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Frequency of Autoimmune Diseases in Myasthenia Gravis: A Systematic Review

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ABSTRACT

The course of myasthenia gravis (MG) may get complicated by the development of other autoimmune diseases. Estimates of the frequency of autoimmune diseases will help inform patients and physicians, direct health policy discussion, provide etiologic clues, and optimize the management of MG. However, the frequency of autoimmune diseases in people with MG is still uncertain. A systematic search for English language studies was conducted by MEDLINE and EMBASE from 1960 through 2010. Incidence studies and case series of all MG subtypes with information about autoimmune diseases were included; 25 studies met the inclusion criteria. Although there was considerable heterogeneity, the pooled estimate of the coexisting autoimmune diseases in MG was 13% (95% confidence interval, 12%–14%). Autoimmune thyroid disease seems to occur more frequently than other autoimmune conditions in MG patients. Heterogeneity in study estimates could be explained by ascertainment bias and case mix. Furthermore, autoimmune diseases occurred significantly more often in females and anti-acetylcholine receptor seropositive MG patients. Patients with MG have an increased frequency of coexisting autoimmune diseases. Autoimmune diseases seem to occur more often in female and seropositive MG patients. Further research is needed to expand our understanding of these associations.

KEYWORDS: Autoimmune diseases, frequency, myasthenia, systematic review

INTRODUCTION

Currently, myasthenia gravis (MG) is considered as one of the best understood autoimmune disorders. Indirect evidence from animal models (Lennon, Lindstrom, & Seybold, 1975), female predominance (Grob, Brunner, Namba, & Pagala, 2008), the pathogenic role of the anti-acetylcholine receptor antibodies (Patrick & Lindstrom, 1973), together with the thymic abnormalities (Roxanis, Micklem, & Willcox, 2001), support the hypothesis that MG has an autoimmune etiology. However, the course of MG is complicated by the development of other autoimmune diseases. Several explanations for the development of autoimmune diseases have been suggested, including a shared genetic background, as well as chronic immune stimulation in the treatment of MG (Goldman, Herode, Borenstein, & Zanen, 1984). Previous studies have reported on the frequency of autoimmune diseases in MG; however, the frequency varies widely across studies because of differences in study populations and ascertainment criteria (Christensen et al., 1995; Kanazawa, Shimohata, Tanaka, & Nishizawa, 2007; Toth, McDonald, Oger, & Brownell, 2006). For example, some studies only recruited patients from hospital (rather than population-based) settings, which might result in a referral and selection

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bias. Thus, there is inadequate conclusive evidence to confirm the frequency of autoimmune diseases in MG patients. A better estimate of autoimmune diseases will help inform patients and physicians, direct health policy discussions, provide etiologic clues, and optimize the management of MG. We conducted a quantitative systematic review of observational studies reporting the frequency of autoimmune diseases in all MG subtypes.

METHODS

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). We collected published studies available from the biomedical literature by searching in MEDLINE (1960 to January 2010) and EMBASE (1980 to January 2010) for such reports. Only papers published in English were included. The key search terms used were "autoimmune diseases," "complications," and "myasthenia gravis." Additional studies were located by searching reference lists of retrieved articles and hand searching the main neurology journals. When several articles were published by the same authors or groups, the publication with the largest sample size was selected. We used Cohen's kappa statistic (κ) to assess agreement between the two reviewers.

This review included incidence studies and case series of all MG subtypes with information on autoimmune diseases. Two types of hospital-based studies were eligible: studies with consecutive patient recruitment; and studies with nonconsecutive unselected recruitment, e.g., MG patients from a hospital register between defined time-limited boundaries. We excluded studies if they had any of the following features: (1) were limited to specific patient characteristics, such as generalized MG only or late-onset MG; (2) limited to specific autoimmune disease rather than global evaluation of autoimmune diseases; (3) used convenience sampling; (4) sample size of less than 20. For the purpose of this review, we proposed a classification of autoimmune diseases based on the two most frequently used classifications (Bache, Nielsen, Rostgaard, Tommerup, & Frisch, 2007; Mellemkjaer et al., 2008). We additionally modified the criteria list on the basis of the framework for assessing epidemiology of autoimmune diseases as described by Cooper, Bynum, and Somers (2009). Thus, the final list consisted of 49 autoimmune diseases (Appendix 1). We considered this classification of autoimmune diseases especially suitable for clinical research, as it covers a wide range of diseases using standard valid definitions.

