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Clinical Studies

Mild Clinical Expression of Myasthenia Gravis Associated with Autoimmune Thyroid Diseases[1]

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Abstract

Myasthenia gravis (MG) may occur in association with autoimmune thyroid diseases (AITD). The aim of this study was to evaluate the features of MG associated with AITD compared to those of MG without AITD. A total of 129 MG patients (34 men and 95 women; age range, 11–81 yr) were subdivided into: group A, 56 MG patients with AITD [25 with autoimmune

thyroiditis and 31 with Graves' disease (GD)]; group B, 21 MG patients with nonautoimmune thyroid diseases; and group C, 52 MG patients without thyroid disease. The severity of MG was ranked according to the Osserman score. Laboratory evaluation included assays for antithyroid and antiacetylcholine receptor (AchRAb) antibodies.

Ocular MG (Osserman's class 1) was more frequent in group A (41.0%) than in group B (14.2%; $P < 0.03$) or C (21.4%; $P < 0.03$). Severe generalized MG (classes ≥2B) was more frequent in groups B (57.1%; $P < 0.03$) and C (51.9%; $P < 0.02$) than in group A (28.5%). GD patients with clinical evidence of ophthalmopathy had a higher frequency ($P = 0.05$) of ocular MG (57.8%) than GD patients without clinical ophthalmopathy (16.6%). Thymic disease was less frequent in group A (26.7%) than in group B (71.4%; $P = 0.001$) or C (59.7%; $P = 0.001$). The prevalence of thymic hyperplasia was 17.8%, 38.0%, and 40.3% in groups A, B, and C, respectively; the prevalence of thymoma was 8.9%, 33.4%, and 19.4%. When only patients with generalized MG were considered, thymic disease was less frequent ($P < 0.02$) in group A (40.6%) than in the remaining groups (69.4%). AchRAb was more frequent in groups B (57.1%) and C (57.6%; $P < 0.03$) than in group A (35.7%).

In conclusion, MG associated with AITD has a mild clinical expression, with preferential ocular involvement and lower frequency of thymic disease and AchRAb. This supports the hypothesis that ocular and generalized MG are separate diseases with different spectra of associated diseases. Nonautoimmune thyroid diseases have no influence on the features of MG. The association of ocular MG and AITD might be due to a common autoimmune mechanism and/or a peculiar genetic background.

Introduction

MYASTHENIA GRAVIS (MG) is an autoimmune disease characterized by impaired neuromuscular transmission due to circulating anti-acetylcholine receptor autoantibodies (AchRAb) (1). The frequent association of MG with thymic disease, such as follicular hyperplasia and thymoma, suggests that the thymus plays a role in its pathogenesis (1, 2, 3). The clinical expression of MG varies, ranging from a mild localized disease such as ocular MG

(OMG) to a severe generalized disease (4). Epidemiological, clinical, and serological studies have suggested that OMG and generalized MG (GMG) may be separate diseases (5, 6, 7, 8, 9).

Patients with MG may have evidence of coexisting autoimmune thyroid diseases (AITD) (8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) as well as other autoimmune disorders (21, 22). Epidemiological studies showed that AITD occur in approximately 5–10% of MG patients (17, 18), whereas a fairly low incidence of MG (~0.2%) has been reported in patients with AITD (18). A higher frequency of thyroid antibodies has been observed in OMG compared to GMG (8), but this increased association between OMG and thyroid autoimmunity has not been confirmed (13, 14, 15, 16). Thus, the question of whether the clinical expression of MG associated with AITD is different from that observed in MG without thyroid autoimmunity remains unresolved.

The aim of this study was to evaluate the clinical and serological features of MG associated with AITD in a large number of patients. Results were compared to those found in MG patients with nonautoimmune thyroid diseases (N-AITD) and without thyroid disorders.

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Subjects and Methods

Patients

A total of 129 MG patients (34 men and 95 women; age range, 11–81 yr) were studied. Ninety-one consecutive patients referred to the Institute of Neurology for MG (18 with OMG and 73 with GMG) were screened for thyroid disease. Among these 91 patients, 39 had thyroid disease (26 AITD and 13 N-AITD). The remaining 38 MG patients (19 with OMG and 19 with GMG) were obtained from approximately 20,000 consecutive patients referred to the Institute of Endocrinology for thyroid disease from 1980 to 1995. Among these 38 patients, 30 had AITD and 8 had N-AITD. Thus, 77 patients had coexistent MG and thyroid disorders. Thirty-seven had a diagnosis of thyroid disease made before the diagnosis of MG (median interval, 20.3 months), whereas 40 patients had a diagnosis of thyroid disease after the recognition of MG (median interval, 28.8 months). When they entered the study, 31 of the 129 MG patients were being

treated with pyrodostigmine, 4 were being treated with prednisone, and 83 were being given both drugs. Azathioprine was given to 19 patients.

