Increased Prevalence of Myasthenia Gravis in a Cohort of Patients with Inflammatory Bowel Disease

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Abstract

Background. Co-morbid auto-immune disorders may affect 0.2% of the population. We evaluated the association between myasthenia gravis and inflammatory bowel disease.

Methods. We present the epidemiological, clinical and electrodiagnostic findings of one patient with ulcerative colitis and three with Crohn's disease (from a Brazilian cohort of 606 patients) and co-morbid myasthenia gravis.

Results. Mean age of onset of inflammatory bowel disease was 33.5±2.7, and patients are currently 45.8±7.3 years old. Two patients were acetylcholine receptor antibody positive, one anti-Muscle specific kinase positive and one seronegative. Three had abnormal repetitive nerve stimulation, all four had normal nerve conduction studies, abnormal skin wrinkling test and mild small fiber neuropathy. None had thymoma and/or accepted thymectomy. According to the Myasthenia Gravis Foundation classification, one was class V, one class IVb and two IIa. Myasthenia gravis diagnosis was masked by immunotherapy in all. The Prevalence ratio of having myasthenia gravis in inflammatory bowel disease patients in comparison with the proportion of myasthenia gravis among all patients seen in our center was 8.56 ($P<0.0001$, CI=3.1-23.5). Considering the lowest and highest prevalence of myasthenia gravis reported in the literature, the Prevalence ratio is 44.0 ($P<0.0001$, CI:16.3-118.4) and 26.4 ($P<0.0001$, CI: 9.8-70.6), respectively.

Conclusions. Myasthenia gravis prevalence is higher in inflammatory bowel disease and may include muscle specific kinase positive disease (first report in the literature). In general, myasthenia gravis clinical course was not significantly modified by inflammatory bowel disease relapses and frequently overlaps with other autoimmune conditions and small fiber neuropathy.

Introduction

Multiple conditions can be associated with myasthenia gravis (MG). Sardu et al [1]. reported a prevalence of 5.1% of one auto-immune disorder in a survey of the population of Southern Sardinia, and co-occurrence of two auto-immune disorders of 0.2% (0.4% in women, 0.08% in men) [1]. A second auto-immune disease occurs in 15% of MG patients, especially with early onset MG and thymic hyperplasia [2]. Early-onset MG is associated with human leukocyte antigen-DR3 (HLA-DR3), HLA-B8 and late-onset disease with HLA-DR2, HLA-B7, and HLA-DRB1. This HLA association is higher than in patients with Multiple Sclerosis [3].

A higher association with several autoimmune disorders, especially thyroiditis and rheumatoid arthritis has been confirmed in a Swedish cohort but no link to inflammatory bowel disease (IBD) was established [3]. In one report, thymectomy led to the development of additional autoimmune disorders in MG [4].

IBD is associated with a wide variety of neurological disorders [5]. Given that few studies have addressed this, we started a cohort study in 2004 to evaluate the prevalence of neurological diseases in IBD [6].

Widely different numbers on the prevalence of neurological disorders in IBD have been reported, likely due to different inclusion criteria and ethnic characteristics [5–12]. Autoimmune diseases reported in IBD include peripheral neuropathy, myelopathy, multiple sclerosis (MS), optic neuritis and MG [5–12]. Here, we present the epidemiological, clinical and electrodiagnostic findings of four IBD patients from our cohort who developed MG, and conducted a systematic literature review about the subject.

Methods

Patients with IBD and neurological diseases seen between 2004 and 2023 at the IBD Clinic of the Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, were invited to participate in a cohort study ("NEURODII") approved by the Institutional Review from the Hospital Universitário Walter Cantídio (CAAE: 62248416.7.0000.5045). They were evaluated for neurological disorders using a published protocol after signing a written informed consent form [6]. Patients underwent antibody testing for MG, electroneuromyography/nerve conduction study (EMG/NCS), repetitive nerve stimulation (RNS) and skin wrinkling test for evaluation of small fiber neuropathy [13, 14]. A pubmed search of the literature of cases of patients with IBD and MG was conducted on 12/01/23 with the terms "inflammatory bowel disease", "Crohn's disease" (CD) and "ulcerative colitis" (UC) and "myasthenia gravis" or "myasthenia gravis registry". All papers written in any language were included, provided minimal epidemiological data (e.g. gender, age, disease onset and course) could be extracted (see Fig. 1 for complete flowchart).

