the receptor consists of the tyrosine kinase domain with the beta subunit. After the IGF-1R receptor binds the binding protein, it undergoes structural rearrangement. IGF-1 binding to IGF-1R occurs at two separate sites: one with high affinity and one with low affinity (28). Transgenic mice lacking the IGF-2 gene show dysfunction in embryonic growth and have approximately 70% less body weight at birth (29). This demonstrates the importance of IGF in pre- and post-natal body development.

CONCLUSIONS

SM is important for the growth of tissues, as well as brain function and development in children. GHs and SMs are very important in the development, maturation, and function of the brain in childhood. Treatments with hGH improve cerebral growth and cognition, and genetic deficiency of SM causes functional brain damage with reduced receptor capacity and possible delays in growth. Further studies are needed to clarify the real effects of SM on the brain. In addition, research is currently targeting IGF-1 and IGF-2 since these two molecules are also involved in other diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

BRAIN T CELL SUBSETS POTENTIALLY PARTICIPATE DYNAMICALLY IN NEUROINFLAMMATION AND NEURODEGENERATION

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ABSTRACT

T cells play a crucial role in the immune response by producing soluble mediators, including cytokines. Mature and activated T cells are effector cells and present different phenotypes. T cells have a certain plasticity that allows them to adapt to different antigens. They are distinguished by their different differentiation and production of molecules and intervene both in modulating the immune system and in brain inflammation. T cells are divided into various subsets including T helper cells (Th), cytotoxic T cells (Tc), and regulatory T cells (Treg). Their activation leads to the production of specific transcription factors that regulate the expression of specific genes. CD4+ T cells are helper cells that aid in the production of antibodies, while CD8+ Tc cells are killer cells that act against infected or abnormal cells and mediate neuroinflammation. CD8+ cells mediate neurodegeneration in neuroinflammatory diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Treg cells are immune regulators and regulate inflammation. Dysregulation of T cells mediates many neurological disorders such as depression and schizophrenia. The in-depth study of T cells and their subsets helps to better understand their mechanism of action and their function in neurological diseases.

KEYWORDS: *T cell, subset, neuroinflammation, neurodegeneration, immune response*

INTRODUCTION

T cells play a crucial role in the immune response and act by producing soluble mediators and by cell-to-cell contact (1). Many T cell subsets have been characterized, and terminally differentiated subtypes are considered effector cells. Data suggests that the phenotype of all existing T cells has not yet been defined (2). T cells can have mixed phenotypes that interconvert from one subset phenotype to another that, through specific signals, can produce molecules with memory. T cells have a certain plasticity to adapt to the immune response and various microenvironments (3). They are particularly important for the defense against pathogens that invade tissues (4). T cell subsets are distinguished by their differentiation and identified by the expressed cell surface markers but can also be classified by the molecules that they produce (5). It is important to understand the markers of T cell subsets, transcriptional regulators, effector molecules, and the function of the subsets in the immune response (6). Understanding these T cell subsets and their regulation can be an important tool in the therapy against immune diseases. T cells and their subsets play an important role in both immune system modulation, neuroinflammation, and neurodegeneration in the brain (7) (Table I).

Received: August 29, 2024
Accepted: 19 November, 2024

2974-6345 (2024)

Table I. *Some T-cell subset receptors (surface phenotype).*

Cell type	Receptors
Naive	IL-7R, CD3, TCR, CD62L, CCR7
Cytotoxic	CD3, TCR, CD8
Exhausted	CD3, CD8, PD1, TIM3, 1B11, LAG3
Anergic	CD3, TRC, BTLA
Helper	Cytokine receptor, CD3, TCR, CD4, Chemokine receptor
Regulatory	GITR, CD3, TCR, IL7R, CCR7
Memory	CD44, CD3, TCR, IL7R, CCR7
NKT	NK1.1, SLAMF1, TCR, SLAMF6, TGFβR
γδ T cell	CD3, γδ TCR
CD8αα	CD3, TCR, CD8αα, B220

T cell subsets are part of the adaptive immune system and are classified based on their function and surface markers. Transcription factors are critical in determining T-cell subset differentiation and function (8). T cells are categorized into various subtypes, including T helper cells (Th), cytotoxic T cells (Tc), and regulatory T cells (Treg), amongst others (9). Each subtype's differentiation is driven by specific transcription factors that regulate the expression of lineage-specific genes (Table II).