For the purpose of this study patients with MG were subdivided into 3 groups. Group A consisted of 56 MG patients with AITD (9 men and 47 women; age range, 13–81 yr). Twenty-five patients had autoimmune thyroiditis (AT); 22 had typical Hashimoto's thyroiditis [HT; 15 untreated at entry (8 euthyroid and 7 with clinical or subclinical hypothyroidism) and 7 treated with L-T_4 (2 euthyroid and 5 hypothyroid], and 3 had euthyroid nodular goiter with focal autoimmune thyroiditis and were not treated. Thirty-one patients had Graves' disease (GD); 3 were untreated hyperthyroid, 14 were euthyroid receiving methimazole, 10 were euthyroid receiving L-T_4 therapy after thyroidectomy or radioiodine treatment, and 4 had euthyroid GD (Graves' ophthalmopathy with no evidence of hyperthyroidism). Among GD patients, 19 had clinical evidence of Graves' ophthalmopathy, as assessed by physical examination. Clinical ophthalmopathy was characterized in all cases by moderate or severe exophthalmos associated with signs and symptoms of soft tissue inflammation. Eye muscles were enlarged in all patients with clinical ophthalmopathy, as assessed by orbital computerized tomography (CT). Diplopia was present in 16 patients. Involvement of optical nerves at CT was present in 4 patients. In the 12 GD patients with no clinical evidence of ophthalmopathy, orbital CT was not performed. Therefore, for the purpose of the present study, Graves' ophthalmopathy was defined as a clinically detectable condition.

Group B consisted of 21 MG patients with associated N-AITD (5 men and 16 women; age range, 22–77 yr). Two had toxic adenoma and were euthyroid after radioiodine treatment, and 19 had nontoxic nodular goiter (13 untreated and 6 receiving L-T_4).

Group C consisted of 52 MG patients with no evidence of associated thyroid disorders (20 men and 32 women; age range, 11–76 yr).

Clinical and serological investigation

Neurological evaluation. All patients underwent neurological assessment, which included physical examination and a Tensilon (edrophonium) test. A repetitive nerve stimulation test (Desmedt test) was performed when necessary. All patients had CT or magnetic resonance imaging (MRI) of the mediastinum performed. Patients with thymic enlargement at CT or MRI were submitted to thymectomy. The diagnosis of thymic hyperplasia or thymoma was based on histological findings. AchRAb was assayed in all patients using a commercial kit (acetylcholine receptor autoantibodies, Immuno Biological Laboratories, Hamburg, Germany).

Thyroid evaluation. All patients underwent a thyroid evaluation, which included physical examination, thyroid ultrasonography, and the following thyroid tests: free thyroid hormones (free T_4 and free T_3 RIA, Lysophase, Technogenetics, Milan, Italy), TSH (Ultrasensitive-TSH immunoradiometric assay, Delfia, Wallac, Finland), antithyroglobulin autoantibodies (TgAb; anti-Tg MELISA, Byk Gulden, Milan, Italy), and antithyroperoxidase autoantibodies (TPOAb; anti-TPO RIA, Sorin Biomedica, Saluggia, Italy). The following tests were also carried out when

necessary: anti-TSH receptor autoantibodies (TRAb; TRAb immunoradiometric assay, Henning, Berlin, Germany), thyroid scan, and thyroid fine needle aspiration biopsy. Patients with clinical evidence of Graves' ophthalmopathy had an orbital CT performed.

Diagnostic criteria

The diagnosis of MG was based on the presence of muscular weakness and abnormal fatigability aggravated by exercise and was confirmed by the Tensilon and Desmedt tests (1). GMG was diagnosed in patients with systemic muscle involvement in whom iv edrophonium administration was associated with unequivocal improvement in an objectively weak muscle (1, 23). The Desmedt test confirmed the diagnosis of GMG in patients showing an equivocal response to the Tensilon test (1, 24). OMG was diagnosed in patients with restricted ocular symptoms (diplopia and palpebral ptosis) and a clear improvement in eye muscle weakness a few seconds after the iv administration of edrophonium (1, 23). None of the OMG patients had generalized muscle involvement during a follow-up period of almost 2 yr. The diagnosis of both OMG and GMG was confirmed by the amelioration of muscle weakness during chronic treatment with pyridostigmine. The severity of MG was ranked according to the Osserman score (4): class 1, OMG; class 2A, GMG with no bulbar involvement; class 2B, GMG with bulbar involvement; class 3, acute rapidly progressive GMG; and class 4, severe GMG with myopathy.

