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Autoimmunity in multiple sclerosis

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Article abstract—Multiple sclerosis reportedly coexists with disorders of autoimmune origin. The prevalence with which such disorders occur in the MS population has not been adequately investigated. We reviewed the medical records of 828 patients with definite MS and found that 4.8% had a past or present associated disorder in which autoimmune mechanisms presumably play a role. The cumulative prevalence of these disorders was no higher than that estimated for the general population. Serum from 105 patients, without clinical evidence of an associated autoimmune disorder, was tested for the presence of antinuclear, thyroid, parietal cell, smooth muscle, and mitochondrial antibodies. A significantly higher prevalence ($p < 0.01$) of generally low titers of one or more autoantibodies was found in serum from the MS group, compared with a control group of 105 patients with other neurologic disorders. The increased frequency of serum autoantibodies probably reflects the existence of a nonspecific B cell overactivity in MS.

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Extensive evidence indicates that immune mechanisms are disturbed in multiple sclerosis. However, it is unclear whether these abnormalities play a primary role in its pathogenesis or represent only an epiphenomenon.[1-3] The autoimmune hypothesis of MS is based mainly on the pathologic similarity of the disease with chronic relapsing experimental allergic encephalomyelitis.[4]

MS in most, but not all, ethnic groups has been linked with particular HLA antigens,[2] and studies of peripheral blood T cell subpopulations in MS patients demonstrated reductions in the number of T suppressor cells.[5-7] An association with specific HLA antigens, which are concerned with the control of the immune response, as well as alterations in the balance of the immunoregulatory T cell subpopulations, have been noted in a variety of autoimmune disorders.[8-10]

Autoimmune diseases tend to occur in combination. The finding that a disease is more frequently associated with recognized autoimmune disorders than would be expected by chance may thus provide an indication that the disease itself has an autoimmune basis. A classic example is myasthenia gravis. Before acetylcholine receptors were discovered, myasthenia gravis was postulated to have an autoimmune pathogenesis,[11] based on associations with other autoimmune disorders.

MS has been reported in combination with disorders of autoimmune origin (see "Discussion"). However, most of these proposed associations are based on case reports. The prevalence of putative autoimmune disorders in the MS population has not been fully investigated. The purpose of this study was to find out if there is evidence for more generalized autoimmune reactions in MS.

Patients and methods. We reviewed the medical records of patients who attended the National Hospital for Nervous Diseases (London), between 1979 and 1984, with clinically or laboratory-supported definite MS, as defined by Poser et al.[12] The study population consisted of 828 patients (537 females and 291 males) ranging in age from 12 to 79 years. We screened the records for past or present associated disorders in which autoimmune mechanisms are considered to play a role.

Serum from 105 MS patients without clinical evidence of an associated autoimmune disorder was analyzed for the presence of antinuclear, thyroid, parietal cell, smooth muscle, and mitochondrial antibodies. None of these patients had been selected on clinical grounds, but the presence of autoantibodies was assessed as part of an initial routine evaluation before the diagnosis of MS was established. A control group consisted of patients with other neurologic disorders, matched for age and sex to the patients with MS,

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Table 1. Associated disorders with autoimmune character

Associated disorders	No. of pts	Prevalence (%)	Estimated prevalence (%)
Rheumatic			
Rheumatoid arthritis	5	0.6	1[39]
Ankylosing spondylitis	1	0.12	0.1[39]
Polymyalgia rheumatica	1	0.12	0.5[40]*
Gastrointestinal			
Ulcerative colitis	2	0.24	0.08[39]
Celiac disease	1	0.12	0.03[41]
Primary biliary cirrhosis	1	0.12	0.014[42]
Chronic atrophic gastritis	1	0.12	?
Dermatologic			
Vitiligo	2	0.24	1[43]
Alopecia universalis	1	0.12	?
Cutaneous lupus erythematosus	1	0.12	?
Endocrine			
Type I diabetes mellitus	4	0.48	0.5[44]
Hyperthyroidism	15	1.8	1.1[45]
Primary hypothyroidism	4	0.48	0.8[45]
Neurologic			
Chronic inflammatory neuropathy	2	0.24	?
Total	41†	4.92	5.12

