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Special Article

Overtraining Syndrome: one more piece of the Central Sensitivity Syndrome puzzle

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ABSTRACT

The initial focus of overtraining syndrome was physical overexertion with inadequate rest, causing severe chronic fatigue and decreased performance. The pathophysiological knowledge has subsequently evolved, and although the exact mechanisms of overtraining syndrome are unknown, several hypotheses arise. The most prominent of these are: the existence of an immunoneuroendocrine imbalance and dysfunction of the central nervous system and of the neuroendocrine axis. On the other hand, central sensitivity syndrome encompasses nosological entities that share the pathophysiological mechanisms that cause them, that is, an immunoneuroendocrine and mitochondrial dysfunction as well as an oxidative stress imbalance. The most common entities within central sensitivity syndrome are fibromyalgia, tension headache and/or migraine, chronic fatigue syndrome, irritable bowel syndrome, multiple chemical syndrome, electrosensitivity syndrome, irritable bladder syndrome, and restless leg syndrome, among others. The pathophysiological and clinical analogy between overtraining syndrome and central sensitivity syndrome raises the possibility of including overtraining syndrome within central sensitivity syndrome, since a stressful stimulus such as chronic overtraining coupled with unbalanced compensatory systems can generate, at a given time, immunoneuroendocrine sensitization and therefore central sensitivity syndrome.
Keywords: Overtraining, Chronic fatigue, Central sensitization.

Síndrome de Sobreentrenamiento: una pieza más del puzle del Síndrome de Sensibilidad Central

RESUMEN

El enfoque inicial del síndrome de sobreentrenamiento ha sido el sobreesfuerzo físico con un descanso no adecuado, que provocaba fatiga crónica severa y disminución en el rendimiento. Posteriormente ha ido evolucionando el conocimiento fisiopatológico, y aunque se desconocen los mecanismos fisiopatológicos exactos del síndrome de sobreentrenamiento, se plantean diversas hipótesis. Las más destacadas son: la existencia de un desbalance inmunoneuroendocrino y disfunción del sistema nervioso central y el eje neuroendocrino. Por su parte el síndrome de sensibilidad central engloba entidades nosológicas que tienen en común las razones fisiopatológicas que las ocasionan, esto es, una disfunción inmunoneuroendocrina, mitocondrial y un desbalance del estrés oxidativo. Las entidades más comunes dentro del síndrome de sensibilidad central suelen ser la fibromialgia, la cefalea tensional y/o migraña, el síndrome de fatiga crónica, el síndrome de intestino irritable, el síndrome químico múltiple, el síndrome de electrosensibilidad, el síndrome de la vejiga irritable, el síndrome de piernas inquietas, entre otros. La analogía fisiopatológica y clínica entre el síndrome de sobreentrenamiento y el síndrome de sensibilidad central, plantea la posibilidad de englobar al síndrome de sobreentrenamiento dentro del síndrome de sensibilidad central, ya que ante la presencia de un estímulo estresante como lo es el sobreentrenamiento crónico, unido a sistemas compensadores desequilibrados, puede generar en un momento determinado una sensibilización.
Palabras claves: Sobreentrenamiento, fatiga crónica, sensibilización central.

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Síndrome do supertreinamento: mais uma peça do enigma da síndrome de sensibilização central

RESUMO

O foco inicial da síndrome do supertreinamento foi o excesso de esforço físico com descanso inadequado, causando fadiga crônica grave e diminuição do desempenho. Posteriormente o conhecimento fisiopatológico evoluiu e, embora os mecanismos exatos da síndrome do supertreinamento sejam desconhecidos, surgem várias hipóteses. Os mais proeminentes são: a existência de um desequilíbrio imunoneuroendócrino e disfunção do sistema nervoso central e do eixo neuroendócrino. Por outro lado, a síndrome da sensibilização central engloba entidades nosológicas que compartilham os mecanismos fisiopatológicos que as causam, ou seja, uma disfunção imunoneuroendócrina e mitocondrial, bem como um desequilíbrio de estresse oxidativo. As entidades mais comuns dentro da síndrome da sensibilização central são fibromialgia, cefaleia e/ou enxaqueca, síndrome de fadiga crônica, síndrome do intestino irritável, síndrome química múltipla, síndrome de eletrosensibilidade, síndrome da bexiga irritável e síndrome das pernas inquietas, entre outros. A analogia fisiopatológica e clínica entre síndrome do supertreinamento e síndrome da sensibilização central levanta a possibilidade de incluir a síndrome do supertreinamento dentro da síndrome da sensibilização central, uma vez que um estímulo estressante, como o supertreinamento crônico, juntamente com sistemas compensatórios desequilibrados, pode gerar, em determinado momento, sensibilização imunoneuroendócrina e, portanto, síndrome da sensibilização central.
Palavras-chaves: Supertreinamento, Fadiga crônica, Sensibilização central.

