Autoimmune Comorbid Conditions in Multiple Sclerosis

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Abstract

Autoimmune comorbidities occur frequently in multiple sclerosis (MS). They may arise as a consequence of a genetic susceptibility to autoimmunity. Certain pathological mechanisms are common to several autoimmune conditions. In the presence of comorbid autoimmune conditions, certain MS therapeutics may be preferable to others. Autoimmune comorbidity associated with MS could be a factor in predicting response to specific MS therapeutics. Treatment with interferon beta has been reported to precipitate immune-mediated abnormalities or to exacerbate existing autoimmune diseases. In comparison, there are fewer reported cases of treatment-associated comorbidities linked with autoimmune disease in patients taking glatiramer acetate. Knowledge of the factors influencing autoimmune comorbidities may provide insights into the complex pathogenesis of MS and help inform treatment choices.

Keywords

Autoimmune, comorbidity, glatiramer acetate, interferon, multiple sclerosis

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Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS). Although it is generally considered to be an autoimmune disease, MS may be a heterogeneous condition incorporating different pathologies. The incidence of autoimmune comorbidities in MS patients may help us elucidate the autoimmune aspects of the disease. Furthermore, the presence of autoimmune comorbidities may help us discover new biomarkers with potential predictive value regarding response to treatment, and understand common factors in pathogenesis. This article aims to review autoimmune comorbidities in MS, their incidence and burden in the MS population, and their possible association with MS treatments. We will address potential measures that might reduce the impact of treatment in triggering comorbidities.

Multiple Sclerosis as an Autoimmune Disease

The most widely accepted hypothesis for the pathogenesis of MS is that it is a primary autoimmune disease. This idea was reinforced following observations on experimental autoimmune encephalomyelitis (EAE) in the late 1960s and early 1970s.[1–4] It has been repeatedly demonstrated that EAE is an autoimmune disorder caused by T-cell sensitization to various myelin proteins capable of triggering encephalomyelitis. The hypothesis is further supported by considerable evidence, such as the presence of elevated lymphocytes, macrophages, and microglia in MS lesions; strong genetic associations with genes in the major histocompatibility complex (MHC) region of chromosome 6; and the efficacy of new treatments that target the immune response. However, there are some aspects of the autoimmune pathogenesis hypothesis of MS that require further clarification. Much of this hypothesis is based on animal models of EAE; however, many agents that can successfully treat EAE have failed to show any clinical benefit in MS. This suggests that EAE is not an accurate model of MS and that the two conditions have some different pathophysiological characteristics.[5] In order to yield clues to the pathogenesis of MS, EAE experimental models should be critically coupled with actual findings in MS.[6]

The most compelling evidence that there is an immune pathogenesis in MS comes from the striking benefit seen when lymphocyte migration to the CNS is blocked with natalizumab, or when lymphocytes are trapped in regional lymph nodes with fingolimod.[7,8] It is difficult to discount the fact that, when monocytes are barred entry to the CNS, the rate of relapse and pace of progression of disability in MS are attenuated.

A further challenge to the autoimmune pathogenesis hypothesis of MS has arisen following findings that some of the antibodies identified in the

cerebrospinal fluid of MS patients are not directed against any of the known myelin proteins.[9] A mitigating argument is that some of these antibodies may be targeting myelin lipids and carbohydrates that are known to play a role in autoimmune inflammation.[10] One hypothesis is that demyelination is caused by oligodendrologlial apoptosis and that inflammation is merely a secondary event initiated to eliminate the products of myelin degeneration.[11] Whether it is apoptosis or infection that triggers the inflammatory response, there is evidence of an unmistakable immune footprint at the site of disease. Inhibiting the entry of immune cells to the brain provides great benefit, as shown by natalizumab, its effects, and its underlying mechanism of action.[7]

