RESEARCH ARTICLE

Exploring Factors That Prolong the Diagnosis of Myasthenia Gravis

Minh Nguyen, FRACP, MBBS, BBSci, Meaghan Clough, PhD, PGDip, BA, Belinda Cruse, FRACP, MBBS, BSc, Anneke van der Walt, FRACP, AFRACMA, PhD, MBChB, Joanne Fielding, PhD, BSc (Hons), BA*, and Owen B. White, FRACP, PhD, MD, MSc, MBBS*

Correspondence
Dr. Nguyen
mnnguyen02@gmail.com

Neurology: Clinical Practice 2024;14:e200244. doi:10.1212/CPJ.0000000000200244

Abstract

Background and Objectives

Myasthenia gravis (MG) is a condition with significant phenotypic variability, posing a diagnostic challenge to many clinicians worldwide. Prolonged diagnosis can lead to reduced remission rates and morbidity. This study aimed to identify factors leading to a longer time to diagnosis in MG that could be addressed in future to optimize diagnosis time.

Methods

One hundred and ten patients from 3 institutions in Melbourne, Australia, were included in this retrospective cohort study. Demographic and clinical data were collected for these patients over the first 5 years from diagnosis and at 10 years. Nonparametric statistical analysis was used to identify factors contributing to a longer diagnosis time.

Results

The median time for MG diagnosis was 102 (345) days. 90% of patients were diagnosed before 1 year. Female patients took longer than male patients to be diagnosed ($p = 0.013$). The time taken for first presentation after symptom onset contributed most to diagnosis time (median 17 [141] days), with female patients and not working as contributory factors. Neurology referral took longer if patients had diplopia ($p = 0.022$), respiratory ($p = 0.026$) symptoms, or saw an ophthalmologist first ($p < 0.001$). Outpatient management compared with inpatient was associated with a longer time to be seen by a neurologist from referral ($p < 0.001$), for the first diagnostic result to return ($p = 0.001$), and for the result to be reviewed ($p < 0.001$). Ocular MG had a median greater time to neurologist review than generalized MG (median 5 [25] days vs 1 [13] days, $p = 0.035$). Electrophysiology tests took longer for outpatients than inpatients (median 21 [35] days vs 2 [8] days, $p < 0.001$). Outpatients were also started on treatment later than inpatients ($p < 0.001$). There was no association of MG severity, ethnicity, age, medical and ocular comorbidities, and public or private health service on diagnosis time. There was also no impact of time to diagnosis on Myasthenia Gravis Foundation of America outcomes, number of follow-ups or hospitalizations, or prevalence of treatments used. This study is limited by low patient numbers and its retrospective nature.

Discussion

This study identified several factors that can contribute to a prolonged diagnosis time of MG. Patient and clinician education about MG and outpatient diagnostic efficiency needs emphasis. Further studies are also needed to explore the delayed presentation time of women and nonworking patients in MG.

*These authors are co-senior authors.

Department of Neuroscience (MN, MC, AW, JF, OBW), Monash Health; Department of Neurology (BC), Royal Melbourne Hospital; and Department of Neurology (MN, AW), Alfred Health, Melbourne, Australia.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction (NMJ) affecting 12.4 people per 100,000 population worldwide,[1] particularly young female patients younger than 50 years and male patients older than 50 years.[2] MG causes fluctuating muscular weakness that, if untreated, can lead to progressive weakness due to NMJ degradation from destruction of acetylcholine receptors over time,[3] affecting quality of life, independence, and employment.[4] It has a broad and variable phenotype, often mimicking other diseases, delaying accurate diagnosis.[5]

Delayed diagnosis can lead to poorer remission rates and poorer quality of life, with a systematic review reporting that a diagnosis made within a year of presentation promoted better treatment response.[6] Furthermore, early treatment with prednisolone and immunosuppressants within 1 year of symptom onset reduces the risk of generalization in patients with ocular MG.[7] Furthermore, the greatest health care costs involve treatments for generalized MG, e.g., intravenous immunoglobulins, plasma exchange, mechanical ventilatory support, and frequent hospitalization.[8] It is therefore a clinical imperative to reduce the time to diagnosis.