Table II. *T helper (Th) cell transcription factors*.

Th1	T-bet, STAT4, STAT1
Th2	GATA3, STAT6, DEC2, MAF
Th9	PU.1
Th17	RORγt, STAT3, RORα
Th22	AHR
TFH	BCL-6, STAT3

DISCUSSION

CD4+ cells have various subtypes such as Th1, Th2, Th17, and Treg (10). These cells act through the release of cytokines and are classified based on their function and surface markers.

CD8+ Tc cells are killer cells and act against infected or damaged cells, causing inflammation (11). These cells also act against abnormal neurons, causing neuroinflammation (12). CD8+ T cells can act against myelin and neuronal antigens, causing damage at the axonal level (13).

Tregs are immune T cells that regulate homeostasis and the immune response when it is too high. Tregs may also help maintain brain health and regulate inflammation (14). Treg cells suppress excessive inflammation and, when reduced, contribute to the progression of brain disease. T cells are found in the brain and cerebrospinal fluid in limited numbers due to the blood-brain barrier (BBB) limiting their entry (15). T cell subsets play a dual role in neuroprotection and neuroinflammation. Neuroinflammation is a pathological effect that occurs in many brain diseases including Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD) (16). Activated innate Th1 cells in the brain produce interferon-gamma (IFN-γ), which causes inflammation and neuronal damage, while Th17 cells produce IL-17, a cytokine that participates in the breakdown of the BBB, allowing inflammatory cells to enter the brain (17).

In neurodegenerative diseases such as AD and PD, T cells are found to be infiltrated in brain regions with amyloid plaques (AD) or Lewy bodies (PD) (18). In these diseases, inflammatory cytokines play a fundamental role in neurodegeneration. In addition, dysregulation of T cells and their subsets mediates many psychiatric disorders such as depression and schizophrenia by activating inflammation (15). In fact, T cells enter the brain after BBB breakdown caused

by systemic inflammation. Cytokines released into brain tissue alter the physiology of neurons and microglia (19). These effects provide the basis for promising therapeutic advancement that may involve enhancing Treg cells or inhibiting pro-inflammatory cytokines such as IL-1, TNF, IL-6, and IL-17 (20).

Naive T cells are crucial elements of our immune system and participate in the pathophysiology of the brain (21). Naive T cells are T lymphocytes that have not yet encountered their specific antigen which are called “virgin cells” and are ready to be activated by a specific antigen presented by antigen-presenting cells (APCs). These cells originate in the bone marrow, mature in the thymus, and then circulate in the blood and lymph nodes, waiting to be activated (22). Once activated, they differentiate into effector T cells or memory T cells. Naive T cells can affect the brain directly or indirectly through several mechanisms. Naive T cells do not normally cross the BBB, but in the case of neurodegenerative disease where the BBB is dysregulated, T cells can enter the brain (23).

“T cell exhaustion in the brain” refers to the phenomenon in which T cells lose their functional capacity after prolonged activation in response to chronic infections, tumors, or autoimmune conditions (24). Prolonged immune activation leads to T cell exhaustion, a reaction which may be particularly important in the context of neuroinflammatory or neurodegenerative diseases (25). Exhausted T cells have reduced cytokine production, proliferation, and cytotoxicity, impairing their ability to fight infections or tumors.

Anergic T cells in the brain play a role in the immune system's regulation to maintain balance and prevent excessive inflammation or autoimmunity (26). T cell anergy is a state of functional unresponsiveness in T cells, where they are alive but fail to proliferate or produce cytokines upon stimulation (27). This occurs when T cells receive signal 1 (antigen recognition via the T-cell receptor) without signal 2 (costimulatory signals, e.g., CD28 interaction with B7 molecules on APCs). T cells infiltrating the brain in certain conditions such as neuroinflammation, infection, or autoimmunity, may encounter signals capable of producing immunological tolerance that leads to anergy (28).

Memory T cells are a subset of T lymphocytes that are primarily associated with the immune system (21). There is growing interest in how they might interact with or influence the brain. Memory T cells can cross the BBB under certain conditions, such as during neuroinflammation (29). In diseases such as MS, memory T cells target myelin, leading to neurodegeneration.