Statistical analysis

Descriptive statistics (mean ± standard error mean) and risk assessment of MG in comparison with the total number of patients seen in our center and worldwide were also conducted (Prevalence ratio). Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software packages. A type I error probability (p-value) of < 0.05 was assumed.

Ethical Statement

This cohort study was approved by the Institutional Review (CAAE: 62248416.7.0000.5045) and was conceived according to the principles of the Declaration of Helsinki.

Results

Over a 19-year period, we diagnosed four patients with MG (three patients with CD and one with UC) in our cohort of 606 patients with IBD (prevalence of 0.66%). Patients are currently 45.75±7.29 years old. Mean age at IBD diagnosis was 33.5±2.69 years, mean age at MG onset was 39.5±2.69 years. There were three women and one man. Preliminary results of two cases were reported elsewhere.[15] The Prevalence ratio (PR) of having MG in IBD patients vs the proportion of MG among all patients in our center was 8.56 (P<0.0001, CI=3.1-23.5). Considering the lowest and highest reported prevalence of MG worldwide, the PR is 44.00 (P<0.0001, CI:16.3-118.4) and 26.40 (P<0.0001, CI: 9.8-70.6), respectively.

Patient 1 (initial findings previously reported) [15]

A man was diagnosed with UC at age 37. Three years later, he underwent total laparoscopic colectomy sparing the rectum for the treatment of colonic dysplasia. A gastro-colonic fistula identified during the surgery led to a partial gastrectomy and a diagnostic shift to CD. After assuming that he was cured by colectomy, he missed follow-up evaluations and 2 months after tapering off prednisone and azathioprine, he developed quadriparesis with bilateral ptosis, dysphagia and slurred speech over a few weeks. His condition progressed and he was admitted to an intensive care unit, intubated and kept on mechanical ventilation. MG was diagnosed. NCS and EMG were normal. RNS revealed basal compound muscle action potential decrements at the right ulnar nerve up to 22% that improved after exercise (correction) and increased two minutes after forced muscle contraction up to 31%. Anti-acetylcholine receptor antibody (Anti-AchRAB) were elevated up to 10.7. Serum Immuno-electrophoresis revealed polyclonal gammopathy, Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) titers were positive (1:640), Thyroid-stimulating hormone was decreased (0.2) and homocysteine elevated (11.7). Anti-nuclear antibody and rheumatoid factor were negative. Chest computed tomography did not disclose thymoma. Subsequently MG remained well controlled with prednisone, azathioprine and pyridostigmine, except for occasional fatigability. Thymectomy was offered repeatedly in the first years after MG diagnosis, but he refused it. He was also diagnosed with small fiber neuropathy, characterized by distal paresthesias and abnormal skin wrinkling test. He was also diagnosed with osteoporosis and had two bouts of nephritic colic with hydronephrosis.

Patient 2 (initial findings previously reported) [15]

A 35 year-old woman was diagnosed with UC and subsequently developed jaundice, severe anemia, hepatosplenomegaly and was diagnosed with primary sclerosing cholangitis. Five years later, she developed speech impairment, bilateral ptosis, disconjugate gaze, fatigability with sustained vertical movements and mild proximal upper limb weakness. NCS and EMG were normal. Right ulnar RNS demonstrate significant decrement with correction after exercise and worsening three minutes post exercise. Skin wrinkling test was abnormal (mean score of 0.5) and she had mild sensory findings consistent with small fiber neuropathy. Anti-AchRAB were above 20, Anti-nuclear antibody was positive and normal Immunoglobulin G-4 (IgG4) level (87,52). Initial treatment with pyridostigmine and prednisone was successful, but her symptoms progressed in severity. Thymectomy was recommended but could not be performed due to persistent thrombocytopenia (idiophatic thrombocytopenic purpura versus myelodysplastic syndrome). She was subsequently treated with prednisone and Intravenous immunoglobulin infusions, since she could not be treated with azathioprine due to cirrhosis. On 8/2021 she was started on rituximab with good MG control since then.