At present, no study has reported a detailed analysis of the factors contributing to delay in diagnosis. This study aimed to identify factors contributing to a greater time to diagnosis of patients with MG and to assess any impact of time to diagnosis on treatment and clinical outcomes.

Methods

The electronic medical records of patients with MG from 3 health services in Melbourne, Australia, were retrospectively reviewed after ethics approval was obtained. 331 patient records were identified; however, only 110 patients fulfilled all eligibility criteria for inclusion (Figure 1). For each patient, demographics, comorbidities, clinical symptoms and signs at first presentation, modified Rankin scores, MGCS, duration to diagnosis and treatment, investigations, treatment including minimum and maximum doses and duration, and Myasthenia Gravis Foundation of America outcomes (refractory, complete stable remission [CSR], pharmacologic remission [PR], and minimal manifestation [MM])[9] were collected in a deidentified Excel spreadsheet.

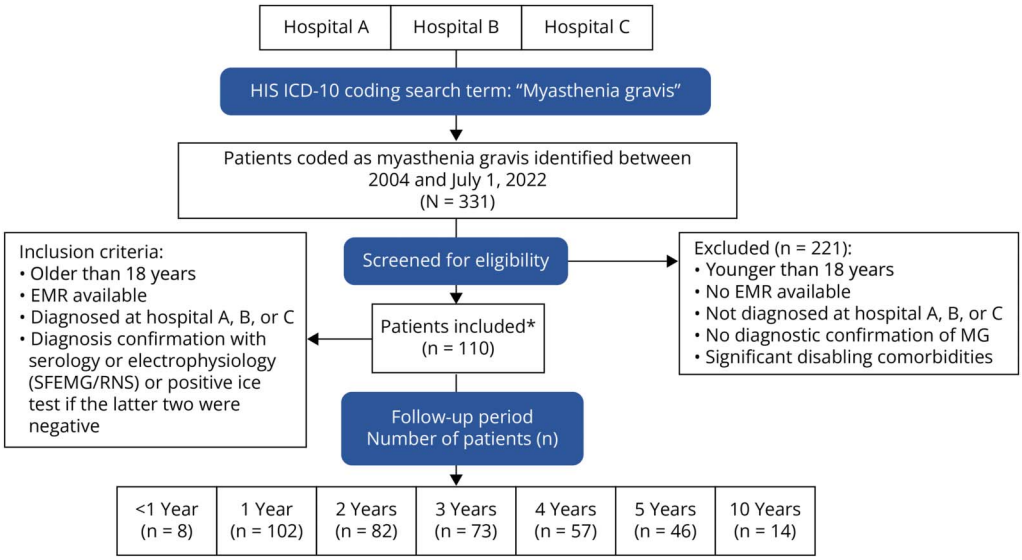
Statistical Analysis

All data were analyzed using SPSS version 29.0. Nonparametric tests were selected where Shapiro-Wilk tests determined that data were not normally distributed. To identify factors contributing to prolonged time point in the diagnosis of patients with MG, the Mood median test was performed. Binary logistic regression was used to assess the relationship of time to diagnosis on treatment and clinical outcomes. Medians were calculated with interquartile ranges (IQR) denoted as median (IQR) and frequencies of events recorded in percentages (%). Both medians and frequencies are rounded up to the nearest whole number.

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective study used deidentified data and received an exemption from the Human Research Ethics Committee (HREC) of Australia. Patient consent was not required.

Figure 1 Consort Diagram Demonstrating the Number of Records Screened, Excluded, and Included in This Study



EMR = electronic medical records; HIS = Health Information Service; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; MG = myasthenia gravis; SFEMG = single fiber electromyography; RNS = repetitive stimulation. Serology: anti-acetylcholine receptor antibodies and anti-MuSK antibodies.