* In the population aged 50 years or older.
† One patient suffered from rheumatoid arthritis and hyperthyroidism.

who had been admitted during the same period. Patients with overt autoimmune disease were not included. The mean age for the patients with MS was 35 years; controls had a mean age of 39 years. The controls suffered from the following conditions: cerebrovascular disorders (19), movement disorders (11), headache and other pain syndromes (41), functional disorders (20), idiopathic epilepsy (8), nerve entrapment (4), and positional vertigo (2). Indirect immunofluorescence was used to screen serum diluted at 1:10 for antibodies reactive with cell nuclei, gastric parietal cells, smooth muscle, and mitochondria. Rat kidney, stomach, and liver (Biodiagnostics Ltd.) were the receptive substrates. All serum positive at 1:10 was further titrated. Thyroglobulin and microsomal antibodies were analyzed by a Thymune-M kit (Wellcome Diagnostic) and titers of, respectively, $\geq$ 1:10 and $\geq$ 1:100 were considered positive. The χ^2 test was used for statistical analysis.

Results. *Associated autoimmune disorders.* Forty patients (4.8%) had a past or present disorder in which autoimmune mechanisms were believed to be implicated. A list is given in table 1.

Rheumatoid arthritis was diagnosed in five patients; in one this was associated with Sjögren's syndrome, and one had previously been treated with ^{131}I for hyperthyroidism. One patient had longstanding ankylosing spondylitis, and a 50-year-old woman was in remission of polymyalgia rheumatica after prolonged treatment with corticosteroids.

Two patients developed a chronic inflammatory demyelinating neuropathy after the clinical onset of MS. They are described in detail by Thomas et al[13] (cases 1

Table 2. Autoantibodies in MS patients and controls*

	MS patients (n = 105)	Controls (n = 105)	p†
Organ-specific antibodies			
Thyroid (thyroglobulin and/or microsomal)	4	2	
Parietal cell	11	4	
Total	15	6	<0.05
Non-organ-specific antibodies			
Antinuclear	20	8	
Smooth muscle	8	10	
Mitochondrial	4	1	
Total	32	19	<0.05
Total patients with one or more autoantibodies	43 (41%)	24 (23%)	<0.01

* Only patients who did not have clinical evidence of associated autoimmune disease are included.
† χ^2 test.

Two patients had a history of ulcerative colitis; one was in remission for many years, and the other was under treatment with sulfasalazine and prednisolone. One patient suffered from celiac disease, one had chronic autoimmune atrophic gastritis with vitamin B_{12} malabsorption, and in another primary biliary cirrhosis was diagnosed by liver biopsy.

Vitiligo was present in two patients; in one this was familial. One patient suffered from alopecia universalis with no regrowth of body hair for a follow-up period of 2 years. Cutaneous lupus erythematosus was diagnosed by skin biopsy in one patient in whom there was no evidence of systemic involvement.

Thirty patients had evidence of past or present thyroid disease. We excluded those who had undergone surgical treatment for an adenoma (2), cyst (2), or unknown reason (2), and those with a goiter in whom available data were insufficient to suspect an autoimmune etiology (5). Hyperthyroidism occurred in 15 (7 had undergone partial thyroidectomy, and 8 had been treated medically with ^{131}I or antithyroid drugs). Primary "idopathic" hypothyroidism was present in four patients. Ten were treated for diabetes mellitus, but only four suffered from the insulin-dependent form (type I diabetes mellitus).

The estimated prevalences for most of these disorders (the prevalence for some is not well established) are also shown in table 1. The cumulative prevalence of the putative autoimmune disorders in the MS group (4.92%) was no higher than that expected for the general population (5.12%).

Autoantibodies. Table 2 shows the prevalence of serum autoantibodies in the 105 MS and 105 control patients, of whom none had clinical evidence of associated autoimmune disease. There was a significantly higher prevalence of organ-specific as well as non-organ-specific antibodies in the MS group than in controls. Forty-one percent of the MS patients had one or more circulating autoantibodies as compared with 23% in the control group ($p < 0.01$). While only titers equal

levels of antinuclear antibodies were low in both groups. The highest titer detected in the MS patients was 1:160, and in controls 1:80. Similarly, the titers of smooth muscle cell, and mitochondrial and parietal cell (with the exceptition of four patients) antibodies were low (not greater than 1:10). Four patients (three of the MS and one of the control group) had higher titers of parietal cell antibodies. All four had normal hematologic and vitamin B_{12} values. The patients with thyroid antibodies were euthyroid.