Patient 3

A 37 year-old woman was diagnosed with CD after a 10-year history of diarrhea, weight loss and abdominal pain. Colonoscopy revealed aphthous ileal, cecal and rectal ulcers (in 2016). She was treated with sulfasalazine and mesalazine and got worse after developing a perianal fistula. She was started on

azathioprine on 5/2019, that was stopped due to abdominal pain and elevated aspartate aminotransferase and alanine aminotransferase. She was referred for neurological evaluation of headache and was initially diagnosed with trigeminal neuralgia. She also had dizziness, distal paresthesias and complained of repeated episodes of left facial palsy. She also met the diagnostic criteria of restless leg syndrome and small fiber neuropathy with an abnormal skin wrinkling test (mean score of 1.75). She had been previously diagnosed with fibromyalgia. Neurological exam revealed bilateral (predominant left) facial weakness, hyperreflexia with bilateral Hoffmann sign as well as distal pin loss. On 7/2021 she was diagnosed with Multiple Sclerosis and started on Copaxone s.c., three times/week (Brain MRI findings with normal cervical MRI). She was also diagnosed with anemia (Hemoglobin = 7.2; Hematocrit = 21) and borderline low Vitamin B12 level = 227. On 5/2022 she was found to have worsening of bilateral facial weakness with disconjugate eye movements and fatigability on sustained vertical gaze evaluation, and was diagnosed with myasthenia gravis. Nerve conduction studies and EMG were normal. RNS did not disclose significant decrement and anti-AchR antibodies were negative. She improved with PO pyridostigmine and prednisone (40 mg/day). Chest computed tomography did not reveal thymoma and thymectomy has not been accepted so far.

Patient 4

A 37 year-old woman was diagnosed with CD after a 8-year history of bloody diarrhea and 17-kg weight loss and abnormal colonoscopy. She was initially treated with mesalazine and prednisone and then azathioprine. After developing an anovaginal fistula she was started on inflixamab. She then developed episodic right eye pain and migraine episodes 20 days prior to inflixamab infusions. On 4/2021, she developed left eye ophthalmoplegia and vision loss. She was admitted for inpatient treatment with i.v. methylprednisolone after being diagnosed with orbital apex syndrome due to a posterior variant of orbital pseudotumor. Since vision loss resolved with steroids but she persisted with eye movement abnormalities, including fatigability, she was evaluated for MG. Nerve conduction studies and EMG were normal. RNS disclosed a greater than 10% decrement on facial nerve RNS. Anti-AchR antibodies were normal but anti-muscle specific kinase (anti-MuSK) antibodies were positive (0,09 NMOL/L). Chest Computed tomography did not disclose thymoma and she had a good response to pyridostigmine and PO prednisone. She only had mild generalized weakness that improved with prednisone. IgG4 levels were normal 53,24 (8-140). Anti-aquaporin-4, thyreoglobulin antibodies were negative. Vitamin B12 levels were also low (173) and treated with intramuscular vitamin B12 replacement. She does have mild distal paresthesias consistent with small fiber neuropathy, that was confirmed by abnormal skin wrinkling test (mean score of 0.5).

Literature review

As can be seen in Table 1 and Fig. 1, our systematic literature review disclosed 22 papers and 28 patients with IBD and MG [3,7,16-42]. In several articles, important demographic details were not provided. Seven additional papers describing MG registries where additional autoimmune diseases could be identified were also evaluated.

Eleven patients (five women and four men, two unknown gender) had MG and CD, mean age of CD diagnosis was 44.6±19.17 years. One of them was included but CD diagnosis was not clearly defined at that time. Seventeen patients had UC and MG, mean age of UC diagnosis 27.9±17.01 years, total of eight men and six women. In most cases, the MG diagnosis was made several years after IBD diagnosis, 3-15 years for CD and 0.2 to 13 years for UC. However, in two UC patients and three CD patients, MG was diagnosed 1-4 years prior to IBD diagnosis (one had undefined duration). Fourteen patients had an additional autoimmune disease (other than MG and IBD), four for CD and 10 for UC. One patient had thyroid cancer and another colon cancer.

According to MG Foundation classification, 30.4% were class IV and V. Pure ocular disease (I) and moderate forms (IIIb) occurred in the same proportion (6/23=26% for each), while milder forms of generalized disease (II) affected 17.3% of the patients. Among 21 patients who underwent antibody testing, 18 (18/21=85.7%) were AchRAB+ and three were negative (3/21=14.28%). Only one had anti-muscle specific kinase antibodies (anti-MuSK) testing, that was negative. No one was tested for Lipoprotein receptor related protein-4 (LRP4) or agrin antibodies. Thymectomy led to improvement of MG in the majority of the patients (6/11=54.5%), but in one patient, despite MG remission, Systemic lupus erythematosus (SLE) and UC started after thymectomy. In four patients no information about thymectomy outcome was provided. Among the seven MG registries detailing the occurrence of associated autoimmune conditions, the prevalence of IBD and MG varied from 0.35% among 565 MG patients from Holland to 2.56% among 39 patients older than ³70 years with MG in the USA.