Another confounding factor in the pathogenesis of MS lies in the available treatment options. MS relapse management treatments, such as systemic steroids and adrenocorticotrophic hormone (ACTH), are also widely accepted for other autoimmune conditions, where they can be used for maintenance or treatment of acute exacerbations. The potential disease-modifying role of ACTH in MS needs to be more extensively studied. Disease-modifying treatments for MS, such as interferon beta (IFNβ), glatiramer acetate (GA), natalizumab, fingolimod, and BG-12, have mostly unknown or insufficiently studied applications for other autoimmune conditions (with the exceptions of the BG-12 analog, which is approved for use in psoriasis, and of natalizumab, which is approved for use in Crohn's disease). GA shows promise in inflammatory bowel disease.[12]

Effect of Autoimmune Comorbidities on Multiple Sclerosis Diagnosis, Treatment, and Outcomes

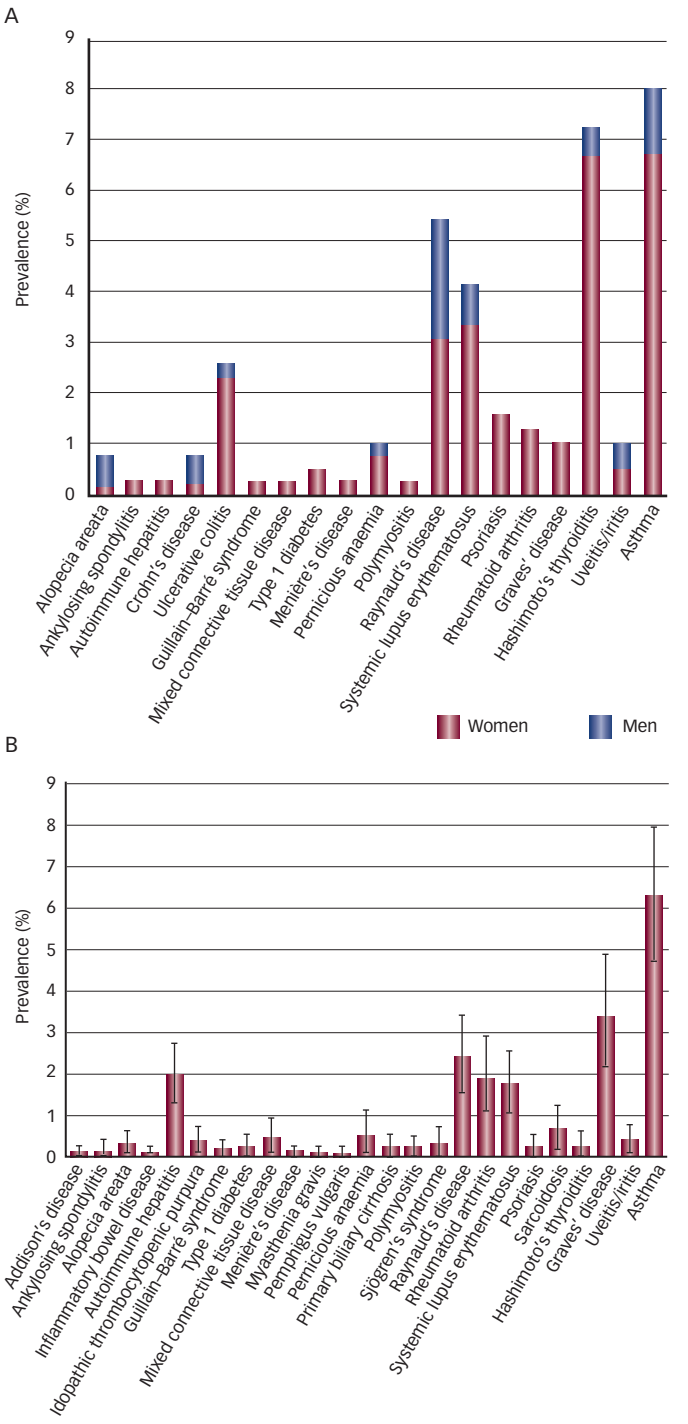
Comorbidities are an important issue in MS. They significantly worsen the impact of the disease and some of them (e.g., vascular disease, Alzheimer's disease) are associated with neurodegeneration in progressive MS.[13] While there are many different types of comorbidities in MS, autoimmune conditions are a common feature in many patients, and some occur more often in MS patients than in the general population.[3,4,14]