DATA EXTRACTION

Two reviewers independently extracted information on study design, population characteristics, and diagnostic criteria of autoimmune diseases. If disagreement persisted after studying the complete manuscript, we consulted the third reviewer. We hypothesized that any heterogeneity in frequency estimates might be explained by differences in study design, with lower frequencies expected in population-based studies (which include patients with minor MG) than in studies recruiting solely from hospital departments. Studies were stratified based on the following three categories that represented degrees of case selection (Hackett, Yapa, Parag, & Anderson, 2005; Pendlebury & Rothwell, 2009): (1) "Population-based studies," considered to be the least biased; (2) "hospital-based studies" using consecutive enrollment (consecutive hospital-based studies); (3) "hospital-based studies" from unselected hospital enrollments or record review (hospital record-based studies).

STATISTICAL ANALYSIS

Pooled frequencies (and 95% confidence intervals (CI)) were calculated with meta-disc version 1.4 (Lew, Pai, Oxlade, Martin, & Menzies, 2008). The DerSimonian Laird (random-effects) method was selected when there was evidence of statistical heterogeneity. Heterogeneity in frequencies across studies was assessed using χ^2 tests. The robustness of pooled proportions was explored by conducting sensitivity analyses. We performed an additional analysis to explain potential heterogeneity by separating studies into different prior defined subgroups: diagnostic standard (provided versus not provided), research type (population-based versus hospital-based; alternatively, we calculated the pooled frequency by combining the consecutive hospital-based and hospital record-based studies together because this data synthesis would provide an evidence-based answer to specific clinical questions regarding the hospitalization data). We performed additional analyses to identify factors associated with the development of autoimmune diseases in MG by pooling odds ratios (OR) for demographic variables, the Myasthenia Gravis Foundation of America (MGFA) clinical classification, and the anti-Acetylcholine receptor (AChR) antibodies test results (seropositive/seronegative). The fixed effects analysis was used unless there was evidence of heterogeneity ($p \leq .1$), in which case the random effects analysis was used. Heterogeneity was quantified using I^2 values. The population- and hospital-based studies were combined for the calculation of the pooled OR.