Table 1.

Discussion

Despite growing understanding of the immunobiology of IBD, to date, major gaps remain in regards to the disease mechanisms of extraintestinal manifestations linked to IBD. Additional autoimmune disorders may affect up to 9.4% of the UC patients (i.e. SLE, vitiligo, thyroid disorders, type I diabetes mellitus and sclerosing cholangitis) [23]. This may be higher in CD [43]. Fifteen % of the MG patients may also have a second autoimmune disorder [2]. In our patients with IBD and MG, all of them had at least a third different autoimmune disorder: orbital pseudotumor, primary sclerosing cholangitis, idiopathic thrombocytopenic purpura, hyperthyroidism, multiple sclerosis, small fiber neuropathy.

MG prevalence was 0.66% in our cohort of IBD patients. This prevalence is eight times higher than in a cohort of rheumatoid arthritis patients [44] and maybe within the same range of patients with SLE: 0.15-1.3% [45]. A national MG registry study in Sweden documented a 2.3 times increased risk of CD in MG patients (CI=1.3-4.0) and 2.1 times increased risk for UC (CI=1.3-3.5) [3]. Our study is the first to provide consistent evidence for increased risk of MG in IBD patients. The Prevalence ratio (PR) of having MG in IBD patients in comparison with the proportion of MG among all patients seen in our center was 8.56 ($P<0.0001$, CI=3.1-23.5). Considering the lowest and highest prevalence of MG in the literature the PR is 44.00 ($P<0.0001$, CI:16.3-118.4) and 26.40 ($P<0.0001$, CI: 9.8-70.6), respectively.

What are possible explanations for this association between IBD and MG? Although we were not able to test HLA, both MG and IBD are associated with certain HLA genotypes [3,46]. It is possible that a specific HLA genotype may explain some of those cases. In both IBD and MG there are abnormalities in both innate and adaptative immunity [46]. A pro-inflammatory environment and imbalance in T-regulatory and T-helper-17 lymphocytes are present in both conditions [23,47]. Increased production of chemokine C-X-C ligand-13 maybe another explanation [47]. Common abnormalities in the gut-brain axis may also be involved in the generation of both diseases, since the thymus also receives major input via the vagus nerve [48]. Lastly, it is important to understand that MG and IBD are complex diseases, with different subtypes and pathogenic mechanisms. Autoimmune MG can be caused by different mechanisms and types of antibodies: anti-acethycholine receptor antibodies, anti-MuSK, anti-lipoprotein receptor related protein-4 (anti-LRP4) and anti-agrin antibodies [37,46]. Anti-MuSK disease is mediated by IgG4 antibodies and the role of anti-LRP4 and anti-agrin antibodies is still very obscure. There are also seronegative subtypes of MG. It is likely that different mechanisms are involved in the predisposition for different MG subtypes. Highlighting this possibility, there are two subtypes of autoimmune pancreatitis that are considered extraintestinal manifestations of IBD [49]. Type II is the most prevalent and may share similar pathogenic mechanisms with anti-AchRAB MG, with overexpression of cellular adhesion molecule Mad-1[49]. Type I pancreatitis is part of the spectrum of IgG4 diseases, similar to anti-MuSK MG [49]. In fact, up to 4% of the IBD patients may have increased IgG4 levels [49]. To our knowledge, our patient 4 is the first instance of anti-MuSK MG in IBD. Her IBD course is unusual and she also had orbital pseudotumor, a rare extra-intestinal manifestation of IBD [8]. A description of anti-SOX1 antibodies in a patient with CD and Lambert-Eaton myasthenic syndrome also points towards a far wider association of different types of neuromuscular involvement in patients with MG [50].