It has been shown that autoimmune comorbidities in MS can affect a number of aspects, including diagnosis, clinical phenotyping of the disease, disease and disability progression, quality of life, and treatment decisions.[15] A North American registry study found a diagnostic delay of one to 10 years in MS patients who had vascular, autoimmune, musculoskeletal, gastrointestinal, visual, or mental comorbidities.[16] No direct association has been reported between autoimmune conditions and disability progression;[17] however, the association between comorbidities and increased disability at diagnosis has led to the suggestion that comorbidities may act pathophysiologically to hasten disease progression.[15]

The presence of autoimmune comorbidities in MS has important implications for therapeutic decision-making. For example, in the presence of comorbid inflammatory bowel disease or uveitis, the use of anti-tumour necrosis factor (TNF) biologic therapies should be avoided. Likewise, it would be inadvisable to treat MS with natalizumab in a patient previously given immunosuppressive therapy for either MS or a comorbid autoimmune condition.[18]

Research into the diagnosis and treatment of autoimmune comorbidities within the MS population has not been given sufficient attention. The resulting information gap adds further complexity to disease management. Addressing this gap is important, particularly because early recognition and treatment of the comorbid conditions can improve prognosis, help define the disease course, and allow better informed and more individualized treatment decisions.

Figure 1: Autoimmune Diseases Reported in Patients with MS (A) and Estimated Prevalence of Autoimmune Disease Among First-degree Relatives (B)



The data come from a study of 176 families (including 386 individuals with multiple sclerosis and 1,107 first-degree relatives). MS = multiple sclerosis. Source: Barcellos, et al., 2006.[23]

Table 1: Overview of Some of the More Frequent Autoimmune Conditions and their Degree of Association with MS

Condition	Description	Frequency in MS Prior to Diagnosis (%)	Frequency in Matched Controls	Adjusted OR (95% CI); p-value	Reference
Autoimmune hepatitis	Rare event, but should be considered when re-exposing MS patients with previous hepatic damage to immunomodulatory drugs	0.06	0.02	2.5 (0.6–9.9) p=0.20	Deltenre, et al., 2009;[68] von Kalckreuth, et al., 2008[69]
Autoimmune thyroiditis	Inflammation of the thyroid and decrease in thyroxin secreted. Significantly more prevalent in male MS patients than in male controls (9.4 versus 1.9 %; p=0.03). Studies are needed to show whether autoimmune thyroiditis influences disease progression	0.17	0.18	1.0 (0.5–1.9)	Niederwieser, et al., 2003;[28] Rotondi, et al., 2011[61]
Guillain–Barré syndrome	Acute inflammatory demyelinating polyneuropathy of the peripheral nervous system, causing weakness and more serious damage to the autonomic system	0.1	0.02	5.0 (1.6–15.4) p=0.006	Langer-Gould, et al., 2010;[24] Flachenecker, 2007[70]
Inflammatory bowel disease	Genetic evidence suggests that inflammatory bowel disease and systemic lupus erythematosus are linked. One case has been reported of an MS patient who developed ulcerative colitis following treatment with IFNβ-1a. An Australian registry study found an association between ulcerative colitis and MS	0.8	0.45	1.7 (1.2–2.5) p=0.002	Marrie and Horwitz, 2010;[33] Schott, et al., 2007;[59] De Jager, et al., 2006;[71] Pokorny, et al., 2007[72]
Scleroderma	Cases of scleroderma developing following MS have been reported	0.06	0.06	1.0 (0.3–3.4)	Jawad, et al., 1997;[73] Trostle, et al., 1986[74]
Type 1 diabetes	A Sardinian cohort study found a fivefold higher prevalence of diabetes in MS patients than in the general population	0.85	0.9	0.9 (0.7–1.3)	Marrosu, et al., 2002[75]
Uveitis	Well-documented association between uveitis and MS. Occurrence varies widely, between 0.4 and 26.9 %. IFNβ-1a has been found to be beneficial in the treatment of MS-associated uveitis	1.3	0.6	2.2 (1.7–2.9) p<0.001	Becker, et al., 2005[76]
Psoriasis	A recent systematic review of the literature concluded that psoriasis does not appear to be more common in patients with MS or their relatives	1.3	1.2	1.1 (0.8–1.4)	Kwok, et al., 2010[77]
Rheumatoid arthritis	MS and rheumatoid arthritis appear to have a reduced chance of coexistence	0.83	0.86	1.0 (0.7–1.3)	Nielsen, et al., 2006;[25] Cooper, et al., 2009;[26] Somers, et al., 2009[27]
Asthma (without chronic obstructive pulmonary disease)	A large North American study found no association between MS and asthma. However, a retrospective study in Wales established an inverse relationship between asthma and MS	2.8	3.0	0.9 (0.8–1.1)	Langer-Gould, et al., 2010;[24] Tremlett, et al., 2002[29]
Systemic lupus erythematosus	A recent American population-based case-control study found no increased likelihood of MS patients having or developing systemic lupus erythematosus	0.4	0.3	1.3 (0.8–2.2)	Langer-Gould, et al., 2010[24]