Table 1 Baseline Demographics of Patients With MG at the Time of Diagnosis

Baseline demographic at time of diagnosis	Patients With MG, N = 110
Female, N (%)	61 (56)
Age (median [IQR] y)	
Female	58 (32)
Male	68 (14)
Ethnicity, N (%)	
European	93 (85)
Asian	10 (9)
African	4 (4)
Indigenous Australian/New Zealand	3 (3)
BMI (mean ± SD kg/m^2)	30.8 ± 10.5
Smoking	9 (8)
Current alcohol consumption	30 (27)
Actively working	51 (57)
mRS score (median [IQR])	0 (0)
Medical comorbidities, N (%)	
Ischemic heart disease	16 (15)
Diabetes mellitus	24 (22)
Hypertension	47 (43)
Dyslipidaemia	34 (31)
Chronic kidney disease	6 (6)
Human immunodeficiency virus	1 (1)
Respiratory disorders	31 (28)
Asthma	13 (42)
OSA	10 (32)
Asbestosis	4 (13)
COPD	2 (7)
Neurologic disorders	26 (24)
Depression	9 (35)
Migraine	7 (27)
Previous stroke/TIA	4 (15)
Epilepsy	2 (8)
Peripheral nerve palsy	4 (15)
Other[a]	6 (23)
Autoimmune disorders	25 (23)
Autoimmune thyroid disorder	8 (32)
Rheumatoid arthritis	4 (16)
Inflammatory bowel disease	3 (12)
Psoriasis	2 (8)
Polymyalgia rheumatica	2 (8)
Other[b]	6 (24)
History of malignancy	18 (16)
Prostate	5 (28)
Bowel	3 (17)
Breast	2 (11)
Ovarian/uterine	2 (11)
Cholesteatoma	2 (11)
Melanoma	1 (6)
Oral cancer	1 (6)
Currently active malignancy	4 (22)
Ophthalmic comorbidities	48 (44)
Cataracts	17 (35)
Glaucoma	10 (21)
Retinal disease	6 (13)
Ocular motility disorder[c]	9 (19)
Other[d]	11 (27)

Abbreviations: BMI = body mass index; IQR = interquartile range; mRS = modified Rankin severity score (out of 5).
[a] Patients with CSF leak, transient global amnesia, previous idiopathic intracranial hypertension, carotid-cavernous fistula, Parkinson disease, polio.
[b] Patients with idiopathic thrombocytopenic purpura, systemic lupus erythematosus, aortitis, Sjogren disease, sarcoidosis, pernicious anemia (antiparietal gastric ab).
[c] Pre-existing strabismus or previous cranial nerve palsy.
[d] Patients with prior refractive surgery, eyelid surgery, astigmatism, previous orbital fracture, orbital inflammatory syndrome.

Data Availability

Anonymized data not published within this article can be made available by reasonable request from any qualified investigator.

Results

Baseline Patient Demographics and Comorbidities of Patients With MG

Baseline demographics and comorbidities of patients are summarized in Table 1. This cohort contained a slightly higher proportion of female patients than male patients. More female patients (77%) than male patients presented as early-onset MG (younger than 50 years), and almost equivalent numbers of male patients and female patients presented as late-onset (older than 50 years). A greater proportion of early-onset patients (40%) presented as generalized MG compared with late-onset patients (25%) at initial presentation.