Natural Killer T (NKT) cells are a subset of immune cells that bridge the innate and adaptive immune systems (30). They are known for their role in recognizing lipid antigens presented by the CD1d molecule and producing large amounts of cytokines (31). Their relationship to the brain and neurological functions is a growing area of research. NKT cells are primarily studied in the context of the immune system but they are also involved in neuroinflammation and brain homeostasis. NKT cells are known to secrete cytokines such as IFN-γ and IL-4, which influence inflammation (32).

Gamma delta (γδ) T cells are a unique subset of T cells that play a role in immune surveillance and tissue homeostasis, including in the brain (33). Unlike the more common alpha-beta (αβ) T cells, γδ T cells have a distinct T cell receptor (TCR) composed of γ and δ chains. These cells are involved in both innate and adaptive immunity and are notable for their ability to respond to non-peptide antigens without the need for antigen presentation by major histocompatibility complex (MHC) molecules (34). γδ T cells are implicated in neuroinflammatory conditions, such as MS and other autoimmune diseases, and are thought to contribute to the breakdown of the BBB and the recruitment of other inflammatory cells into the central nervous system (CNS) (35).

CD8αα T cells express a homodimer of the CD8α chain, unlike conventional CD8αβ T cells, which express a heterodimer of CD8α and CD8β (36). CD8αα T cells often express TCRs with limited diversity, such as γδ TCRs or invariant αβ TCRs, which are associated with innate-like immune responses. These cells are involved in immune regulation, tissue repair, and maintaining homeostasis, and they are generally less cytotoxic than CD8αβ T cells (37).

CONCLUSIONS

Today we know that T cells can infiltrate the CNS in both physiological and pathological conditions and their presence is tightly regulated by the BBB. Th1 cells release IFN-γ, which activates microglia and astrocytes, exacerbating neuroinflammation, while TH17 cells produce IL-17, which disrupts the BBB, allowing further immune infiltration. T cell subtypes have been implicated in MS, AD, and PD. CD8+ cells can directly target neurons, contributing to neurodegeneration, while Treg cells suppress excessive inflammation. It is interesting to understand which T cell subtypes mediate the pathophysiological state of the brain and their functions.

Modulating T cell responses using immune inhibitors, Treg-based therapies, or cytokine blockade could offer potential treatment strategies for neurodegenerative diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

PHYSIOPATHOLOGY OF TYROSINE KINASE RECEPTORS IN THE BRAIN

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ABSTRACT

Tyrosine kinase receptors (TKRs) are a subclass of cell surface proteins with phosphorylating enzymatic activity, selective for tyrosine residues. At the level of brain neurons, these receptors play an important role in axonal growth, synapse formation, neuroprotection and plasticity. The TKR family includes receptors TkrA, TkrB, and TkrC, that can bind several specific ligands such as the neurotrophin-3 (NT-3). TKRs also include epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), and insulin-like growth factor receptors (IGFR). In healthy neurons, TKRs play physiological roles such as survival and differentiation. Ligand-induced TKR activation participates in axonal guidance and branching. NT-3 is an important protein in the nervous system, is involved in neuronal pathophysiology, and during early brain development, NT-3 influences synapse formation and stabilization. Epidermal Growth Factor (EGF) is a protein ligand that stimulates cell growth, proliferation, and differentiation by binding to its receptor EGFR. EGFR is a member of the TKR family of receptors and when it is activated it dimerizes its receptor and its tyrosine kinase domain becomes active, leading to autophosphorylation. Microglia express TKRs as colony-stimulating factor 1 receptor (CSF1R), which is important for microglial survival and activation. This reaction can trigger inflammation that contributes to neurodegenerative diseases. Inflammation may be due to dysregulation of TKRs in astrocytes and blood-brain barrier (BBB) disruption. TKRs play an important role in brain inflammation and targeting these molecules could provide therapeutic effects.

