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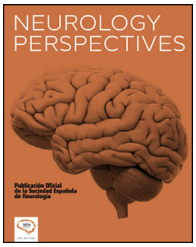

EDITORIAL

Management of the most prevalent autoimmune diseases co-occurring with Multiple Scleosis

Manejo de las enfermedades autoinmunes más prevalentes que coexisten con la esclerosis múltiple

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS). Multiple environmental, genetic, and lifestyle-related risk factors have been identified, and some of them may even be implicated as a causal factor (eg. Epstein-Barr virus); despite this, its aetiology remains unknown and its pathophysiology is only partially understood.[1]

Comorbidity is an area of growing interest in the field of MS. Comorbidities are associated with diagnostic delays, increased numbers of relapses, greater progression of disability, increased MRI lesion load, therapeutic inertia and limitations, increased numbers of treatment-associated adverse events, and reduced quality of life and life expentancy.[2,3]

Patients with immune-mediated diseases are more likely to develop different types of comorbidities. The concomitant presence of other autoimmune diseases associated with MS has acquired special relevance. There is a clinical perception that autoimmune diseases tend to coexist in the same patient (polyautoimmunity) and in families (autoimmune diathesis). The frequent co-occurrence of two or more diseases raises several key questions: (1) it suggests the possibility that they may share pathological characteristics or autoimmune phenotypes that may be favoured by common genetic and/or environmental factors; (2) the treatment used for one disease may be associated with the onset of another, although causality is not always established. The chronological order of onset, the latency between the development of the first and the second disease together with the therapies used for the first, and the increase in frequency of association of a comorbidity with a certain treatment, may help in understanding this relationship; (3) clinical and/or radiological manifestations that appear to be typical of an organ-specific autoimmune disease may in fact be symptoms of a systemic disease, creating diagnostic difficulties; this is the case, for example, of sarcoidosis, considered one of the greatest mimics of other diseases; (4) 2 or more coexisting autoimmune diseases may coincide by chance in the same individual.

The identification of new molecular targets has been shown to be therapeutically useful in controlling autoimmune diseases, and has enabled specific, selective targeting of treatments, leading to a paradigm shift in the therapeutic management of this group of diseases. The use of biological therapies has not only decreased the number of side effects with regard to the classic non-selective immunosuppressants but also has enabled a better understanding of the pathophysiological basis of autoimmune diseases. Thus, some autoimmune diseases have been observed to share pathogenic and molecular features, and some drugs initially developed for a certain disease have been used to treat other conditions. For example, sphingosine-1-phosphate receptors (S1PR1-S1PR5) mediate several physiological and cellular processes, including lymphocyte and other haematopoietic cell trafficking; as a result, they are involved in several autoimmune diseases, inhibiting lymphocyte output from lymph nodes (action mediated by the S1PR1). Although S1PR modulators were initially developed to prevent graft-versus-host disease after kidney transplantation, the only indication for which they were approved for many years was MS (fingolimod, siponimod, ozanimod, ponesimod), a disease in which they limit the entry of inflammatory cells into the CNS.[4]

Beyond MS, the use of this group of drugs has been extended to treat other inflammatory diseases.[5] Thus, ozanimod has been shown to decrease inflammation not only in animal models of experimental acute encephalomyelitis (leading to its subsequent approval for MS) but also in different models of inflammatory colitis,[6] so it is also currently indicated for ulcerative colitis.[7]

S1PR signaling plays a pivotal role in the inflammatory responses of autoimmune rheumatic diseases. Circulating

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sphingosine-1-phosphate (S1P) interacts with endothelial S1PRs, maintaining vascular integrity and blood flow while preventing leukocyte extravasation.[8] Consequently, S1PR modulators are under investigation for the treatment of conditions such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis.[5,8]

In psoriasis, characterized by abnormal keratinocyte proliferation and lymphocyte infiltration into the dermis and epidermis, therapies that induce lymphocytopenia and inhibit lymphocyte migration may be beneficial. Ponesimod, a selective S1PR1 modulator, has shown efficacy in phase 2 and 2b clinical trials for this condition.[9,10] However, it has not yet been evaluated in phase 3 trials.

Many other drugs currently used in the treatment of MS have also been shown to be useful in other autoimmune diseases; for example, anti-CD20 monoclonal antibodies, especially rituximab, in different rheumatic/systemic and skin diseases[11–13]; fumaric acid esters in psoriasis[14]; and leflunomide (a precursor of teriflunomide) in rheumatoid arthritis.[15] However, this evidence is not always from randomised clinical trials, but rather from case series, cohorts, or case reports. These findings have prompted researchers to explore the potential of applying the same therapy across multiple autoimmune diseases, although further controlled studies are needed to confirm efficacy and safety.