CI = confidence interval; IFNβ = interferon beta; MS = multiple sclerosis; OR = odd ratio. Frequency and adjusted ORs of autoimmune comorbidities prior to MS diagnosis taken from a population study of MS patients enrolled in a medical care program (i.e., Northern California Kaiser Permanente [NCKP] medical care program) compared with matched controls. ORs adjusted for age, gender, and NCKP membership duration. p-values >0.20 not reported. Source: Langer-Gould, et al., 2010.[24]

Table 2: Some of the Autoimmune Conditions More Frequently Associated with Disease-Modifying Agents used in MS

Condition	Description	Reference
Liver dysfunction	In a study of 40 RRMS patients treated with IFNβ, transient liver function alteration was seen but did not require treatment discontinuation, with the exception of one patient who was already suffering from a drug-induced hepatopathy at baseline	Durelli, et al., 1999[55]
Myasthenia gravis	Cases of myasthenia gravis have been reported in MS patients following IFNβ therapy	Blake and Murphy, 1997;[60] Dionisiotis, et al., 2004;[78] Gharagozli, et al., 2011[79]
Panniculitis	Several cases of panniculitus associated with IFNβ treatment and GA treatment in MS patients	Soós, et al., 2004;[48] Ball, et al., 2009;[80] Poulin, et al., 2009;[81] Soares Almeida, et al., 2006[82]
Psoriasis	Worsening of cutaneous psoriasis and activation of psoriasis in an MS patient during IFNβ therapy, which resolved after treatment discontinuation. Cases of activation of psoriasis reported during IFNβ treatment in MS patients	López-Lerma, et al., 2009;[83] La Mantia and Capsoni, 2010;[84] Navne, et al., 2005[85]
Thyroid dysfunction	In a study of 40 RRMS patients treated with IFNβ, three cases of persistent autoimmune thyroid dysfunction were reported. Autoimmune thyroid disease has been reported in patients receiving IFNβ, but not in patients receiving GA	Durelli, et al., 1998;[54] Rotondi, et al., 2011[61]
Ulcerative colitis	Several reported cases of ulcerative colitis in MS patients during IFNβ therapy	Schott, et al., 2007;[59] Rodrigues, et al., 2010;[86] Tuna, et al., 2011;[87] Palao-Duarte, et al., 2005[88]
Vasculitis	Several reported cases of vasculitis in MS patients during IFNβ therapy	Daza-Barriga, 2008;[89] Débat Zoguéreh, et al., 2004;[90] Szilasiová, et al., 2009[91]

GA = glatiramer acetate; IFNβ = interferon beta; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

Studies of Autoimmune Comorbidities in Multiple Sclerosis

Until recently, clinical data relating to the co-occurrence of autoimmune diseases in MS have been predominantly based on uncontrolled case series or small case-control studies, with few studies accounting for confounding factors such as age and sex. There are many difficulties inherent to such studies, such as selection or ascertainment bias. Results may differ depending on which conditions are included and how the diagnosis is reached.[18] In ethnically-mixed populations such as that of North America, the use of spouses as controls allows ethnic matching[19] (the use of such controls is fairly common in genetic studies but much less widespread in clinical trials[20–22]). However, since MS is significantly more prevalent in females, this approach can increase a potential gender imbalance between cases and controls.