KEYWORDS: *Tyrosine, kinase, receptor, CNS, neuron*

INTRODUCTION

Tyrosine kinase receptors (TKR) are a subclass of cell surface receptors that are necessary for phosphorylating enzymatic activity and are selective for tyrosine residues (1). They play a key role in neuronal signaling, development, and plasticity, and have intrinsic tyrosine kinase activity, which is essential for their function in signal transduction (2). At the neuronal level, these receptors are involved in processes such as axonal growth, synapse formation, and neuroprotection (3). TKRs have a transmembrane protein structure consisting of an extracellular domain that binds specific ligands such as growth factors. The transmembrane domain attaches the receptor to the neuronal membrane; while the intracellular domain contains the tyrosine kinase domain that auto-phosphorylates upon activation. In neurons, TKRs include TkrA, TkrB, and TkrC receptors that bind neurotrophin-3 (NT-3), nerve growth factor (NGF), and brain-

Received: 02 December, 2024
Accepted: 30 December, 2024

2974-6345 (2024)

derived neurotrophic factor (BDNF) (4). In addition, TKRs also include epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), and insulin-like growth factor receptors (IGFR) (5).

DISCUSSION

TKRs play a physiological role in healthy neurons by mediating some important processes related to neurotrophic signaling (6). TkrA promotes the survival and differentiation of sympathetic and sensory neurons by binding to NGF, while TrkB supports synaptic plasticity and survival via BDNF, and TkrC aids development via NT-3 (7). Moreover, ligand-induced TKR activation participates in axonal guidance and branching.

TKRs support oligodendrocyte precursor cells, which are responsible for producing myelin (8). Ligand-induced TKR activation participates in axonal guidance and branching. TkrB plays a key role in synaptic plasticity, long-term potentializing and memory formation (9). TKRs are involved in neuroprotection, and during stress, they improve neuronal survival (10).

NT-3 is an important protein in the nervous system which is involved in neuronal physiopathology (11). It is part of the neurotrophin family, which includes NGF, BDNF, and neurotrophin-4/5 (NT4/5) (12). These molecules participate in neuronal survival, differentiation, and maintenance (13). During early brain development, NT-3 influences the formation and stabilization of synapses, ensuring that neuronal circuits are properly connected (14). NT-3 is involved in learning and memory maintenance, modulates the growth of dendrites and axons, promotes the myelination of neurons, and improves signal transmission in the central nervous system (CNS) (15).

TKRs are membrane proteins involved in cell survival, proliferation, differentiation, metabolism, and migration (16). They play an important role in brain function, including immunology, bridging neurobiology and neuroimmunology (17). They are high-affinity cell surface receptors and can bind various growth factors, hormones, and cytokines (18). After TKRs bind to their ligand, they undergo dimerization and autophosphorylation on specific tyrosine residues, which activates downstream signaling cascades (19). TKRs are crucial for neuronal development, survival, and synaptic plasticity. The main TKRs in the brain are neurotrophins NGF, BDNF, and NT-3. These are crucial for neuronal physiology and cellular homeostasis. EGFR is involved in the proliferation and repair of glial cells, while the vascular endothelial growth factor receptor (VEGFR) is important in the formation of new vessels (angiogenesis) of the cerebral system and also in neurovascular processes (20). EGF is a protein that stimulates cell growth, proliferation and differentiation by binding to its receptor, the EGFR, a member of the TKRs receptor family. By binding to its receptor EGFR, EGF dimerizes it and its tyrosine kinase domain becomes active, leading to autophosphorylation. This reaction triggers the cascade of the MAPK/ERK and PI3K/AKT biochemical pathways, promoting cell survival and proliferation (21).

The platelet-derived growth factor receptor (PDGFR) regulates the development of oligodendrocytes and astrocytes, which are important for myelination and neuroinflammation, while FGFR is implicated in neurogenesis and repair mechanisms following injury (22). Microglia are immune cells with macrophagic activity that express TKRs such as colony-stimulating factor 1 receptor (CSF1R), which is crucial for microglia survival and activation (23). This activation triggers inflammation, contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's. In the brain, EGFR and FGFR are expressed by astrocytes and modulate the response to injury and inflammation (24). Dysregulation of TKRs in astrocytes can disrupt the BBB and cause inflammation (16).