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│ Potentially relevant articles        │
│ identified and screened for          │
│ retrieval from MEDLINE and           │
│ EMBASE (n = 1,864)                   │
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│ evaluation (n = 83)                  │
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                 ├─────────────────▶│ Articles excluded: (n = 66)  │
                 │                  │   Not about MG (n = 3)       │
                 │                  │   Selected patients (n = 21) │
                 │                  │   Insufficient sample size   │
                 │                  │     (n = 5)                  │
                 │                  │   Selected MG (n = 4)        │
                 │                  │   No autoimmune diseases     │
                 │                  │     information (n = 31)     │
                 │                  │   Reviews, letters,          │
                 │                  │     comments, or editorials  │
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│ Articles included in the systematic  │
│ review (n = 25)                      │
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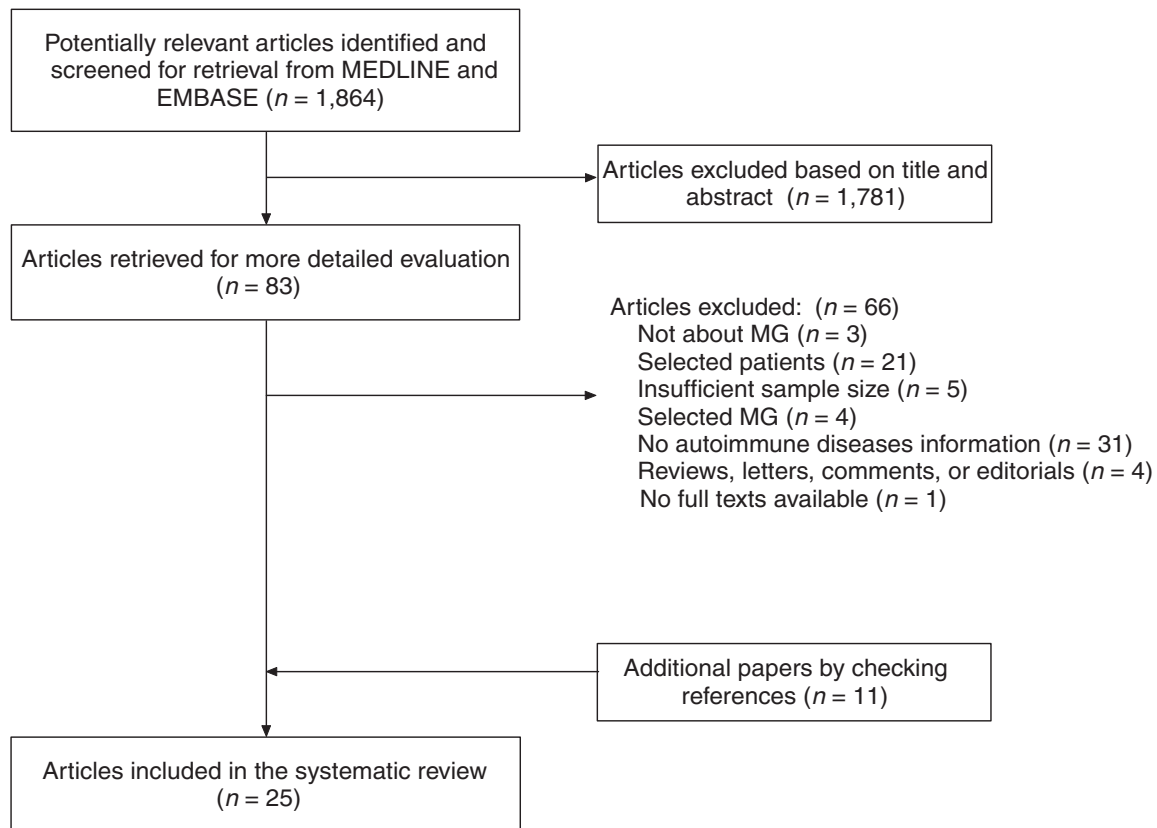
FIGURE 1.   Flow chart of systematic review of search strategy.

RESULTS

Search Results

Our search performed on April 10, 2010 identified 1,864 articles (Figure 1). Of these, 1,781 reports were excluded on the basis of titles or abstracts and 83 were identified for full-text review. Eleven additional reports were identified by searching relevant reference lists or manual searches of important neurology journals. Finally, 25 studies fulfilled the inclusion criteria and were included in this review (Al-Moallem, Alkali, Hakami, & Zaidan, 2008; Bache et al., 2007; Beekman, Kuks, & Oosterhuis, 1997; Christensen et al., 1993, 1995; Citterio et al., 2009; D'Alessandro et al., 1991; Goulon, Estournet, & Tulliez, 1980; Guidetti et al., 1998; Kanazawa et al., 2007; Lavrnic et al., 1999; Levin et al., 2005; Matsui et al., 2009; Oopik, Kaasik, & Jakobsen, 2003; Oosterhuis, 1981a, 1981b, 1989; Oosterhuis & de Haas, 1968; Potagas et al., 2004; Poulas et al., 2001; Rastenyte, Vaitkus, Neverauskas, & Pauza, 2002; Robertson, Deans, & Compston, 1998; Suzuki et al., 2005; Tellez-Zenteno, Cardenas, Estanol, Garcia-Ramos, & Weder-Cisneros, 2004; Toth et al., 2006; Tsinzerling, Lefvert, Matell, & Pirskanen-Matell, 2007;

Yu, Hawkins, Ip, Wong, & Woo, 1992). The agreement between reviewers for inclusion of articles was 94.0%, with gave a $\kappa = 0.90$ (95% CI, 0.81–1.00; almost perfect agreement) (Chmura Kraemer, Periyakoil, & Noda, 2002).