In a study of families in which several members had been diagnosed with MS (176 families, 386 individuals with MS, and 1,107 first-degree relatives), participants were studied for a history of coexisting autoimmune disorders (see *Figure 1*).[23] Of the 386 individuals with MS, 26 % had a coexisting autoimmune disorder. Of the 1,107 first-degree relatives, 64 % had a history of autoimmune conditions. The most commonly reported autoimmune conditions in MS patients and their relatives were Hashimoto's thyroiditis, psoriasis, and inflammatory bowel disease (IBD).

A recent American population-based case-control study using a large database (5,296 MS cases and 26,478 matched controls) found that individuals with MS were more likely than controls to have uveitis, IBD, and Bell's palsy prior to MS diagnosis.[24] They were also more likely to develop Guillain–Barré syndrome and bullous pemphigoid. However, the study found no increased likelihood of MS patients having or developing rheumatoid arthritis (RA), lupus, or thyroiditis. The study concluded that MS may share environmental triggers, genetic susceptibilities, and/or alterations in immune homeostasis with IBD and uveitis, but not with other autoimmune disorders. The study had limitations relating to its methodology and reliance on electronic patient records. By grouping certain diseases together, opportunities to gain valuable information were lost; for example, IBD incorporates Crohn's disease and ulcerative colitis (UC), which have immunopathological differences, and to differentiate between the two might have given clues to shared mechanisms with MS.

A Danish registry study showed that autoimmune disorders tended to co-occur with MS and to occur in MS patients' families, but that this was not a uniform phenomenon across all diseases.[25] Patients with type 1 diabetes were found to have more than a threefold increased risk of developing MS. Compared with the general Danish population, MS patients were found to have increased incidences of type 1 diabetes, UC, autoimmune thyroiditis, and pemphigoid, but a decreased incidence of RA. MS and RA appear to have a reduced likelihood of co-existence.[26] This inverse association between MS and RA has also been found in a population-based cohort study using the UK General Practice Research Database.[27]

While the above studies show similarities, there are inconsistencies in the data regarding the association between thyroiditis and MS. Autoimmune thyroiditis was found to be significantly more prevalent in male MS patients than in male controls (9.4 versus 1.9 %; p=0.03). However, there was no significant difference in the prevalence of autoimmune thyroiditis in female MS patients and female controls (8.7 versus 9.2 %). Further studies are required to determine the cause of this increased prevalence of autoimmune thyroiditis in males with MS.[28] This finding illustrates the importance of avoiding gender bias in studies of comorbidities in MS.

A large North American study found no association between MS and asthma,[24] although asthma associated with chronic obstructive

Table 3: Single Case Studies of Autoimmune Conditions Associated with Disease-modifying Agents used in MS

Condition	Description	Reference
Autoimmune hepatitis	One case has been reported of GA-induced acute exacerbation of autoimmune hepatitis in an MS patient	Neumann, et al., 2007[46]
Systemic lupus erythematosus	One case has been reported of a patient with RRMS who developed lupus syndrome after 32 months of IFNβ therapy	Bonaci-Nikolic, et al., 2009[92]
Rheumatoid arthritis	One case has been reported of new-onset rheumatoid arthritis in an MS patient during IFNβ therapy	Alsalameh, et al., 1998[58]
Urticarial vasculitis	One case has been reported of urticarial vasculitis induced by GA treatment in an MS patient	Cicek, et al., 2008[49]