Discussion. The present study shows that 4.8% of patients with MS had an associated disorder in which autoimmune mechanisms are generally believed to play a role. However, the cumulative prevalence of these disorders is no higher than that expected for the general population and is considerably lower than that reported for myasthenia gravis (11%).[14]

Thyroid disease, rheumatoid arthritis, hypothyroidism and insulin-dependent diabetes mellitus were most commonly encountered. However, these diseases also occur with a higher frequency than the others in the general population, and their prevalence in the MS group did not differ significantly from their expected prevalence. The prevalence in the MS group of some of the more uncommon disorders, such as primary biliary cirrhosis, may well appear to be statistically significant. However, the fact that this occurred in only one out of 828 patients makes such associations clinically insignificant.

A similar study by Baker et al[15] identified only nine cases out of 328 patients with MS (2.7%) who had an associated autoimmune disease. They found four cases with thyroid disease (one of whom also suffered from chronic atrophic gastritis), two with rheumatoid arthritis, one with pemphigus vulgaris, one with autoimmune Addison's disease, and another with chronic atrophic gastritis. None of the previously reported associations in case studies, including myasthenia gravis,[16-19] systemic lupus erythematosus,[20-22] bullous pemphigoid,[23] eosinophilic vasculitis,[24] and chronic idiopathic thrombocytopenic purpura[25] were represented in the present as well as in Baker's series.

Rang et al[26] reported an unexpectedly high incidence of MS in females with ulcerative colitis who had undergone total colectomy and terminal ileostomy. A number of cases of MS developing in patients with ankylosing spondylitis have been described.[27-29] We found only two patients with ulcerative colitis and one with ankylosing spondylitis, which does not support a strong association between MS and these two disorders.

Particularly intriguing is the concurrence of a chronic inflammatory demyelinating neuropathy with MS. A number of cases with the chronic as well as with the acute form of inflammatory demyelinating neuropathy have been reported.[13,30-32] The two cases included in this study are described in the recent paper by Thomas et al,[13] who collected four other similar cases.

In contrast with the lack of a significant association with autoimmune disorders is the finding that serum specific as well as non-organ-specific antibodies than controls. The increase was mainly due to a higher frequency of parietal cell and antinuclear antibodies. However, the titers of all these antibodies were generally low. These data agree with the findings of Dore-Duffy et al,[33] that significantly more patients with MS than controls have low levels of antinuclear antibodies in their serum. In addition, Kiessling and Pflughaupt[34] reported a higher incidence of microsomal thyroid antibodies in MS patients, although thyroid function was not disturbed to a greater degree than in other forms of chronic disease.[35]

T cells seem to play a crucial role in the regulation of humoral immune responses by acting as potentiators (T helper cells) or inhibitors (T suppressor cells) of the immunoglobulin production by B cells. Tolerance for self-antigens is brought about through the action of T suppressor cells.[8-10] Impaired T suppressor cell function is thus one of the proposed mechanisms for the generation of autoimmune responses. Reductions in circulating T suppressor cells occur in MS patients,[5-7] but whether these changes contribute to the pathogenesis of the disease or represent only secondary effects of the disease process is not clear.[2,7,9] A decline in T suppressor cells could theoretically account for the higher frequency of low levels of various autoantibodies in the MS serum. The findings that MS patients and their siblings tend to have increased serum antibody titers against a variety of viruses[36,37] also points to the existence of a possibly genetically determined, nonspecific B cell overactivity in MS. However, the role of the T suppressor cells in causing this B cell overactivity is uncertain; reconstitution experiments with T and B cells from MS patients and controls suggest that this B cell overactivity cannot entirely be explained by a defect in T suppressor activity.[38] Further study is required to achieve a full understanding of the immune dysfunction in MS. Numerical abnormalities of T suppressor cells alone probably cannot lead to overt autoimmune disease[10]; this may explain why MS is no more frequently associated with autoimmune disorders than might be expected by chance.

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