Our systematic literature review disclosed 22 papers and 28 patients with IBD and MG and 7 MG registries detailing IBD patients (Table 1) [3,7,16-42]. In several articles, important demographic details were lacking. The age of MG presentation was similar to the early peak in non-IBD patients. Although female predominance was evidenced in CD patients, there was a slightly higher number of male patients with UC and MG. Close to 90% were AchRAB+. However, since most of the papers were from old literature (case reports or series prior to anti-MuSK description), only one had a negative anti-MuSK testing. No one was tested for LRP4 or agrin antibodies. Therefore, it is not possible to sort out whether there are IBD patients with more than one antibody. Thymectomy led to improvement of MG in the majority of the patients. Similar to our patients, a large number of additional auto-immune diseases was found. Our patient 1 had hyperthyroidism, patient 2 had primary sclerosing cholangitis in addition to MG and UC, a triple association has only been reported once [25]. Patient 3 had MG, CD and multiple sclerosis, a previously unreported association and patient 4, anti-MuSK MG, CD and orbital pseudotumor, a triple association never reported previously. In addition, all of our four patients had small fiber neuropathy and low-borderline low vitamin B12 level. The small fiber neuropathy could have resulted at least partially due to the low vitamin B12 levels, but immune-mediated small fiber neuropathy cannot be excluded. As previously described, our patient 1 illustrates that immunosuppression for IBD may mask MG and lead to misdiagnosis. However, prednisone, azathioprine and infliximab may have also delayed the MG diagnosis

in patients 2, 3 and 4, due to partial or even complete control of MG. This pattern was reported elsewhere [22,34,35].

None of our patients underwent thymectomy. Reasons included patient refusal and persistent thrombocytopenia with increased surgical risk. In our literature review, thymectomy usually produced good results, occasionally improving both IBD and MG. However, in at least one patient SLE and UC started after thymectomy [26]. Two patients experienced total regression of MG after colectomy [23,27], while three patients developed MG after colectomy [29,32]. Pyridostigmine did not exacerbate diarrhea and other gastrointestinal symptoms in our patients, similar to most reports from our literature review.

Conclusions

In summary, MG prevalence was 0.66% in our cohort of IBD patients. This prevalence is at least 8 times higher than in the other patients seen in our center and 26-44 times higher than in the general population worldwide. The spectrum of MG in IBD may include anti-MuSK positive disease. In general, MG clinical course was not significantly modified by IBD relapses. Therefore, MG needs to be considered in IBD patients with new onset ocular, bulbar or limb symptoms, in particular after changes in immunosuppression.

Abbreviations

AchRAB: Anti-acetylcholine receptor antibody; ALT: Alanine aminotransferase; ANA: Anti-nuclear antibody; AQP4: Aquaporin-4; AST: Aspartate aminotransferase; CD: Crohn disease; CI: Confidence interval; CMAP: Compound muscle action potential; CT: Computed tomography; CXCL 13: Chemokine C-X-C ligand 13; EMG: Electromyography; Hb: Hemoglobin; HLA: Human leukocyte antigen; HT: Hematocrit; IBD: Inflammatory bowel disease; ICU: Intensive care unit; IgG4: Immunoglobulin G-4; IM: Intramuscular; IVIg: Intravenous immunoglobulin; LRP4: Lipoprotein receptor related protein-4; MadCAM1: Cellular adhesion molecule Mad-1; MG: Myasthenia gravis; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; MuSK: Muscle specific kinase; NCS: Nerve conduction study; P-ANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; PR: Prevalence ratio; RF: Rheumatoid factor; RNS: Repetitive nerve stimulation; SEM: Standard error mean; SLE: Systemic lupus erythematosus; Th17: Helper T-17; Treg: Regulatory T; TSH: Thyroid-stimulating hormone; UC: Ulcerative colitis.

Declarations

Ethics Approval and Consent to Participate

This cohort study was approved by the Institutional Review Board from the Universidade Federal do Ceará (Comitê de Ética em Pesquisa do Hospital Universitário Walter Cantídio/UFC), study number CAAE: 62248416.7.0000.5045, and was conceived according to the principles of the Declaration of Helsinki. All invited patients signed a written informed consent form.

Consent for Publication

All patients signed the written consent form authorizing publication of their clinical findings.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors have no relevant financial, intellectual or other competing interests about the current manuscript.

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Author Contributions to Manuscript

AMFL and FAAG carried out the conception, design, data collection and interpretation, wrote the original manuscript, revised and approved the final version. FPT participated in the conception, review of the manuscript and approved the final version. MHLPS and LLBCB performed data analysis and interpretation, revised the manuscript and approved the final version.