Study Characteristics

Appendices 2–4 show the demographic details, study design, and methods used to diagnose autoimmune diseases in all the publications that were relevant to each source of recruitment (13 studies) (Christensen et al., 1993, 1995; D'Alessandro et al., 1991; Guidetti et al., 1998; Lavrnic et al., 1999; Oopik et al., 2003; Oosterhuis, 1981a, 1989; Oosterhuis & de Haas, 1968; Poulas et al., 2001; Robertson et al., 1998; Tellez-Zenteno et al., 2004; Yu et al., 1992), consecutive hospital-based studies (four) (Beekman et al., 1997; Kanazawa et al., 2007; Levin et al., 2005; Matsui et al., 2009), and hospital record-based studies (eight studies) (Al-Moallem et al., 2008; Citterio et al., 2009; Goulon et al., 1980; Potagas et al., 2004; Rastenyte et al., 2002; Suzuki et al., 2005; Toth et al., 2006; Tsinzerling et al., 2007). Most studies were performed in European countries, five in

Asia (Al-Moallem et al., 2008; Kanazawa et al., 2007; Matsui et al., 2009; Suzuki et al., 2005; Yu et al., 1992), and another in Canada (Toth et al., 2006). All studies included patients with standard clinical criteria for MG. No prospective studies were included (one study combined prospective and retrospective criteria (Tsinzerling et al., 2007). Only four studies provided diagnostic criteria for ascertainment of autoimmune diseases (Christensen et al., 1995; Kanazawa et al., 2007; Oosterhuis & de Haas, 1968; Toth et al., 2006).

Frequency of Autoimmune diseases

The I^2 statistic ranged from 6.5% in consecutive hospital-based studies to 95.6% in hospital record-based studies, indicating heterogeneity among the included studies. We therefore used a random effects model to pool the data. Although there was considerable variation in the reported frequency of autoimmune diseases in MG across individual studies, the pooled estimate of all three categories indicates that the frequency of autoimmune diseases was 13% (95% CI, 12%–13%) in MG patients. There pooled frequencies were 13% (95% CI, 12%–14%) and 12% (95% CI, 11% –13%) in the population-based and the hospital-based studies, respectively (Figure 2). However, the pooled frequency was 21% (95% CI, 17%–24%) in the consecutive hospital-based studies (Figure 2).

Sensitivity analyses were conducted to explore the robustness of this observation. Removal of those studies did not specify the diagnosis criteria of autoimmune diseases, and the recalculated pooled frequency of all three categories yielded significant higher result (20%, 17%–23%; $p = .000$). In addition, a separate sensitivity analysis was conducted by removing the studies that originally classified diabetes into autoimmune diseases but did not differentiate type 1 diabetes mellitus from type 2 diabetes mellitus, and the recalculated pooled frequency was similar to the primary pooled results (data not shown). In order to explore potential heterogeneity, we performed additional analysis on different subgroups. For the hospital-based studies (combined consecutive hospital-based with hospital record-based studies together), the pooled frequency was similar (569/4,474; 13%, 12%–14%) to that from the population-based studies ($p = 1.000$). In studies providing diagnostic criteria for autoimmune diseases, the pooled frequency was 20% (128/653; 17%–23%), which was higher than studies not providing diagnostic criteria (827/6,839; 12%, 11%–13%; $p = .000$). We further explored two population-based studies providing diagnostic criteria for autoimmune diseases (Christensen et al., 1995; Oosterhuis & de Haas, 1968), because they represented key studies originally intended to report frequency of autoimmune diseases. All these

