

Prevalence of autoimmune thyroid disorders in a Spanish multiple sclerosis cohort

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The aim of the study was to determine the prevalence of thyroid autoimmune disorders in a cohort of untreated multiple sclerosis (MS) patients and compare it with a stratified sample of an adult population. We prospectively studied 93 untreated MS patients. The control group included 401 healthy subjects selected by stratified sampling in a non-iodine-deficient area. Antithyroid antibodies (ATA) (antibodies against peroxidase and thyroglobulin) were considered positive at titres ≥ 149 IU/ml. Antibodies were positive in 11 MS patients (11.8%; 95% CI 5.3–18.4%). This prevalence was five times higher ($P = 0.0001$) when compared with that in the control population. We found six cases with subclinical hypothyroidism (6.45%; 95% CI 1.4–1.5) in contrast to 2.24% in the control group. Comparing MS with positive and negative ATA, there was a non-significant, slightly higher frequency of low Expanded Disability Status Scale (EDSS) score in the ATA-positive group (81% vs. 73.2%). One year after start of interferon (IFN) treatment, only one patient developed subclinical thyroid dysfunction. MS patients have a higher prevalence of ATA compared with the general population. An initial ATA and thyroid-stimulating hormone (TSH) determination is recommended in all MS patients. A periodic assessment of thyroid function during IFN treatment only seems to be justified in those cases where positive ATA or dysfunction is present before treatment.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system of unknown etiology. The presence of autoantibodies and the coexistence of other autoimmune disorders in patients and first-degree relatives suggest an autoimmune physiopathological hypothesis [1–3]. Autoimmune thyroid disease is one of the most frequently studied disorders in MS patients. The presence of thyroid dysfunction and antithyroid antibodies (ATA) in MS patients has been assessed by several studies showing a prevalence of 2.5–10% for hormonal dysfunction [4–7] and 4–21% for antibodies [5,6,8,9]. However, some studies were performed after the start of interferon (IFN) treatment, lacked a control group [6,10], or they used patients admitted to Hospital for general consultation as controls, who are not representative of the general population [4,7,8]. The aim of our study was to evaluate in our region the prevalence of thyroid autoimmune disorders in a cohort of untreated MS patients, comparing it with a stratified adult sample of the general population and to evaluate the possible influence of thyroid disorders on the clinical MS course.

Patients and methods

We prospectively studied consecutive patients admitted to our Neurology Department with a diagnosis of MS according to the McDonald criteria [11]. The degree of disability was assessed by the Kurtzke Expanded Disability Status Scale (EDSS). None of the patients had been previously treated with IFN or immunosuppressant drugs.

Thyroid function and ATA were evaluated at baseline in all patients before any treatment was initiated. Clinical symptoms of thyroid dysfunction were evaluated according to Billevicz [12] and Crooks [13] scales. The follow-up period of the study was 24 months. Patients were examined every 6 months by a neurologist evaluating the presence of MS relapses, the EDSS and clinical thyroid disorders. Thyroid function and ATA were assessed again 1 year after the start of treatment in those patients who started IFN in the follow-up period. An unfavourable clinical MS course was defined as a sustained increment of at least one point in the EDSS or the need for immunomodulatory treatment based on the current criteria used by our local committee of IFN treatment.

The control group included 401 healthy subjects representative of the adult population of the area of Lleida (Catalunya) [14], who were selected by stratified sampling from a study of the prevalence of goitre and

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	Multiple sclerosis (<i>n</i> = 93) (%)	Population sample (<i>n</i> = 401) (%)	χ^2 -value	<i>P</i> -value
Gender				
Female	56 (60.2)	210 (52.2)	–	–
Male	37 (39.8)	191 (47.6)		
Age (range), years	17–58	16–75	–	–
Ac. TPOAb positive (> 149 UI/ml)	11 (11.8)	10 (2.49)	16.16	0.001
Women	11 (19.6)	6 (2.8)	20.4	0.001
Men	0	4 (2.1)	0.79	ns
Ac. TPOAb detectable (79–149 UI/ml)	3 (3.2)	4 (0.99)	2.68	ns
Subclinical hypothyroidism	6 (6.45)	9 (2.24)	4.54	0.033
Women	5 (8.9)	7 (3.8)	3.2	0.07
Men	1	2	0.53	ns
Subclinical hyperthyroidism	0 (0)	15 (4.6)	3.59	ns
Low TSH (<0.35)	3 (3.2)	14 (3.5)	0.2	ns

Table 1 Antithyroid antibodies and thyroid dysfunction prevalence in MS patients and controls

thyroid disorders in the general population (Table 1). The mean iodine urinary excretion rate in the population sample was 120.2 mg/dl (SD 68), indicating a non-iodine-deficient area.