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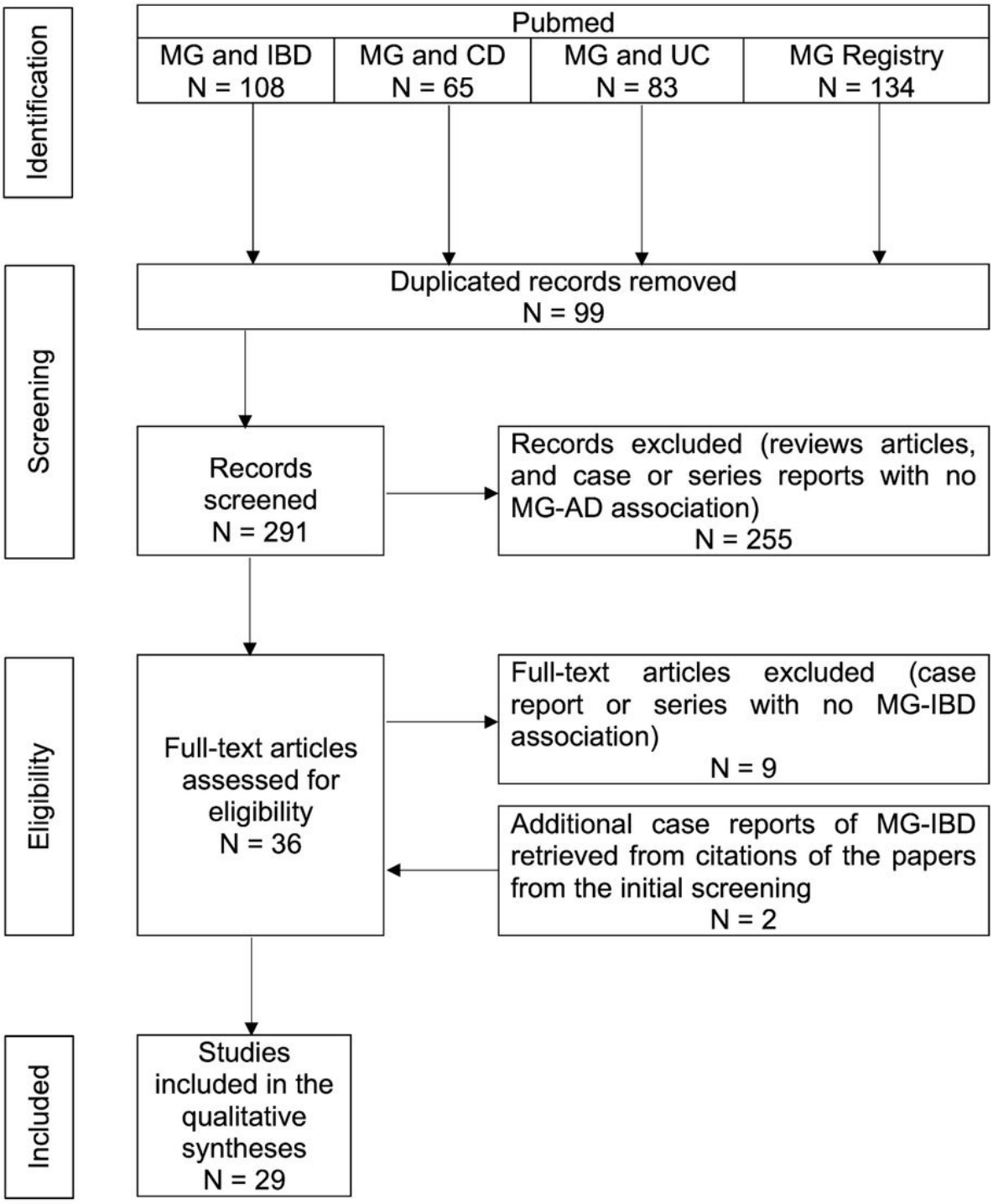
Tables

Table 1 is available in the Supplementary Files section.

Figures



Source: own elaboration

Figure 1

Flowchart of the literature review of patients with myasthenia gravis and inflammatory bowel disease

AD: Autoimmune diseases; CD: Crohn's disease; IBD: Inflammatory bowel disease; MG: Myasthenia gravis; UC: Ulcerative colitis.

Supplementary Files

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