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Circulating thyroid and gastric parietal cell autoantibodies in patients with multiple sclerosis

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Multiple sclerosis (MS) is associated with complex abnormalities of immunoregulation and a role of autoimmunity in its pathogenesis has been accepted. MS is reportedly associated with several autoimmune diseases, but few studies are available on the prevalence of organ-specific autoantibodies in this condition. The aim of this study was to assess the frequency of anti-thyroglobulin (TgAb), anti-thyroid microsomal (MAb) and gastric parietal cell (PCA) antibodies in 113 patients (63 females, 50 males, age ranging 15-62 years) with MS and in 51 neurological controls. The diagnosis of MS was made according to McDonald and Halliday criteria. TgAb and/or MAb were detected by passive hemagglutination in 19 (16.8%) patients with MS and in 3 (5.9%) of the controls. All positive TgAb and/or MAb were observed in MS females (19/63 = 30.1%), with significantly higher frequency than in female controls ($X^2 = 5.15, p < 0.025$). The presence of circulating thyroid antibodies was higher in patients with clinically definite or progressive probable MS and in those with long standing disease. In contrast with thyroid antibodies, no difference in the frequency of PCA, as assessed by radioimmunoassay, was observed between MS and controls. These data support a specific association between thyroid autoimmunity and MS. The appearance of thyroid autoimmune phenomena seems to be related to the reliability of the diagnosis of MS and the duration of the disease.

Key-Words: Multiple sclerosis — autoimmune diseases — autoimmune endocrinopathies — thyroid autoantibodies — gastric autoantibodies

Introduction

Multiple sclerosis (MS) has been reported to be associated with several well established or potential organ-specific or non organ-specific autoimmune disorders including Hashimoto thyroiditis, Graves disease, idiopathic Addison disease, atrophic gastritis, rheumatoid arthritis and pemphigus vulgaris [2], systemic lupus erythematosus [5, 7, 18, 19], ankylosing spondylitis [9], ulcerous colitis [16],

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TABLE I. *Main clinical features of patients with multiple sclerosis (MS)*

Type of MS*	Total	Females	Males	Age (years, mean ± SD)	Disease duration (years, mean ± SD)
Clinically definite	38	23	15	34.2 ± 9.4	7.5 ± 4.9
Early probable or latent	22	8	14	32.5 ± 9.3	4.9 ± 4.0
Progressive probable	28	22	6	41.7 ± 11.6	5.8 + 4.9
Progressive possible	5	1	4	37.8 ± 8.7	1.4 ± 3.1
Suspected	20	9	11	32.5 ± 10.0	1.4 ± 4.9
Total	113	63	50	36.0 ± 10.7	4.9 ± 4.9

*) Defined on the basis of Mc Donald and Halliday's criteria (12).

insulin-dependent diabetes mellitus [21] and myasthenia gravis [1,15]. These observations are in keeping with the concept of a possible autoimmune pathogenesis of MS (17), since it is well recognized that autoimmune diseases may occur as single entities, but more often show a variable degree of multiple organ involvement in predisposed individuals or families [4, 20]. Autoimmune associations are even greater at serological level, with the coexistence of several autoantibodies, often in the absence of overt clinical manifestations [4, 20]. While an increased prevalence of anti-nuclear antibodies has been reported in MS [6], few data are available on organ-specific autoantibodies with the exception of a brief report indicating increased prevalence of thyroid autoantibodies in this neurological disorder [10].

The aim of the present investigation was therefore to further assess the frequency of circulating antithyroglobulin (TgAb) and anti-thyroid microsomal (MAb) antibodies in a large series of patients with MS and in age-matched neurological controls.

Furthermore, since thyroid and gastric autoimmunity show a significant degree of clinical and, more frequently, serological association [20], the presence of serum gastric parietal cell antibody (PCA) was also evaluated in the majority of MS patients.

Materials and methods

Patients.

The study was carried out on 113 consecutive patients with MS (63 females, 50 males, aged 15-62 years), seen at the Istituto di Clinica Neurologica, University of Pisa. The diagnosis of MS and the division in 5 types of disease was based on the criteria of McDonald and Halliday [12]. The main clinical features of the patients with MS are reported in Table I.

51 age- and sex- matched patients with miscellaneous neurological diseases were studied as controls.