Table 2 Clinical Characteristics of Patients With MG at the Time of Diagnosis, Including Precipitating Factors, Diagnostic and Ancillary Tests Ordered, and Thymus Characteristics

Clinical characteristics at time of diagnosis	Patients with MG, N = 110
Outpatient diagnosis, N (%)	72 (66)
Initial presentation	
Purely ocular	79 (72)
Predominantly bulbar	16 (15)
Oculobulbar	12 (11)
Predominantly respiratory	2 (2)
Classification of MG at 2 y (N = 82)[a]	
Ocular	25/82 (31)
Generalized	57/82 (70)
Concurrent thyroid eye disease found	11 (10)
Potential precipitants identified	37 (34)
Prior infection (respiratory or gastrointestinal)	8 (7)
Surgery with general anesthesia	9 (8)
Stressful life events	6 (6)
Medication-related	4 (4)
Flu vaccine	1 (1)
Other illness	9 (8)
Diagnostic tests (positive test/total tests performed, %)	
Icepack test[b]	30/40 (75)
Cogan lid twitch	10/15 (67)
Anti-AChR Ab	70/107 (65)
Anti-MuSK Ab	3/42 (7)
RNS	33/64 (52)
SFEMG[c]	61/75 (81)
Ancillary tests performed, N (%)	
Thyroid function tests	97 (88)
CT brain	55 (50)
MRI brain	63 (58)
CT chest	96 (87)
Gastroscopy/barium swallow/ manometry	6 (6)
Respiratory function tests	35 (32)
Thymus status	
Thymoma	10 (9)
Thymectomy	22 (20)
After diagnosis[d]	19 (86)
Before diagnosis	3 (14)

Abbreviations: Ab = antibody; AChR = acetylcholine receptor; MuSK = muscle-specific kinase; RNS = repetitive nerve conduction studies; SFEMG = single fiber electromyography; VATS = video-assisted transthoracic surgery.
[a] Twenty-eight patients had <2 y follow-up.
[b] Icepack test not performed on all 71 patients with ptosis.
[c] Frequency of SFEMG muscles tested: frontalis (77.0%), orbicularis (12.0%), extensor digiti communis (6.67%).
[d] Median time to thymectomy after diagnosis 7.75(IQR 20.3) months.

One-quarter of patients had a coexisting autoimmune disease and pre-existing neurologic diagnoses without sequelae affecting their function. Four patients had active cancer during the study. One patient had metastatic small bowel endocrine cancer on lanreotide, 2 had local prostate cancer, and one had stage III melanoma whose treatment was stopped at MG diagnosis. No patient was pregnant at diagnosis.

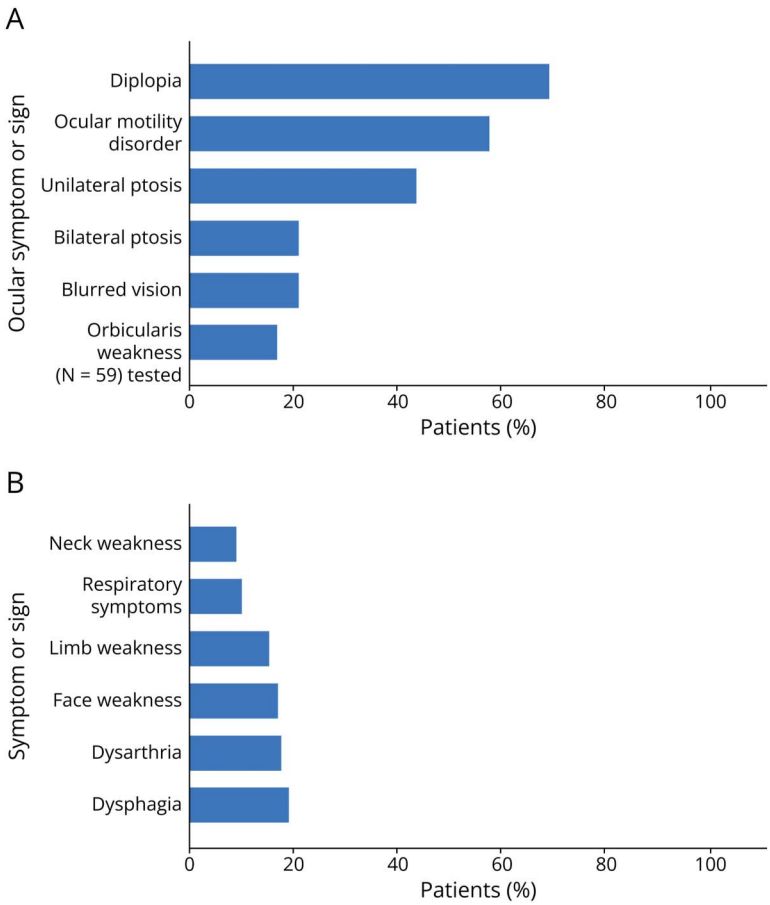
Patients were being treated with various medications at presentation. Of relevance, 4 patients were on monoclonal antibodies (ustekinumab, tocilizumab, adalimumab, and nivolumab) for either autoimmune disease or malignancy, which were ceased either immediately before or after MG diagnosis, 5 patients were on long-term low-dose prednisolone (≤5 mg) for other autoimmune conditions, 2 patients were on long-term methotrexate, and 32 patients were on lipid-lowering therapy. One patient was on long-term nucleoside reverse transcriptase inhibitor for human immunodeficiency virus. Six patients were on thyroxine replacement for hypothyroidism.