The diagnosis of GD was based on the presence of hyperthyroidism (25) and/or Graves' ophthalmopathy associated with diffuse goiter and circulating thyroid antibodies including TRAb (26). The diagnosis of ophthalmopathy in all GD patients with clinical evidence of Graves' ophthalmopathy was confirmed by the presence of eye muscle enlargement and an increase in fibroadipose retrobulbar tissue determined by CT (27). Euthyroid GD was diagnosed in patients with Graves' ophthalmopathy who did not have previous or actual clinical and biochemical evidence of hyperthyroidism. This was always associated with small diffuse goiter, circulating thyroid antibodies (including TRAb), and undetectable TSH. Patients with clearly diagnosed Graves' ophthalmopathy who had an unequivocal improvement of palpebral ptosis and diplopia after the iv administration of edrophonium were diagnosed as having coexistent Graves' ophthalmopathy and OMG. The improvement of diplopia, but not of palpebral ptosis, after the Tensilon administration was not considered a sufficient criterion for the diagnosis of OMG in patients with Graves' ophthalmopathy. All patients with primary hypothyroidism associated with positive TgAb/TPOAb were considered to have HT. The diagnosis of HT was also made in patients with positive TgAb/TPOAb associated with a firm goiter and a hypoechogenic pattern on ultrasound examination of the gland and/or lymphocytic infiltration at fine needle aspiration biopsy (28, 29, 30, 31). Patients with nodular goiter and circulating TPOAb at high levels (range, 277-2000 U/mL) were considered to have nodular goiter with focal autoimmune thyroiditis (28) and were included in group 1. Five euthyroid patients with nodular goiter and circulating TPOAb at low levels (range, 12–47 U/mL) did not have a hypoechogenic pattern on ultrasound examination or lymphocytic infiltration on fine needle aspiration biopsy. Furthermore, none of them had a family history of AITD. Therefore, for the purpose of the present study, these 5 patients were considered to have N-AITD (32) and were included in group B.

Statistical analysis

Results were analyzed by χ^2 test, using a personal computer software (Stat-View, Abacus Concepts, Berkeley, CA).

Results

Distribution of Osserman's classes

As shown in Table 1 and Fig. 1, OMG (class 1) was more frequent in group A (41.0%) than in group B (14.2%; $P < 0.03$) or C (21.4%; $P < 0.03$). The frequency of mild GMG (class 2A) was similar among the three groups. The frequency of bulbar, acute, and severe GMG (classes 2B, 3, and 4 grouped together) was higher in groups B (57.1%; $P < 0.03$) and C (51.9%; $P < 0.02$) than in group A (28.5%). Classes 3 and 4 were observed only in group C (two and one patients, respectively). No difference was observed between groups B and C and in group A between GD (with or without ophthalmopathy) and AT (data not shown). GD patients with clinical evidence of ophthalmopathy had a higher frequency ($P = 0.05$) of ocular MG (57.8%) than GD patients without clinical ophthalmopathy (16.6%).

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TABLE 1. Clinical and laboratory features of MG patients with coexistent AITD (group A) or N-AITD (group B) and without associated thyroid disorders (group C)

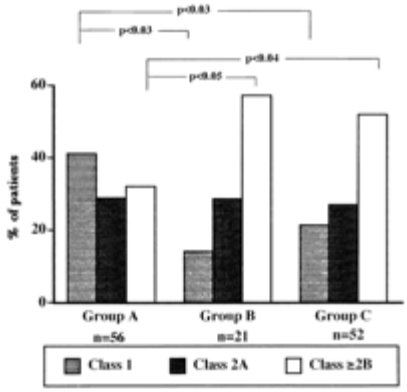

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FIGURE 1. Distribution of Osserman's classes (class 1, ocular MG; class 2A, generalized MG with no bulbar involvement; class ≥2B, generalized MG with bulbar involvement) in MG patients with associated AITD (group A), with associated N-AITD (group B), or without thyroid disorders (group C).