Some biological agents designed to act on specific immune system targets have also been implicated in the development of secondary autoimmune diseases. One of the best-known examples is alemtuzumab, a drug used for highly active forms of relapsing–remitting MS,[16] which has been associated with the development of autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis)[17] or immune-mediated glomerulonephritis,[18] among others.

Such organs as the skin, digestive tract, CNS, lungs, and connective tissues are targets of the adverse effects of some immunomodulatory therapies, which may manifest as psoriasis, immune-mediated enterocolitis, CNS demyelination, or systemic lupus erythematosus.[19] For instance, tumor necrosis factor alpha (TNF-α) inhibitors used for controlling rheumatoid arthritis have on rare occasions triggered CNS demyelinating events.[20–22] Anti-CD20 drugs have been associated with immune-mediated enterocolitis[23] and with the development or exacerbation of psoriasis.[24,25] Cases have also been described of natalizumab exacerbating psoriasis.[26,27] Teriflunomide has also been associated with cases of immune-mediated colitis[28,29] and psoriasis.[30,31] The majority of clinical data on these associations are published as case reports or anecdotal reports from specific consultations for this type of diseases, and not as large-scale epidemiological studies; this limits our ability to establish a clear causal relationship, as we cannot rule out other reasons for their coexistence.

Epidemiological studies on autoimmune comorbidities in multiple sclerosis (MS) populations often exhibit methodological limitations, as data are primarily derived from clinical histories, medical records, diagnostic tests, and administrative sources, among others.[2,32,33] Thus, the reported prevalence of autoimmune comorbidities in MS greatly varies depending on the sample size and the disease being considered, as well as the characteristics of the population under study. Limitations are even greater for incidence data. These limitations are even more pronounced concerning incidence data, with few large-scale, population-based studies available. Reliable prevalence and incidence data are crucial for assessing changes in comorbidity frequencies, which may be associated with demographic changes in the population or exposure to different environmental factors, for example, the use of certain drugs. The different exposure to these treatments in the various published studies may at least partially explain the heterogeneity of the results obtained.[2,32,33] Despite the lack of definitive epidemiological relationships or a clear understanding of the nature of these associations, existing data have prompted caution in therapeutic decision-making when multiple autoimmune diseases coexist.

This monographic issues explores the therapeutic management of MS coexisting with other autoimmune diseases. It emphasizes identifying therapies that are contraindicated in such scenarios—those that may ameliorate one condition while exacerbating another—and those that are recommended, either due to their efficacy in both conditions or their safety profile in one without adversely affecting the other. Given the low prevalence of many of these comorbidities, conducting randomized clinical trials poses significant challenges, often resulting in a lack of formal indications. Consequently, much of the available guidance is derived from expert opinions, case reports, or observational studies rather than robust clinical trial evidence. Therefore, when a patient with MS presents with a pre-existing autoimmune comorbidity or develops one during the disease course, clinicians should consider the following questions:Can a single treatment effectively manage both conditions?Could the current treatment be contributing to the onset of the new autoimmune disease?Might the therapy for one condition potentially worsen the other?

This monographic issue presents a comprehensive overview of the therapeutic management of multiple sclerosis (MS) when coexisting with various autoimmune diseases. It encompasses articles addressing the management of MS alongside autoimmune dermatological conditions, inflammatory bowel disease, autoimmune ophthalmological disorders, rheumatological and systemic diseases, as well as other autoimmune conditions such as myasthenia gravis, autoimmune encephalitis, combined central and peripheral demyelination, and Guillain–Barré syndrome. Each article includes therapeutic algorithms designed to provide clinicians with concise, practical guidance for managing these complex comorbidities.

Given the dynamic nature of this field, readers may encounter additional bibliographic data not included in this issue or have personal experiences that have yet to be documented in the medical literature. Such anecdotal evidence, while not a substitute for rigorous scientific research, can offer valuable insights and generate new hypotheses for further study. Clinicians are encouraged to share these observations through appropriate channels, such as case reports, to contribute to the broader understanding and management of multiple sclerosis and its associated autoimmune comorbidities.

Patient informed consent

No patient data are reported.

Ethical considerations

Not applicable.

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Conflicts of interest

None.

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