They included 17 with cerebrovascular disease, 12 with epilepsy, 5 with cerebral atrophy, 5 with migraine, 6 with compressive myelopathy, 3 with motor neuron disease and 3 with peripheral neuropathy.

At the time of the present investigations all patients were untreated or had not received corticosteroid and/or immunosuppressive therapy for at least three months.

Antibody tests.

They were carried out on serum samples stored at −20 C until used. TgAb and MAb were assayed by passive hemagglutination using commercial kits (Thyroid test Kit and Microsome Test Kit, Fujizoki Pharmaceutical Co., Tokyo, Japan). By this technique, antibody titers > 1/100 were considered positive results [13]. PCA were assayed in 68 patients with MS and in all neurological controls by a solid-phase radioassay, as previously reported [14]. Briefly, sera diluted 1/100 or more were incubated in plastic microtiter wells coated with solubilized gastric microsomal antigen. After incubation and extensive washing, PCA specifically bound to the solid-phase was detected and quantitated by adding [^{125}I] - labeled purified anti-human IgG antibody (anti-IgG Ab). Antibody titers were expressed semiquantitatively as percent of specific [^{125}I] -anti-IgG Ab binding; values >0.80% were considered as positive PCA tests. Serum thyroxine (T4) and triiodothyronine (T3) were determined by radioimmunoassay using commercial kits; free T4 index (FT4I) and free T3 index [FT3I) were calculated in all cases on the basis of T3 resin uptake (T3RU) test.

Statistical analysis

Statistical evaluation was carried out by X^2 test.

Results

MAb and TgAb in patients with MS and in neurological controls. In the 113 patients with MS TgAb were found in 6 (5.3%) and MAb in 17 (15.0%) (Fig. 1); MAb and TgAb were simultaneously present in 4 patients, while 13 had only MAb and 2 only TgAb. Taken together, TgAb and/or MAb were detected in 19 (16.8%) cases. The frequency of TgAb and/or MAb was lower (3/51 = 5,9%) in patients with miscellaneous neurological disorders, but the difference between the two groups did not reach statistical significance ($X^2 = 3.61$, $0.05 > p < 0.1$). When the results were separately

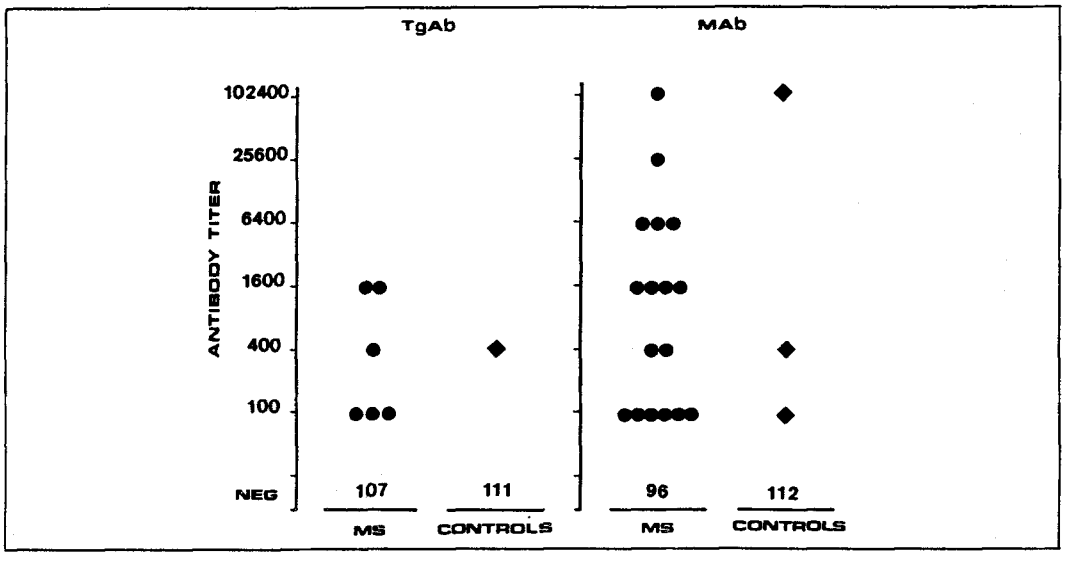

Fig. 1. *Circulating TgAb and MAb titers as assessed by passive hemagglutination in patients with MS and in neurological controls.*