Thymic involvement

Sixty-one of 129 patients had an abnormal thymus; 39 patients had thymic hyperplasia, and 22 had thymoma. Fifty-four of the 61 patients with thymic abnormalities had a thymectomy before entering the study, and the remaining 7 underwent thymectomy after entering the study. No evidence of thymic enlargement was detected by CT or MRI in the remaining 68 patients. As expected, the frequency of thymic disease was lower in patients with OMG (8.8%) than in those with GMG (63.0%).

Thymic disease was less frequently observed in group A (26.7%) than in groups B (71.4%; $P = 0.001$) and C (59.7%; $P = 0.001$; Fig. 2). When the frequencies of various thymic diseases were analyzed (Table 1 and Fig. 2), a lower prevalence of thymic hyperplasia was observed in group A (17.8%) than in group B (38.0%) or C (40.3%); the difference was statistically significant between groups A and C ($P < 0.01$). Similarly, the prevalence of thymoma was lower in group A (8.9%) than in group B (33.4%) or C (19.4%), with a statistically significant difference between groups A and B ($P < 0.01$). The frequency of thymic disease did not differ between groups B and C or in group A between GD and AT (data not shown). No difference in thymic disease was observed between GD patients with or without ophthalmopathy (data not shown). Among patients with GMG (Osserman classes >1), the frequency of thymic disease was significantly lower ($P < 0.005$) in patients in group A (40.0%) than in those in groups B and C taken together (69.0%; Fig. 2).

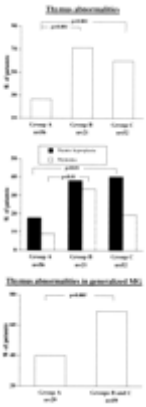

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FIGURE 2. Thymic disease in MG with associated AITD (group A), with associated N-AITD (group B), and without thyroid disorders (group C). *Upper panel*, Prevalence of thymic involvement. *Middle panel*, Prevalence of thymic hyperplasia and thymoma. *Lower panel*, Prevalence of thymic involvement in generalized MG patients.

Serum TgAb and TPOAb

As expected, the frequency of TgAb and TPOAb was higher in group A (TgAb, 37.5%; TPOAb, 78.5%) than in groups B (TgAb 0%; TPOAb 8.7%) and C (TgAb, 0%; TPOAb, 15.3%; Table 1 and Fig. 3).

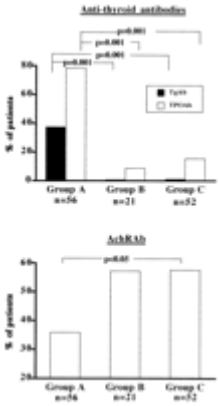

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FIGURE 3. Circulating antibodies in MG with associated AITD (group A), with associated N-AITD (group B), and without thyroid disorders (group C). *Upper panel*, Prevalence of circulating TgAb and TPOAb. *Lower panel*, Prevalence of AchRAb.

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Serum AchRAb

As expected, AchRAb was less frequent in patients with OMG (8.1%) than in those with GMG (64.1%). As shown in Table 1 and in Fig. 3, the prevalence of AchRAb was higher in groups B (57.1%) and C (57.6%) than in group A (35.7%), with a statistically significant difference between groups A and C ($P < 0.03$). No difference was observed between groups B and C.

Analysis of MG features in AITD patients according to their referral to different institutions

To determine whether the referral of patients to two different institutions influenced our results, patients with MG and AITD were subdivided according to their referral to the Institute of Neurology or to the Institute of Endocrinology. As shown in Table 2, no difference was observed for any of the clinical or serological features of MG between the two referral sites.

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TABLE 2. Clinical and laboratory features of MG patients with coexistent AITD according to their referral site

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Discussion

MG is an autoimmune neuromuscular disorder often associated with thymic disease (1, 2, 3). Its

clinical presentation varies from a mild ocular to a severe generalized disease, but the question of whether OMG and GMG are different diseases is controversial (5, 6, 7, 8, 9). The hypothesis that they are separate diseases is supported by several features, such as the greater frequency of thymic disease and serum AchRAb in GMG compared to OMG (6, 7, 8). The coexistence of other autoimmune diseases in MG is well recognized (1, 10, 11, 21, 22), including the association with AITD (8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). However, the influence of AITD on the clinical expression of MG has not been defined. Whether AITD is more frequently associated with OMG or GMG has not been carefully evaluated, and scanty data are available on the prevalence of thymic disease and serum AchRAb in MG with coexistent AITD (8, 12, 13, 14, 15, 16). The features of MG associated with N-AITD have not been reported, and whether the clinical expression of MG with coexistent AITD is related to thyroid disease *per se* or to its autoimmune component remains to be clarified.