CONCLUSIONS

In conclusion, TKRs are involved in both physiological and pathological mechanisms of the CNS, depending on the specific receptors and ligands. TKRs are proteins that also play an important role in neuroinflammation. This suggests that targeting TKRs as therapeutic factors could be useful for treating neurodegenerative and neuroinflammatory diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

HYPERKALEMIA AND BRAIN FUNCTION

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ABSTRACT

Hyperkalemia is an increase in blood potassium (K+) that can affect multiple organs, including the functioning of the brain. K+ remains stable between meals due to K+ release primarily from muscle and liver cells, while it decreases with renal excretion and sequestration from muscle cells. K+ resides almost entirely within cells and is absorbed in the small intestine. Increases in this electrolyte can occur with impaired renal excretion or cellular dysfunction. Hyperkalemia is regulated by the kidneys, which dispose of excess K+. Physiological central nervous system (CNS) K+ levels are involved in nerve signaling and hyperkalemia can dysregulate normal brain processes and it may also play a role in neuroinflammation. Increased K+ can cause muscle weakness, fatigue, and, in severe cases, even cognitive dysfunction with confusion, disorientation, and coma. An abnormality in K+ levels can be reflected in the membrane potential of neurons and affects their polarization and excitability. Mild hyperkalemia can cause increased neuronal excitability, muscle spasms, paresthesias, and neuronal and muscular paralysis with respiratory failure and/or cardiac arrhythmias.

KEYWORDS: *Hyperkalemia, potassium, brain, neuron, membrane potential*

INTRODUCTION

Hyperkalemia is a pathology that varies from mild to severe and very often also involves neuronal dysfunction. Hyperkalemia is a common electrolyte abnormality with high levels of potassium (K+) in the blood (1). It can significantly impact brain function and may cause neuroinflammation (2). Hyperkalemia can result in life-threatening arrhythmias and is associated with an increased risk of mortality (3). The development of hyperkalemia is often exacerbated by concomitant comorbidities such as diabetes mellitus or cardiovascular diseases (4). Hyperkalemia is managed by eliminating risk factors and through interventions aimed at directly lowering serum K+.

Most intracellular K+ is contained in muscle cells where it acts on the membrane potential. The physiological effect of this electrolyte depends on a normal serum concentration. K+ concentration decreases after renal excretion and sequestration of muscle and liver cells (5). K+ remains stable between meals due to its release mainly from muscle and liver cells. The distribution of K+ between the intracellular and extracellular space is maintained by balancing the activity of the Na/K-ATPase with K+ leak (6) (Table I). Effectors of K+ uptake and leak include insulin, catecholamines, mineral corticoids, tonicity, exercise, and acid-base status (7). More than 95% of K+ resides intracellularly and most of it is absorbed in the small intestine.

Received: 29 November, 2024
Accepted: 31 December, 2024

2974-6345 (2024)

Table I. *Na^+/K^+ ATPase dysfunction can cause the following dysfunctions to occur.*

- Accumulation of intracellular Na^+ and accumulation of extracellular K^+.
- Alteration of channels affecting repolarization.
- The elevation of K^+ normally stimulates aldosterone release via the adrenal cortex by increasing expression of the Na^+/K^+ ATPase channel in the kidneys for K^+ excretion.
- Impaired aldosterone function (Addison's disease, ACE inhibitors) worsens hyperkalemia.

Increased K+ intake causes hyperkalemia which may result in impaired renal excretion and/or cellular redistribution (8). The kidney has an important role in maintaining K+ homeostasis and healthy kidneys possess a great ability to dispose of excess K+, maintaining normal K+ serum levels even with intakes as high as 400 mmol per day (9). Most of the filtered K+ is reabsorbed in the proximal convoluted tubule and the loop of Henle. Renal K+ balance is largely determined by K+ secretion occurring in the distal nephron and collecting duct (10).

DISCUSSION

In the brain, K+ is crucial for nerve signaling and for central nervous system (CNS) functioning, but excessive levels can disrupt normal neurological processes (11). Hyperkalemia is defined as an elevated level of K+ in the blood. It can significantly impact brain function and may contribute to neuroinflammation (12). In the brain, K+ is crucial for nerve signaling and CNS function, but excessive levels can disrupt normal neurological processes (13). Hyperkalemia impairs nerve transmission, causing muscle weakness, fatigue, and in some cases, even paralysis (14). In addition, severe cases of hyperkalemia can cause cognitive dysfunction with confusion, disorientation, and coma (12). In rarer cases, seizures can occur due to disrupted neuronal excitability.