GA = glatiramer acetate; IFNβ = interferon beta; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

pulmonary disease was excluded from the study—presumably to select specifically for atopic asthma. However, a retrospective study in Wales established an inverse relationship between asthma and MS (odds ratio 0.33; 95 % confidence interval 0.15–0.77).[29] This was supported by a study of general practitioner prescribing data from Wales, which found that MS patients were prescribed fewer anti-asthma drugs (e.g., bronchodilators and inhaled corticosteroids) compared with controls (but the authors noted that treatments given to MS patients could improve asthma symptoms, thus potentially reducing the need for anti-asthma medication).[30] Conversely, an Australian study of 136 MS cases and 272 matched controls reported that MS patients were more likely (p=0.02) than controls to have asthma that started before the onset of MS symptoms.[31] Some researchers believe that there may be a link between asthma and autoimmune conditions including MS; the detection of certain autoantibodies (e.g., antibodies to the β-2 adrenergic receptor) in asthmatics may support this.[32] This link, however, is controversial, and much more data are needed to clarify putative associations and possible common mechanisms.

In summary, the data published to date show a marked association between MS and certain autoimmune comorbidities. *Table 1* gives an overview of some of the more frequent autoimmune conditions and their degree of association with MS. Future studies should look at comorbidities as well as taking into account the modifying effects of socioeconomic status, ethnic origin, and cultural factors in MS.[33]

Autoimmune Comorbidities in Multiple Sclerosis—Genetic and Environmental Factors

Autoimmune conditions have been shown to be more common in families at high risk of multiple sclerosis than in the general population, suggesting that these diseases might arise on a genetic background of generalized susceptibility to autoimmunity.[23] On the other hand, a population-based study found that, when data were adjusted for sex, no excess of common autoimmune diseases could be identified in MS patients or their families.[19] Such conflicting results lead to four questions:

- Are MS patients indeed more likely to have other autoimmune diseases?
- Is there anything special (clinically, radiologically, immunologically, genetically) in patients with MS and autoimmune comorbidities that can help us better understand MS?
- Are MS treatments beneficial or harmful to other autoimmune conditions?
- Can we identify biomarkers to help us predict the outcomes of these treatments?

Studies investigating genetic susceptibility to MS have identified a number of genomic regions and specific genes of interest, most of which are associated with immune response, in particular the MHC region on chromosome 6.[34–38]

Although epidemiological data have suggested an inverse association between MS and RA, genome-wide association studies (GWASs) have found that MS and RA share many genetic factors.[39] However, certain genetic loci for susceptibility to autoimmune disease, delineated in GWASs, are not associated with both MS and other autoimmune diseases; for example, the *PTPN22* risk allele has been strongly associated with type 1 diabetes, RA, and thyroiditis, but not with MS.[40]

In addition to genetic factors, synergistic interactions between environmental factors that trigger autoimmunity—such as Epstein–Barr virus infection or vitamin D deficiency—may underlie comorbidities.[18] Vitamin D receptor knockout and vitamin D-deficient mice have a surplus of a type of effector T-cell that has been implicated in the pathology of MS and IBD.[41] In addition, smoking is associated with an increased risk of comorbid autoimmune disease in MS.[3]

Effects of Disease-modifying Drugs on Autoimmune Comorbidities

First-line agents approved for the treatment of MS include IFNβ and GA.[42–45] Some of the autoimmune conditions more frequently associated with disease-modifying agents used in MS are shown in *Table 2*, and isolated cases are summarized in *Table 3*. These and other autoimmune comorbidities could possibly serve as biological markers predicting good response to GA and unfavourable response to IFNβ.

It is evident from *Tables 2* and *3* that there are more reported cases of autoimmune comorbidities in MS patients treated with IFNβ than in those treated with GA. There have been individual case reports of exacerbation of autoimmune conditions—e.g., autoimmune hepatitis—in patients treated with GA.[46] Other reported conditions that may have an autoimmune basis and are associated with GA include necrotising cutaneous lesions,[47] panniculitis,[48] and urticarial vasculitis.[49] It must be emphasized, however, that these reports are from single case studies.