In the present study we evaluated the clinical and serological features of MG associated with AITD compared with those found in MG patients with N-AITD or without thyroid disease. The clinical presentation of MG associated with AITD was characterized by neuromuscular involvement, frequently restricted to the eye muscles. In contrast, GMG was more frequent in MG patients with N-AITD and in those without thyroid disease. Thymic abnormalities were less frequent in MG associated with AITD than in MG without thyroid autoimmunity. This lower frequency of thymic abnormalities in AITD patients was also present when only OMG patients were considered. Moreover, the prevalence of serum AchRAb was lower in patients with AITD than in the other groups of MG patients. The majority of MG patients without thyroid autoimmunity had GMG and were receiving immunosuppressive therapy when they entered the study. Therefore, this difference in circulating AchRAb is almost certainly greater in untreated patients.

Our finding of an increased association between OMG and thyroid autoimmunity supports the observation of Garlepp *et al.* (8), who reported a greater frequency of thyroid antibodies in OMG than in GMG. On the other hand, a higher frequency of associated autoimmune disorders (including AITD) in GMG compared to OMG has been observed by others (13, 14, 15, 16). This discrepancy might be due to the different diagnostic criteria employed and/or the limited number of patients studied. Furthermore, several earlier studies on the association of MG with thyroid disease failed to distinguish between autoimmune and nonautoimmune thyroid disorders (10, 11, 21, 22). In the present study a large number of patients with MG have been evaluated and subdivided on the basis of strict diagnostic criteria for their thyroid disorder. Patients with coexisting AITD or N-AITD have been studied. Our data clearly demonstrate that a milder clinical expression of MG occurs in patients with associated AITD than in those without thyroid autoimmunity. No difference was observed in any of the clinical and laboratory findings between MG patients with coexistent N-AITD and those without thyroid disease. This suggests that the mild clinical expression of MG associated with AITD is not related to the presence of a thyroid disorder *per se*, but to the presence of thyroid autoimmunity. In agreement, the coexistence of N-AITD has no effect on the type or the clinical course of MG, and the presence of goiter in MG patients should be considered a random association. The study was carried out in an Italian

population from Tuscany, where mild to moderate iodine deficiency is still present, and the prevalence of endemic goiter ranges from 22–59% (33).

The reason for the association of AITD with ocular MG is unknown, but several hypotheses can be considered. First, OMG and GMG might actually represent separate diseases (5, 6, 7, 8, 9) with different spectra of associated diseases. Second, an immunological cross-reactivity against epitopes or autoantigens shared by the thyroid and the eye muscles might be the basis of this association. Several experimental data suggest that thyroid antigens are present in ocular tissues (34, 35, 36, 37, 38, 39, 40, 41, 42). Circulating autoantibodies directed to eye muscle components have been identified in GD and HT (36, 37, 43, 44) and recently also in GD patients with associated MG (45). Further studies are needed to clarify whether autoantibodies against antigens shared by the thyroid and the eye muscles are present in sera from patients with MG and AITD. In particular, it would be useful to evaluate the presence of autoantibodies directed against a membrane 64-kDa protein that has been suggested to play an important role in the pathogenesis of Graves' ophthalmopathy (46, 47). A third explanation for the higher frequency of OMG in AITD could be that these disorders have a common genetic background. Among the various major histocompatibility complex (MHC) haplotypes associated with AITD and MG (48, 49, 50, 51, 52, 53), a high frequency of human leukocyte antigen-B8 and -DR3 has been reported in both disorders (48, 49, 50). A difference in the MHC repertoire was also found between OMG and GMG (6, 12, 54, 55), supporting the hypothesis that they are separate entities. Further studies are needed to evaluate the MHC repertoire in MG patients with associated AITD compared to MG patients without associated AITD.

In conclusion, MG associated with AITD has a mild clinical expression characterized by preferential involvement of the eye muscles. This is consistent with the hypothesis that OMG and GMG are separate diseases with different spectra of associated diseases and different immunogenetic backgrounds. The association of OMG with AITD might also be due to a common immunopathogenetic mechanisms acting through antigens shared by the eye muscles and the thyroid. Further immunological and genetic studies are needed to verify these hypotheses. The important clinical implication of this study is that the coexistence of MG with thyroid autoimmunity might have prognostic relevance in the identification of a subgroup of MG patients with a mild form of the disease.

Footnotes

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