studies found increased coexistence of other autoimmune diseases in MG, compared with that expected using population-based incidence rates during the same time period. However, both the studies were conducted between 15 years and 40 years ago and identified autoimmune diseases using a non-broader ascertainment method (mainly focused on the most common autoimmune diseases).
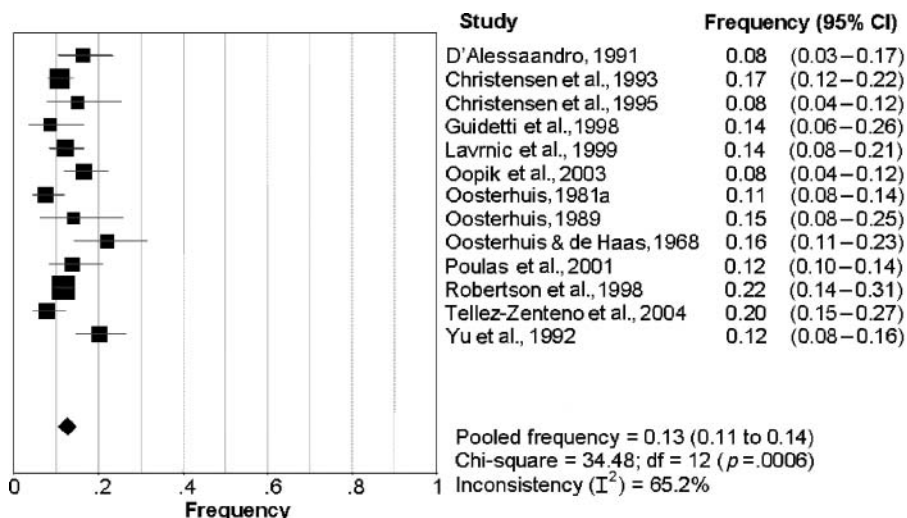
We performed further analyses for each autoimmune disease (Table 1). Overall, there are 23 diseases described in the included studies. The pooled frequency of autoimmune thyroid diseases (Grave's disease and Hashimoto's disease) seems to be higher than other autoimmune diseases. The most common diseases coexisting within MG were Grave's disease (7%, 5%–8%), Hashimoto's disease (3%, 2%–4%), and rheumatoid arthritis (3%, 2%–4%). The remainder of diseases is presented in Table 1.

The data on the clinical association of the frequency of autoimmune diseases in MG were available from seven population-based studies (Christensen et al., 1993; D'Alessandro et al., 1991; Oosterhuis, 1981a, 1989; Oosterhuis & de Haas, 1968; Poulas et al., 2001; Robertson et al., 1998), one consecutive hospital-based study (Beekman et al., 1997), and four hospital record-based studies (Al-Moallem et al., 2008; Goulon et al., 1980; Rastenyte et al., 2002; Toth et al., 2006) (Table 2). Pooled analysis showed that the frequency of autoimmune diseases was significantly higher in females (OR 2.71; $p <.00001$), and seropositive (OR 3.68; $p = .004$) MG patients. There were no clear differences in risk by age at onset or the MGFA clinical classification.
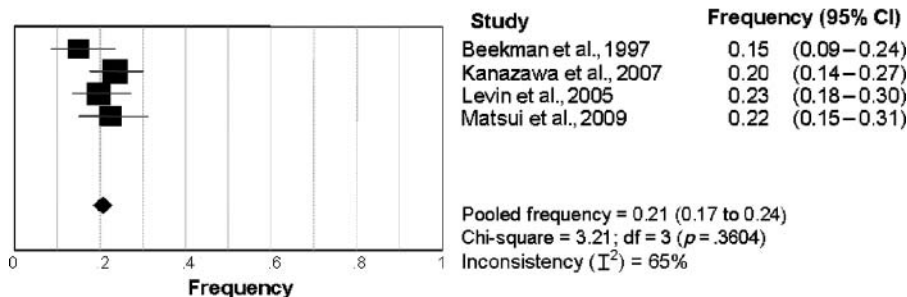
Discussion