Laboratory methods

Antibodies against thyroid peroxidase (TPOAb) and thyroglobulin antigens (TgAb) were detected by the chemoluminescence method (threshold of detection of 0.1 IU/ml). Patients were considered positive for ATA, when ATA levels were higher than 149 IU/ml and negative when levels were lower than 79 IU/ml, based on the reference values of our laboratory. A level between 79 and 149 IU/ml was considered detectable but not pathologic. Thyroid-stimulating hormone (TSH) was measured by a sensitive chemoluminescence assay (Roche Diagnostics, Basel, Switzerland). The intra- and interassay coefficient of variation for the TSH assay were 1.0–1.3% and 3.3–7.1%, respectively. The limit of detection was 0.05 μ U/l and the normal range was 0.3–5 μ U/l. Serum free T3 (fT3) and T4 (fT4) were measured by the chemoluminescence method (Roche Diagnostics). The normal range for fT4 was 0.72–1.52 ng/dl and 58–159 ng/dl for fT3. Thyroid dysfunction was defined if patients had clinical hypothyroidism, with TSH level \geq 5 μ U/l and free T4 < 0.72 ng/dl. Patients with a TSH level \geq 5 μ U/l and normal free T4 value were classified as having subclinical hypothyroidism. Patients with TSH < 0.1 μ U/l and free T4 > 1.52 ng/dl were classified as having overt hyperthyroidism and those with TSH < 0.1 μ U/l and normal free T4 and T3 as having subclinical hyperthyroidism.

Ethics

The information of the study was collected from the prospective clinical protocols of our hospital, which fulfilled the local ethical guidelines. Therefore, patients signed no specific informed consent.

Statistical analysis

Patients were classified for statistical analysis based on the detection of ATA and the development of thyroid dysfunction. Differences in the presence of thyroid disease between MS patients and the control group were assessed using the chi-squared test and Fisher's exact test. Differences in age, EDSS, and disease duration in MS patients with or without thyroid disease were compared using the Wilcoxon test. EDSS was dichotomized for statistical analysis in \leq 3.5 and $>$ 3.5 based on the presence of walking disturbances. A *P*-value < 0.05 was considered statistically significant. Odds ratios (OR) with 95% confidence interval (CI) were calculated for the frequency of thyroid disorders in MS patients compared with controls. Statistical analysis was performed using the statistical package SPSS for Windows (v. 12.0).

Results

A total of 93 MS patients were evaluated – 56 women (60.2%) and 37 men (39.8%), mean age 33.2 years (range 17–58). The mean duration of disease was 8 years (range 1–18, median 6). Sixty-seven patients (72%) had relapsing–remitting MS, 17 patients (18.3%)

secondary progressive MS and nine (9.7%) primary progressive MS. The mean EDSS was 2.54 (95% CI 2.52–2.56). Sixty-nine patients had an EDSS \leq 3.5 and 24 patients $>$ 3.5.

At the time of inclusion in the study, 11 MS patients were ATA-positive ($>$ 149 UI/ml) (11.8%; 95% CI 5.3–18.4%; seven patients positive for both TPOab and TGAb, and four for TPOab). None of the patients had clinical thyroid dysfunction according to Crooks and Billewicz scores. The prevalence of positive ATA in patients with MS compared with controls was significantly different ($P < 0.001$; OR 5.5%, 95% CI 12.2–2.16) (Table 1). ATA were detected below the pathologic range (79–149 μ U/l) in three more patients and in four controls. Female MS patients had a higher prevalence of TPOab than female controls ($P = 0.001$, OR 8.3; 95% CI 23.7–2.93). No male MS patients had positive TPOab, whereas in the control group, TPOab was positive in four of 191 males (2.1%).

Disorders of hormonal levels in MS patients were present in nine cases (9.68%; 95% CI 15.7–3.7) with a Billewicz score \leq 30 in all patients. Six patients had subclinical hypothyroidism (6.45%; 95% CI 11.4–1.5): five females with high levels of TPOab and one male was TPOab-negative. Compared with MS patients, subclinical hypothyroidism was found in eight females and one male in the control group (2.24%) ($P = 0.003$; OR 3; 95% CI 8.2–1.1). No clinical (Crooks score \geq 11) or subclinical hyperthyroidism was found in the MS group, whereas in the control group the prevalence of subclinical hyperthyroidism was 4.6%. In three patients with MS, TSH levels were below the normal limit but detectable (TSH $<$ 0.01), with normal levels of free T4 and T3, and positive TPOab in only one case. Figure 1 shows the odds ratio for the presence of TPOab and thyroid dysfunction in our MS series compared with controls.

Multiple sclerosis patients with positive ATA compared with those with negative ATA did not differ in

age, duration of disease, or proportion of MS clinical forms. Patients with positive ATA had a higher frequency of low EDSS score (81%, 9/11 patients) than those with negative antibodies (73.2%, 60/82), but the difference was not statistically significant.