Introduction

Overtraining Syndrome (OTS) is defined as a marked and sustained decrease in physical performance and a state of fatigue that may limit the performance of daily activities in the individual with this disorder. Its origin is attributed to an imbalance between excessive exercise and an inadequate period of rest.

Although the exact pathophysiological mechanisms of OTS are still unknown, neuro-endocrine findings,[1] immunological alterations,[2] increased inflammatory markers[3] and oxidative stress[4] targeted in this process have generated different pathophysiological hypotheses that explain the true origin of OTS.[5-8]

The most prominent hypotheses include:

- OTS could be caused by a dysfunction of the central nervous system, produced mainly by the involvement of the hypothalamus, via activation of the Hypothalamus-Pituitary-Adrenal (HPA) axis and via activation of the Autonomic Nervous System (ANS).[4,9]
- OTS may be related to the local inflammatory process caused by musculoskeletal microtraumas that occur in the practice of sport and the consequent production of inflammatory cytokines. These act as messengers between the immune system and the Central Nervous System (CNS), which can cause an alteration in its functioning.[10]
- OTS may be due to free radicals acting as signals for the production of the endogenous antioxidant substances necessary for an adequate adaptive response (Theory of Hormesis). When a sustained excess of these free radicals occurs, they can cause an imbalance between these and the antioxidant substances, producing excess oxidative stress and mitochondrial dysfunction,[10] which can give rise to immunoneuroendocrine dysfunction and chronic fatigue.[9]

During high intensity exercise there is a marked decrease in blood flow in the digestive tract, which causes alterations in intestinal motility, inflammation of the digestive mucosa, increased intestinal permeability and bacterial translocation.[11] All this brings with it a hyperstimulation of the immune system of the digestive tract and a possible immunological sensitization. Direct interaction of digestive immune cells with the enteric nervous system facilitates dysfunction and sensitization of the central nervous system. This axis is closely related to the interaction of the food we ingest and the intestinal microbiota. This reinforces the need for and importance of good nutrition and a good digestive function in the athlete's performance and in the health status of the general population.

The presence of dysfunction of the immune and neuroendocrine systems, of the intestinal microbiota and an uncontrolled increase in oxidative stress and secondary mitochondrial dysfunction explain the appearance of the multiple symptoms that accompany the lack of performance and fatigue.

Central Sensitivity Syndrome

Central Sensitivity Syndrome (CSS) was defined by Yunus in 1994, and encompasses other nosological entities such as fibromyalgia, tension headache and migraine, chronic fatigue syndrome, irritable bowel syndrome, multiple chemical syndrome, electrosensitivity syndrome, irritable bladder syndrome, and premenstrual syndrome, among others.[12,13] All these have in common the pathophysiological mechanisms that cause them, that is, a central sensitization to the different stimuli, a dysfunction in the immunoneuroendocrine and autonomic nervous systems, as well as an excess of oxidative stress with mitochondrial dysfunction, among others.[14] The existence of a genetic predisposition in these patients has been described, as well as a series of trigger factors that favor the development and manifestation of the disease such as stressful situations, infections, exposure to chemicals, electromagnetic fields, and food.

Central sensitization is considered the most important pathophysiological mechanism in the genesis of this syndrome. It is produced by the excitation of cell membranes and dysfunction in the processing of various peripheral stimuli in various areas of the CNS, resulting in an amplification of ascending neurological pathways and a decrease in descending inhibitory pathways.[15]

The close interrelation of the immune system with the peripheral and central nervous systems facilitates the activation of the immune system to trigger central sensitization activation[16] through the release of proinflammatory cytokines, neural growth factors, or humoral substances such as histamines, by the immune cells acting both at the peripheral and central nervous system levels, specifically in the thalamus.[17] The communication between the immune system and the central nervous system is bidirectional, able to cause a secondary hypersensitization of the immune cells that undoubtedly can chronify the dysfunction between the systems. Therefore, the sensitization of the immune cells to different environmental stimuli can influence central sensitization, generating or even increasing central dysfunction, causing the chronification of symptoms, since there is an incorrect communication between the immunological cells (mast cells) and the central nervous system cells (neurone-glia-microglia).[18,19]

The neuroendocrine system formed by its main axis, hypothalamus-pituitary-peripheral glands and the ANS is altered in patients with fibromyalgia and chronic fatigue syndrome,[20] mainly via the Corticotropin-releasing hormone (CRH-ACTH)-cortisol and catecholaminergic pathway. The Growth hormone (GH) and thyroid axis are also affected. These systems are

intimately related to the immune system (via cytokines and/or through receptors that have estrogens in T cells, B cells, dendritic cells, natural killer (NK), etc.), and it has been shown that both innate and acquired immune function and the CNS can be activated. This explains how factors acting on these systems, such as stress, can influence immunoneuroendocrine dysfunction.