To our knowledge, the present study is the first systematic review to evaluate the coexistence of autoimmune diseases in MG. Our study suggests that (1) approximately 13% of MG patients reported other coexisted autoimmune diseases; (2) autoimmune thyroid diseases seem to occur more frequently in MG patients compared with other conditions; (3) autoimmune diseases seem to occur more often in female and seropositive MG patients. However, we recognize that this is likely to be a conservative estimate because, first, potential under-reporting (or under-recognition) of autoimmune diseases in the population-based and hospital-based studies. This may have contributed to the difficulties inherent in identifying autoimmune diseases in some patients. For example, MG patients with coexisting mild autoimmune thyroid disorders may fail to reach hospital attention. Second, some uncommon autoimmune diseases may be undiagnosed and contribute to ascertainment methods in included studies
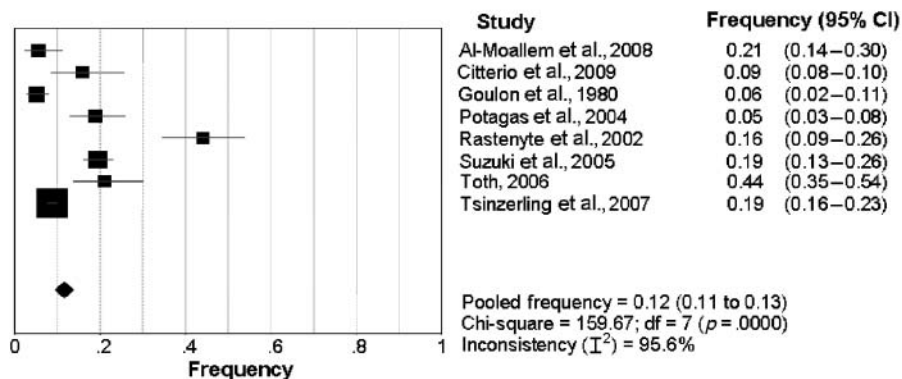
FIGURE 2.   Frequency of autoimmune diseases in myasthenia gravis: a meta-analysis plot.

resulting in surveillance bias. In addition, subgroup analyses of studies providing diagnostic standards for autoimmune diseases (to evaluate autoimmune disease originally) showed considerably higher frequency than those that did not. Furthermore, the universally poor quality of studies has affected the estimation.

Generally, our results seem to support the hypothesis that patients with MG have a higher frequency of other autoimmune diseases when compared with the population-based data (Cooper & Stroehla, 2003; Eaton, Rose, Kalaydjian, Pedersen, & Mortensen, 2007; Jacobson, Gange, Rose, & Graham, 1997), even using the estimation from recent studies by correcting for under-ascertainment (Cooper et al., 2009). It should be noted that the shortcomings of some included studies preclude a definitive estimate. First, this indication relies

TABLE 1.   Frequency of separate autoimmune disease in myasthenia gravis

	No. of studies	Frequency (95% CI)	I^2 (%)
Graves' disease	11	0.07 (0.05–0.08)	71.6
Hashimoto's disease	9	0.03 (0.02–0.04)	82.7
Rheumatoid arthritis	17	0.03 (0.02–0.04)	44.8
Alopecia	5	0.02 (0.01–0.03)	45.7
Multiple sclerosis	3	0.02 (0.01–0.05)	0
Psoriasis	2	0.02 (0.00–0.04)	0
Sarcoidosis	2	0.02 (0.00–0.05)	0
Systemic lupus erythematosus	13	0.02 (0.01–0.02)	0
Type 1 diabetes	7	0.02 (0.01–0.03)	47.3
Autoimmune thrombocytopenic purpura	4	0.01 (0.00–0.01)	56.4
Pemphigus vulgaris	2	0.01 (0.00–0.02)	0
Pernicious anemia	6	0.01 (0.01–0.02)	45.6
Sjögren's syndrome	4	0.01 (0.00–0.02)	0
Vitiligo	4	0.01 (0.00–0.03)	42.5
Ankylosing spondylitis	2	0.00 (0.00–0.01)	0
Crohn's disease	3	0.00 (0.00–0.01)	0
Ulcerative colitis	2	0.00 (0.00–0.01)	0
Autoimmune hemolytic anemia	1	NA	NA
Behcet disease	1	NA	NA
Pemphigoid	1	NA	NA
Polymyositis	1	NA	NA
Rheumatic fever	1	NA	NA
Systemic sclerosis	1	NA	NA