During the follow-up period, two of 11 patient with positive ATA had one or more relapses in contrast to 26 of 82 patients with no ATA ($P = 0.4$). An increase in the disability score was present in 19 patients (20.4%). Immunomodulatory treatment was initiated in 34 patients (35.6%, three patients with positive ATA). Patients with subclinical hypothyroidism had a favourable neurological clinical course, but the condition of one patient with an EDSS of 2.5 worsened after 2 years of follow-up to an EDSS of 3.5. A new thyroid function analysis performed 1 year after IFN treatment in 24 patients showed the development of thyroid dysfunction in only one case. This patient was a female with a baseline positive ATA (TPOab 1000 mIU/l) and normal TSH who presented persistence of ATA and increase of TSH up to 7.54 mIU/l with normal circulating hormone levels after treatment. None of the patients who were not on IFN treatment developed clinical symptoms of thyroid dysfunction and those who were ATA-positive (eight cases) showed no changes in ATA status throughout the follow-up period.

Discussion

The presence of disorders of the thyroid function in MS patients has been extensively studied because of the importance of thyroid disorders on the normal process of myelination [15,16], and on the disability and the progress of the disease experienced by MS patients. In addition, there is an association of IFN therapy with the development of new-onset thyroid dysfunction. The most frequent finding in MS patients is the detection of positive TPOab with a normal thyroid function.

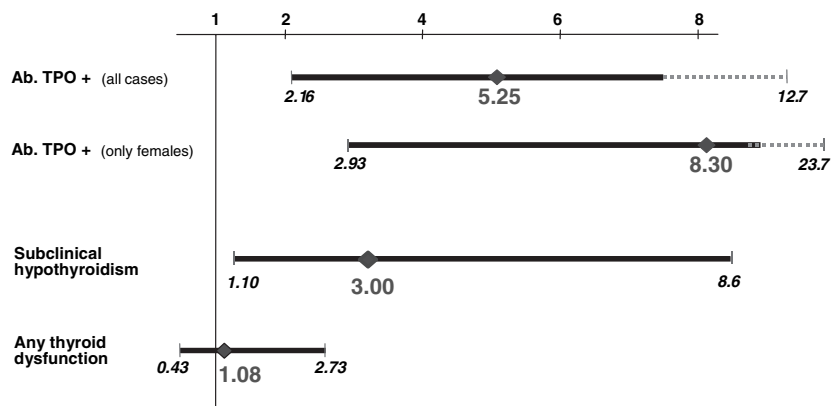


Figure 1 Odds ratio for thyroid disorders in multiple sclerosis.

However, the pathological significance of these antibodies is controversial. Some long-term epidemiological surveys have shown that they are a risk factor for the development of clinical hypothyroidism. In the Wickham population survey, the risk of clinical hypothyroidism was 2.1% per year with positive TPOab, and the risk increased to 4.3% if they were associated with slightly increase in TSH levels [17].

The prevalence of positive ATA in patients with MS ranged from 4% to 22% in previous reports [9]. The prevalence found in our study (11.8%) was similar to that found in some previous reports [4], a value five times higher than the prevalence found in our stratified population survey with a normal iodine excretion. There are several reasons for the variability of the results obtained in previous reports. Some studies lacked a control group, or they compared patients with controls not representative of the general population. In addition, it is well established that iodine-deficient areas are associated with lower prevalence of ATA, and most studies do not take into consideration the iodine intake of the control group. Another possible bias could be that some studies consider as positive TPOab levels below 100 UI/ml [6,18], a range with a prognostic value not well established in epidemiological studies.

According to the general literature, the prevalence of thyroid dysfunction in MS varies between 1.6% and 11% [6,9]. In our study, the only thyroid dysfunction found in MS patients was subclinical hypothyroidism, with a significant higher prevalence compared with the control group (6.45% vs. 2.24%, $P = 0.03$) (Fig. 1). The prevalence in male patients was similar to that in the general population, as previously reported [4]. The frequency of overt/subclinical hyperthyroidism found in MS in other series was lower than that in our study (0.8–1.5%) [4,9]. We found no cases of clinical or subclinical hyperthyroidism, although 3.2% of patients had TSH levels below the normal limit (< 0.3) but detectable, with normal free T4 and T3. These rates are similar to those found in our control group (4.2%) and as previously reported (5.3%) [18]. We found no association between thyroid disorders and the clinical course of MS throughout the follow-up period. Neither positive ATA seemed to play a role in the clinical evolution of MS based on our results, although limited by the reduced number of patients studied.

A transient rise of ATA levels in the first year of IFN treatment was observed in some MS patients [19,20], although with a wide variability in the frequency according to previous reports. However, some published series lack pre-treatment data. The presence of thyroid dysfunction in patients treated with β -IFN has been reported to range from 8% to 13% [5,6,10]. In our study, during the 2 years of follow-up after IFN treat-

ment, we did not observe any change in TPOab levels in those patients previously negative for TPOab, and there was only one case of new-onset subclinical hypothyroidism.

In conclusion, our findings show a higher prevalence of ATA in patients with MS compared with a general population from a non-iodine-deficient area, with an eightfold risk in female MS patients. Because of this high prevalence, we suggest an initial plasma TPOab and TSH determination in all MS patients. A periodic assessment of ATA during IFN treatment does not seem justified except in those cases where TPOab are clearly elevated or in patients with thyroid dysfunction before the start of the treatment with β -IFN.

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