The effect of GA on autoimmune conditions comorbid to MS has been studied in experimental animal models. GA has been found to alter the clinical course of type 1 diabetes in animal models,[50] and has exerted beneficial effects on uveoretinitis in rodents,[51] but had no effect on rodent models of systemic lupus erythematosus (SLE)[52] and was found to exacerbate RA.[53] These variable results in animal models suggest that GA may exert its immunomodulatory effect in an antigen-independent manner.

As discussed above, IFNβ therapy can precipitate immune-mediated abnormalities or exacerbate an existing autoimmune tendency. Following reports of autoimmune thyroid and liver disorders in two MS patients treated with IFNβ,[54] the thyroid and liver function and the serum level of 12 autoantibodies against organ-specific (thyroid, gastric, pancreatic) and non-organ-specific antigens were serially monitored. In contrast to control patients, autoantibodies (anti-nuclear, anti-smooth muscle or anti-thyroid antigens) were detected in 13 patients treated with IFNβ and, in many cases, these were associated with thyroid or liver function alteration.[55] In a separate study of MS patients treated with IFNβ, serum anti-microsomal and anti-thymocyte globulin autoantibodies were detected, with one case of autoimmune hepatitis reported.[56]

Since these studies were completed, several major autoimmune comorbidities have been found to be associated with IFNβ treatment, including SLE,[57] RA,[58] UC,[59] and myasthenia gravis.[60] Autoimmune thyroiditis has been reported in MS patients receiving IFNβ, but not in those receiving GA.[61] In 2010, we presented to the American Academy of Neurology four clinical cases of comorbid MS and psoriasis; all four patients had previously not responded to treatment with IFNβ and, later, all four responded to treatment with natalizumab.[62] The association of IFNβ treatment with systemic autoimmune diseases may be explained in several ways. IFNβ modulates gene expression and the immune system, providing pathogenic influences in some cases, while in other cases providing protection.[63]

Recent studies have enhanced our understanding of the role of T-helper type 1 (Th1) and T-helper type 17 (Th17) effector cells. A growing body of evidence suggests that Th17 cells, along with Th1 cells, play a major role in the pathogenesis of MS.[64] Th1 and Th17 responses counter-regulate each other. Both Th1 and Th17 cells have the capacity to cause autoimmunity independently of each other. These findings are important in understanding the role of IFNβ in the treatment of MS and MS-associated comorbidities. In animal model studies, it was found that treatment with IFNβ reduced EAE symptoms induced by Th1 cells, but exacerbated symptoms induced by Th17 cells. Furthermore, non-responsiveness to IFNβ in patients with relapsing-remitting multiple sclerosis (RRMS) was associated with high serum levels of the TH17 cytokine IL-17F.[65] High serum levels of IL-7, particularly when paired with low serum levels of IL-17F, are predictive of response to IFNβ.[66] IFNβ and other type I IFNs appear to be immunomodulatory in diseases driven predominantly by Th1, but inflammatory in diseases resulting from a Th17 response.[67]

Summary and Future Directions

Autoimmune comorbidities are an important component of the range of comorbid conditions seen in MS and contribute to the substantial disease burden experienced by many MS patients. Autoimmune comorbidities are often associated with MS and can worsen the impact of the disease. These conditions need to be treated and managed by neurologists and specialist MS nurses in collaboration with other specialists.

It is important to be aware that the predisposition of MS patients to autoimmune comorbidities is not uniform across all diseases. Further studies are required to establish which genetic and environmental factors influence autoimmune comorbidities in MS. More standardized methods of measuring and analysing autoimmune comorbidities and their associations with MS are needed. More studies are also needed to address the effects of autoimmune comorbidities on MS. These future studies should assess a wider range of comorbidities and examine how the frequency of comorbidities changes over time. Finally, the effects of MS treatments on autoimmune comorbidities can potentially inform choices about therapeutic regimens, and more research in this area is greatly needed. ■

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