K+ is also an important element for the function of immune cells (15). In cases of hyperkalemia, there may alterations in the functioning of immune cells, such as T lymphocytes, causing an Ig deficiency, because, in the immune system, antibody-producing B lymphocytes and T cells (particularly IL-4-producing T helper cells) are interdependent (16). Excess K+ can affect other immune cells such as macrophages by altering their ability to phagocytose infectious agents and to present antigen correctly (17,18). Immune dysfunction due to hyperkalemia affects inflammation and activation of the NLRP3 inflammasome (19). High extracellular K+ inhibits the NLRP3 inflammasome, reducing excessive inflammatory responses. In hyperkalemia, the dysregulation of immune cells can lead to chronic inflammatory disorders, while initially it may suppress inflammation (20).

Hyperkalemia significantly affects neurons because of the crucial role of K+ in maintaining resting membrane potential and neuronal excitability (21). Hyperkalemia causes neurons to depolarize from their resting membrane potential. Neurons maintain a resting membrane potential of about -70 mV, largely due to the Na^+/K^+ pump and K+ leak channels. Extracellular hyperkalemia reduces the K+ gradient with less influx, causing depolarization and mild hyperkalemia can produce increased neuronal excitability (22). If there is mild extracellular hyperkalemia of 5.5-6.5 mEq/L, neurons are more excitable because they are closer to the threshold for action potentials. These effects can lead to spontaneous or excessive discharges, potentially causing muscle spasms, paresthesias, or seizures, while severe hyperkalemia can lead to reduced excitability and paralysis. In severe hyperkalemia (>7.0 mEq/L), persistent depolarization inactivates voltage-gated Na^+ channels, preventing them from reopening for further action potentials. These effects cause neuronal and muscle paralysis, which may contribute to respiratory failure or cardiac arrhythmias (23).

Non-physiological neuromuscular transmission leads to muscle weakness and paralysis, clinical manifestations related to neuronal dysfunction (24). In addition, abnormal sensations such as tingling or numbness (paraesthesia), and in extreme cases, seizures, and altered mental states such as confusion, lethargy, or coma may occur (25).

CONCLUSIONS

Hyperkalemia disrupts neuronal function by altering the resting membrane potential and action potential generation. Mild cases increase excitability, while severe cases lead to neuronal paralysis. Proper management of K+ levels is essential to prevent life-threatening complications.

Conflict of interest

The author declares that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

Letter to the Editor

CAN ASTHMA AFFECT BRAIN ACTIVITY AND VICE VERSA?

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KEYWORDS: *Asthma, CNS, brain, inflammation, chronic disease, neurotransmitter*

INTRODUCTION

Asthma is a recurrent lung disease characterized by respiratory noises, paroxysmal coughing and dyspnea due to hyperactivity with bronchospasm of the tracheobronchial airways that results in difficulty in breathing (1). Asthma is a chronic inflammatory disease of the airways which affects the respiratory system but also has complex interrelationships with the brain through biochemical and neuroimmune pathways (2). Chronic asthma affects neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are essential for mood regulation and cognition.

The onset of the disease can occur at any age but is more frequent between the ages of three to eight years old, with a higher incidence in males. Some risk factors for asthma include low birth weight, living in urban areas, and a family history of asthma or allergies (3). The etiology is multifactorial, from exposure to inhaled or ingested allergens, to infections, smoking, or inhalation of airway irritants. Two-thirds of subjects have allergic diathesis with immune responses mediated by IgE (4). Some studies have highlighted the role of gastroesophageal reflux in adenoid hypertrophy and chronic sinusitis (5).

The symptomatology of asthma is characterized by dyspneic crises with prolonged, labored, and noisy expiration, accompanied by rhonchi, rales, and wheezing. During the attack, the patient may become cyanotic, with sweating, bradycardia, and emission of fluid and bronchial secretion. Critical episodes may be rare or frequent and may involve the heart and pulmonary circulation, which could possibly lead to cardiac failure in the most serious cases (6).

DISCUSSION

Asthma and the central nervous system (CNS) are linked because the CNS regulates the airway muscles and inflammatory responses (7). Stress or anxiety can trigger asthma symptoms or worsen them by affecting airway control and inflammation (8). In fact, CNS activity can influence asthma symptoms, primarily through the interaction between the nervous and respiratory systems. Stress and emotional distress are processed in the CNS and can cause hyperventilation or airway constriction, leading to asthma exacerbation. Stress triggers the release of cortisol and other hormones, worsening airway inflammation (9). The autonomic nervous system regulates airway tone. Overactivation of the parasympathetic nervous system can lead to bronchoconstriction, while sympathetic stimulation may affect airway relaxation (10). Some medications that act on the CNS, such as sedatives or certain opioids, may depress respiratory drive or affect airway responsiveness, potentially triggering symptoms in asthmatic individuals (11).