Fig. 2. *Age-dependence of circulating MAb titers in patients with MS and in neurological controls.*

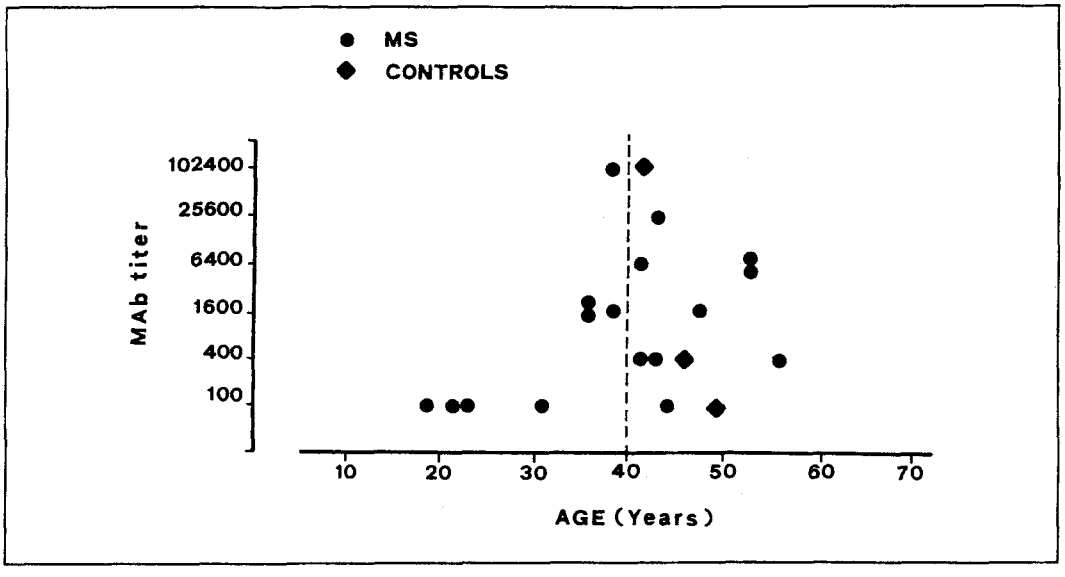

TABLE II. *Frequency of positive serum anti-thyroid microsomal (MAb) and anti-thyroglobulin (TgAb) autoantibodies in patients with multiple sclerosis (MS)*

Type of MS*	No.	Positive for MAb	Positive for TgAb	Positive for either antibody
Clinically definite	38	8 (21.0) **	2 (5.3)	8 (21.0)
Early probable or latent	22	0 (0)	1(4.5)	1(4.5)
Progressive probable	28	6(21.4)	2(7.1)	6(21.4)
Progressive possible	5	0(0)	1(20.0)	1(20.0)
Suspected	20	3(15.0]	0(0)	3(15.0)

*)Defined as in Table 1
**)Numbers in parentheses indicate percentages

analyzed by sex, all positive TgAb and/or MAb tests in MS were in females (19/63 = 30,1%). This frequency was significantly higher than that (2/26 = 7.7%) observed in female controls ($X^2 = 5.15$, $p < 0.025$).

The presence of circulating thyroid antibodies was age-dependent in both study groups, since the frequency and the titers of both TgAb and MAb were higher in subjects aged more than 40 years (Fig. 2). However, the increased antibody frequency observed in females with MS was confirmed even when the analysis was limited to the subgroups aged >40 years (10/26 = 38.5% in MS; 2/18 = 11.1% in controls; $X^2 = 4.01$, $p < 0.05$).

The distribution of positive thyroid antibody tests in the different diagnostic categories of MS is reported in Table II. The highest antibody frequency was observed in progressive probable (21.4%) and definite (21%) MS. It was higher in patients with long standing disease (12/47 [25.5%] patients with MS of more than 5 years duration vs. 7/66 [10.6%] with MS for less than 5 years ($X^2 = 3.37$, $0.1 > p > 0.05$). It is interesting to note that this difference became statistically significant when the analysis was limited to female patients with MS. In this subgroup positive antibody tests were found in 12/27 (44.4%) patients with MS of >5 years and only in 7/36 (19.4%) of the remaining patients ($X^2 = 4.578$, $p <$.