NA: Not available.

on non-direct comparisons with historical epidemiological data, thus there is no appropriate control group. In addition, given the inherent low frequency of autoimmune diseases, accurate estimation of frequency could be affected by limited sample size. Moreover, most studies provided few methodological details on identification of autoimmune diseases. This made it difficult to judge the adequacy of the methods of these studies. Lessons from the recently conducted national, multicenter, population-based study focusing on the frequency of coexistence of autoimmune diseases in multiple sclerosis (MS) should be noted (Ramagopalan et al.,

2007). By using spousal controls to minimize any surveillance bias and adjusting for age and sex, this study did not record an increased frequency of common autoimmune diseases in MS patients. Furthermore, we could not rule out the possibility that treatment with immunosuppressive agents affects the risk of developing other autoimmune diseases. However, the absence of a detailed description of treatments associated with the occurrence of autoimmune diseases during the cohort period in most studies hampers the interpretation. Taken as a whole, it is likely that, considering the underestimation of frequency, the frequency of coexisting

TABLE 2.   Pooled odds ratios for factors associated with frequency of autoimmune diseases in myasthenia gravis

	No. of studies	Patients with factor/total		OR (95% CI)	*p*-value*	I^2	*p*-value**
		With AID	Without AID				
Female sex	9	216/267	1111/1863	2.71 (1.96–3.76)	< 0.00001	0	0.49
<50 years[a]	1	8/13	51/69	0.56 (0.16–1.95)	0.37	0	NA
<35 years[a]	1	1/7	60/118	0.16 (0.02–1.38)	0.10	0	NA
Seropositive[b]	1	39/48	33/61	3.68 (1.52–8.89)	0.004	0	NA
Generalized[c]	1	7/7	107/116	1.33 (0.07–25.04)	0.85	0	NA

OR: odds ratio; AID: autoimmune diseases; NA: not available.
*Significance of pooled OR results.
**p-value for heterogeneity.
aCut-off point of age at onset derived from selected studies.
bAnti-acetylcholine receptor antibodies test results.
cMyasthenia Gravis Foundation of America Clinical Classification.

autoimmune diseases in MG was increased; however this result warrants further confirmation.

Although autoimmune thyroid diseases (Grave's disease and Hashimoto's disease) were the most frequent autoimmune diseases (7% and 3%, respectively) in MG in our analysis, other studies indicate a far more frequent data (e.g., 43% in Marino et al., 1997) compared with this study. This is possibly because of the under-ascertainment in the majority of the included studies, in which clear and validated ascertainment criteria are not provided. This could result in surveillance bias. Likewise, the frequency of other specific autoimmune diseases needs further investigation. It is interesting to explore whether MG coexists with a limited range of specific autoimmune diseases in order to seek potential etiologic clues, like the association between MS and rheumatoid arthritis (Somers, Thomas, Smeeth, & Hall, 2009). However, separate analyses of each autoimmune disease would be unstable given the limited sample size at this stage.

The most consistent finding in risk evaluation is that females have a higher relative risk for the coexistence of other autoimmune diseases in MG. Although unsurprising, this factor was broadly in accordance with other autoimmune diseases research and supports an important role for pathology in MG patients. Risk factor analyses also suggest that seropositive MG patients yielded a higher frequency of autoimmune diseases in MG. However, this estimation was affected by low statistical power in only one study providing information from serology results (Toth et al., 2006). In addition, we did not find a clear association between other clinical variables (age at onset and MGFA classification) and coexistence of autoimmune diseases because of paucity of data in this area. It should be noted, both female and serology factors could be influenced by age; thus these two factors currently may not be representatives of generally independent predictors of the coexistence of other autoimmune diseases in MG. This emphasizes the importance of future research with multivariate adjustment to confirm these findings.