Received: 28 October, 2024
Accepted: 27 December, 2024

2974-6345 (2024)

CNS-driven hyperventilation can irritate the airways, reduce CO2 levels in the blood, and cause bronchoconstriction. This can mimic or worsen asthma symptoms. Asthma is linked to higher rates of anxiety, depression, and cognitive impairments, likely through the shared inflammatory and neurochemical pathways. Activated Th2 immune responses lead to the elevation of IL-4, IL-5, IL-13, and IgE levels, contributing to lung inflammation and potentially signaling neuroimmune changes (12).

Some activated immune cells, such as mast cells (MCs) in the airways and brain, can release neuropeptides on site, causing airway inflammation, mucus production, and constriction, which worsens asthma symptoms (13). Asthma, MCs, and the brain are interconnected in ways that highlight the intricate link between the immune system, inflammation, and the nervous system (14). MCs are white blood cells involved in allergic reactions and are central to asthma pathophysiology. They reside in tissues like the airway epithelium, where they release histamine, leukotrienes, and cytokines in response to allergens. MCs contribute to bronchoconstriction, airway inflammation, and mucus overproduction, which are all hallmarks of asthma (15). MCs are present in the brain, especially near blood vessels and the meninges and contribute to neuroinflammation by releasing histamine and cytokines that may potentially influence conditions like migraine, multiple sclerosis, and mood disorders (16).

Inflammatory signals from MCs in asthma may influence the blood-brain barrier (BBB), leading to increased neuroinflammation (15). Their overactivation has been implicated in neuropsychiatric conditions such as autism spectrum disorders, anxiety, and post-traumatic stress disorder. Understanding the interrelationship between asthma, MCs, and the brain allows for a better understanding of asthma management by considering not only respiratory symptoms, but also the broader systemic and neurological impacts. The interaction between Th2 immune responses, asthma, and brain function is an important area that still needs to be explored further (17).

T helper cells (CD4+ T cells) are a subset of Th2 cells that orchestrate immune responses against extracellular pathogens. In allergic asthma, Th2 cells are central to allergic responses, driving IgE production and recruitment of other immune cells such as eosinophils and MCs (18). Th2 cells drive IgE production and recruitment of other immune cells. Th2 cells secrete cytokines such as IL-4 that promote IgE class switching in B cells. Inflammatory mediators in asthma, such as IL-1, IL-6, and TNF, might affect cognitive function, mood, and behavior (19). Stress or neural dysfunction can exacerbate asthma by promoting Th2-biased immune responses.

IL-4 and IL-13 are mediators of allergic asthma inflammation and may restrict the brain by promoting systemic inflammation (20). IL-6, although not strictly related to Th2 cells, may have downstream effects on both asthma and neuroinflammation, while IL-33, an alarmin cytokine, may be involved in Th2-mediated responses and neuroimmune interactions.

There's also evidence that asthma can influence brain function, possibly due to low oxygen during severe attacks or chronic inflammation (21). Asthma inflammation can increase the BBB's permeability, allowing systemic inflammatory mediators such as cytokines and chemokines to enter the brain and affect its homeostasis. This may exacerbate neuroinflammation, cognitive decline, or psychiatric disorders. Asthma triggers oxidative stress in both lung and brain tissues due to excessive production of reactive oxygen species (ROS), which can impair mitochondrial function in neurons and contribute to neurodegeneration. Pro-inflammatory cytokines can decrease serotonin availability, contributing to depression or anxiety, which are common comorbidities of asthma.

CONCLUSIONS

Novel therapies focusing on vagal nerve stimulation or antioxidants might benefit asthma and brain dysfunction. Anti-inflammatory drugs including corticosteroids and biologics targeting cytokine mediators might also indirectly improve brain health. Anti-IgE treatments such as omalizumab (a monoclonal antibody used during the treatment of severe-to-moderate persistent asthma in patients who cannot control symptoms with corticosteroids) reduce the symptoms of allergic asthma. Cytokine inhibitors are now also used in severe asthma. In addition, addressing stress and improving mental health can modulate immune responses and potentially improve asthma outcomes.

Conflict of interest

The authors declare that they have no conflict of interest.

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