Circulating thyroid hormone levels. Total serum T4, T3, T3RU and the calculated FT4I and FT3I were all in the normal range both in MS patients and in neurological controls, irrespective of the presence or the absence of circulating thyroid autoantibodies.

Serum PCA. Positive serum PCA were found in 6/68 (8.8%) patients with MS; a similar incidence (7.9%) was found in the control group and no clear association was found between the presence of PCA and several clinical characteristics of the patients studied.

Discussion

The present study confirms and extends the preliminary report of Kiessling [10] indicating a higher frequency of serum thryroid autoantibodies in patients with MS. In our series the increased autoantibodies frequency was apparenty restricted to female MS patients. Female prevalence of positive serum thyroid autoantibodies is a well-known phenomenon, often observed in population studies involving subjects with no clinical evidence of thyroid disorders [4, 20]. However, the frequency of positive antibody tests found by us in MS was significantly different from age and sex-matched controls with miscellaneous neurological disorders. This suggests a specific association between thryroid autoimmunity and MS, rather than an artifact due to the age and sex of the patients studied. This concept is supported by the finding of a higher frequency of positive antibody tests in progressive probable and in definite MS, the diagnostic categories which include patients better fulfilling the criteria for this disease. The increased frequency of thyroid autoantibodies in long-standing MS suggests that the appearance of autoimmune phenomena could also be related to the duration of the disease.

In agreement with an other report by Kiessling et al. [11], in all patient with MS circulating thyroid hormone concentrations were within the normal range and no clinical evidence of hyper — or hypothyroidism was found. From these studies, however, it is impossible to exclude mild subclinical hypothyroidism (as detected by exaggerated serum thyrotropin (TSH) response to TSH-releasing hormone (TRH) injection, which is not infrequently present in apparently normal subjects with positive serum thyroid autoantibodies [3,8]. We are presently carrying out a complete follow-up study of thyroid function in MS patients with or without circulating thyroid antibodies, in order to ascertain the actual risk of thyroid dysfunction in this neurological disorder.

In contrast with thyroid antibodies, in our study we did not find any evidence of increased frequency of gastric parietal cells autoantibodies. This observation indicates that the association of thyroid and gastric autoimmunity, although frequently found in many organ-specific autoimmune disorders [4, 20], is not characteristic of MS. Further studies are needed to better define the extent of serological association of MS and organ-specific autoimmune disorders.

Sommario

La Sclerosi Multipla (MS) è associata a complesse alterazioni della immunoregolazione e nella sua patogenesi è stato accettato l'intervento di meccanismi autoimmunitari. Sono state anche riportate associazioni tra MS e numerose malattie autoimmuni, ma pochi sono i dati relativi alla presenza di autoanticorpi organo-specifici nella MS. Con questo studio è stata verificata l'incidenza di anticorpi anti-Tireoglobulina (TgAb), anti-microsomi di tiroide (MAb) e anti-cellule parietali gastriche (PCA) in 113 casi con MS (63 femmine e 50 maschi, di età compresa fra 15 e 62 anni) e in 51 controlli neurologici. I criteri per la diagnosi di MS erano quelli di McDonald e Halliday. Con la metodica dell'emoagglutinazione passiva sono stati rilevati TgAb e/o MAb in 19 (16.8%) pazienti con MS e in 3 (5.9%) controlli. Tutte le positività anticorpali sono state osservate nei soggetti con MS di sesso femminile (19/63 = 30.1%), con un'incidenza significativamente maggiore rispetto ai soggetti di controllo di sesso femminile ($X^2 = 5.15$; $p < 0.025$). Gli anticorpi antitiroide circolanti sono stati rilevati con maggior frequenza nei pazienti con MS clinicamente definita o progressiva probabile, e in quelli con maggiore durata di malattia. Nessuna differenza tra i casi di MS e i controlli è stata osservata per l'incidenza di PCA, dosati con metodica RIA. Questi dati confermano una specifica associazione tra autoimmunità tiroidea e MS. La comparsa di fenomeni autoimmuni tiroidei sembra in relazione con il grado di certezza diagnostica della MS e con la durata di malattia.

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