An increase in oxidative stress and mitochondrial dysfunction[20] as well as a deficit in coenzyme Q10[21], have been described in CSS, especially in fibromyalgia and in chronic fatigue syndrome. Free radicals can develop peripheral and central sensitization.[22] Moreover, oxidative stress and mitochondrial dysfunction may increase mast cell activation and thus immunological and central sensitization.[23]

The intestinal microbiota has multiple functions including immune, defense and maintenance of the digestive epithelial barrier. It is a vitamin producer and serves as a reservoir as well as regulating multiple functions. Alterations can cause dysfunction in the different systems in which it is involved, such as the immune system and the CNS.[24] The intestinal microbiota plays an important role in the bidirectional relationship between the CNS and the digestive tract, involving the neurological, endocrine and immunological pathways. Deregulation of any of these may lead to the destabilization of the entire system.[25] Therefore, the health of the intestinal microbiota and the intestinal barrier affect the pathophysiology of CSS.

Overtraining Syndrome and Central Sensitivity Syndrome

Symptoms of OTS and CSS are usually similar. Table 1 lists the symptoms, signs and biomarkers of these syndromes.

Table 1. List of common manifestations of overtraining syndrome and central sensitivity syndrome

Clinical	Physiological
• Muscle pain • Headache • Continued tiredness and intolerance to efforts • Sleep disorders • Low-grade fever, cold, night sweats • Gastrointestinal manifestations • Concentration and memory disorders • Sensitivity to stress and various environmental stimuli	• Tachycardia or palpitations, hypotension • Tachypnea, sensation of dyspnea • Decreased mechanical efficiency • Increased basal metabolism
• Neuroendocrine	• Immune
• Negative nitrogen balance • Hypothalamic-pituitary-adrenal axis; CRH, ACTH, TRH, TSH, GH, Altered levels of catecholamines, tiroxine, testosterone, cortisol, etc. • Significant deficiency in key minerals (Mg, Zn, Cu, etc.)	• Increased inflammatory markers, especially cytokines (IL6, TNFα, IL1) • Alterations in innate and acquired response, non-specific alterations in lymphocytes T, B, leukocytes

* Table is a guide and not exclusive of other factors. CRH: Corticotropin-releasing hormone; ACTH: Adrenocorticotropic hormone; TRH: Thyrotrophin releasing hormone; TSH: Thyroid-stimulating hormone; GH: Growth hormone; Mg: Magnesium; Zn: Zinc; Cu: Copper; IL6: Interleukin 6; TNF-α: Tumor necrosis factor alpha; IL1: Interleukin 1.

CSS and OTS have many similarities and share pathophysiological processes such as dysfunction in immunoneuroendocrine interaction, microbiota axis-intestinal permeability, and oxidative stress axis-mitochondrial dysfunction. They also share the same multiple symptoms: limiting fatigue, pain, digestive disorders, symptoms affecting the psycho-affective area and certain symptoms dependent on the immune dysfunction presented. There are a number of triggers that favor the manifestation of CSS, such as light stimuli, chemicals, drugs, stress and infections.

The physical and mental stress that elite athletes are subjected can cause chronic fatigue, contractures and sleep disorders. The pathophysiological and clinical similarities between OTS and CSS bring up the possibility that occurred previously with electrosensitivity syndrome and multiple chemical syndrome. In these syndromes the condition developed after exposure to chemical or electromagnetic stimuli, and although they were initially described as independent disorders, they were later encompassed in CSS. A similar situation occurs with OTS, which occurs in a specific population, and the stimulus that produces it is generated by the level of training itself. Therefore, it is logical that it has only been studied in the field of sports medicine. As in other conditions, it is reasonable to state that when compensatory systems do not have the capacity to regulate a stressful stimulus such as chronic overtraining, at a specific point an immunoneuroendocrine sensitization and, therefore, CSS can develop. This is important to be considered for elite athletes in order to apply preventive measurements to avoid the onset of OTS.

Considering the above, we suggest that OTS may be another syndrome that forms part of CSS because they share the same pathophysiological mechanisms and symptoms. Concerning the treatment, a multidisciplinary approach, as expressed by Blanco et al.[26] designed to act on the different systems in order to develop synergies that achieve better responses than approaches to a single system, it would be better.

More research in this new field should be done. In particular, it is important to find out biological markers able to identify this syndrome and their evolution, as well as, to study the molecular pathways involved in the syndrome. This will allow us to develop more effective and accurate treatments.

Authotship. All the authors have intellectually contributed to the development of the study, assume responsibility for its content and also agree with the definitive version of the article. **Provenance and peer review.** Not commissioned; externally peer reviewed. **Ethical Responsabilities.** *Protection of individuals and animals:* The authors declare that the conducted procedures met the ethical standards of the responsible committee on human experimentation of the World Medical Association and the Declaration of Helsinki . *Confidentiality:* The authors are responsible for following the protocols established by their respective healthcare centers for accessing data from medical records for performing this type of publication in order to conduct research/dissemination for the community. *Privacy:* The authors declare no patient data appear in this article.

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