Heterogeneity between studies remained an important factor limiting the interpretation of our results. In this review, although we have attempted to minimize heterogeneity by grouping studies by source of case selection, the I^2 statistics generally indicated great heterogeneity within subgroups. Potential sources of heterogeneity include methods of diagnosis of autoimmune diseases, which was often not provided. This seriously affects the comparability among the included studies. For instance, frequency may be underestimated if diagnosis is just based on clinical signs, compared with those based on both clinical and laboratory evidences; although studies that used self-reported autoimmune disease history may potentially suffer from exposure misclassification. Certainly, heterogeneity in study results can also be attributed to differences in case mix, including variation in clinical course, sample size, and ethnic distribution. We attempted to investigate the characteristics of the population (spectrum of ages, MGFA clinical classification) from the included studies, but most studies did not report the detailed information. This should be a call to the MG community to set up a better uniformity in the evaluation of autoimmune diseases. It should also be noted that all included studies in this review were of retrospective design. As retrospective studies are more prone to selection bias, it is difficult to determine whether heterogeneity in study findings represents true differences in characteristics of populations, or was caused by ascertainment criteria bias and other errors. Given these considerations, the results should be interpreted with caution.

Strengths and Weaknesses of This Review

By synthesizing all the published data on autoimmune diseases, we provide a more precise frequency estimate than previously available one. The influence of variations in study design might be diluted by pooling data across the studies, and we were able to explore this heterogeneity in study characteristics and design subgroup analyses. Furthermore, despite the limitations of the arbitrary method of defining autoimmune diseases (Appendix 1), we believe that the use of this approach gave the best possible correction for the estimated frequency, which considers both available and unavailable specific codes in the International Classification of Diseases (ICD). However, our study also had some limitation. First, some of the studies were not designed to report on the frequency of autoimmune diseases. This results in an unreliable reference standard of assessment of autoimmune diseases and incomplete case ascertainment (e.g., a patient with minor MG may not be willing to participate in an autoimmune disease assessment). Hence, the frequency could have been underestimated. Second, this study could not further evaluate the autoimmune diseases developed prior or after the onset of MG, and the role of immunotherapy (especially thymectomy) in the development of autoimmune diseases, mainly because of both fairly low frequency and lack of available information in most studies. In addition, case ascertainment may also differ in studies designed to look at "any autoimmune disease" versus those with a predesignated list of diseases. Furthermore, given the low prevalence of many autoimmune diseases, we might have missed a stable estimation because of inadequate sample sizes. Finally, like most meta-analytic reviews, we pooled together studies conducted under different circumstances despite significant heterogeneity (Lew et al., 2008; Pendlebury & Rothwell, 2009).

In conclusion, this study suggests that patients with MG have an increased frequency of coexisting autoimmune diseases. However, whether this phenomenon is generalized across all autoimmune diseases is unknown. This study also highlights that even when using meta-analyses by systematically identifying and synthesizing available data on the coexistence of autoimmune disease in MG, power was limited to investigate some rare disease combinations and to perform meaningful subset analyses. Our finding also emphasize the importance of ascertainment to identify autoimmune diseases in MG. Thus, a well-planned population-based prospective case-control study (e.g., having controls from the same geographic region matched sex and ethnicity) on the frequency of autoimmune diseases in MG is needed to expand our understanding of association of these conditions (Grimes & Schulz, 2002) despite the acknowledged difficulties in achieving statistical power to detect these diseases with heterogeneous clinical presentations and complex case definitions. A standardized ascertainment of autoimmune diseases should be given to the participating MG patients. Finally, we are pleased to dedicate this special issue to Dr. Simpson's outstanding contributions to autoimmune hypothesis of MG (Simpson, 1960).

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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