Clinical Presentation of Patients With MG

Clinical characteristics of patients with MG at initial presentation are summarized in Table 2, and the frequency of ocular and extraocular symptoms and signs are depicted in Figure 2. Most patients presented with pure ocular symptoms, with two-thirds of these patients being older than 50 years. 62% of ocular patients generalized within 2 years with a median duration of 6 (12.2) months. At initial presentation, the generalized patients (30%) were identified as having bulbar, respiratory, or generalized weakness, with or without ocular complaints. These patients were more frequently women (66%) older than 50 years. Potential precipitants of MG were only identified in one-third of patients, the most common being undergoing major surgery and prior infections. Immunotherapies were the likely precipitant in 4 patients.

The main differential diagnoses for ocular complaints on initial presentation were cranial nerve palsies (28%), upper motor neuron causes such as stroke or demyelination (25%),

Figure 2 Symptom and Signs in Patients With Myasthenia Gravis (MG) at Initial Presentation



(A) Frequency of ocular symptoms and signs in patients with MG on initial presentation. (B) Frequency of bulbar, respiratory, and peripheral symptoms and signs in patients with MG on initial presentation.

thyroid eye disease (12%), mitochondrial etiology (10%), malignancy (3%), or ophthalmic disease (1%). Female patients were more often believed to have an upper motor neuron cause than male patients (30% vs 19%). Those with purely extraocular complaints were often believed to have gastrointestinal or cardiorespiratory disease.

Time to Diagnosis of Myasthenia Gravis

The median time from symptom onset to a definitive diagnosis of MG was 102 (345) days. Female patients took longer than male patients to be diagnosed overall (median 145 [418] days vs 54 [279] days, $p = 0.013$). 90% of patients were diagnosed within 1 year; 38% of these were diagnosed within 1 month. The remaining 10% of patients were diagnosed more than 1 year after symptom onset; 6 were diagnosed after 3 years, and one was diagnosed after 10 years. The confirmed diagnosis was most frequently made in an outpatient setting (66%), with 93% of these diagnosed by neurology/neuro-ophthalmology, 5% by ophthalmology, and 2% by general medicine.

There are several time points that may be prolonged during the diagnostic journey of MG. Factors prolonging these individual time points are explored in the following sections.

Factors Affecting Time to Presentation From Symptom Onset to a Health Service

The time point contributing most to a longer time to diagnosis was between patient symptom onset and initial presentation to health service (median 17 [141] days). Most patients saw their primary physician (54%), emergency department (25%), or optometrist (16%) at the onset. Seven patients were already seeing an ophthalmologist or other specialist for other reasons at the onset of symptoms. Patients who were not working at time of symptom onset (retirees, stay-at-home carers, and unemployed) presented later than those who were working (median 59 [124] days vs 10 [220] days, $p = 0.015$). Female patients also took longer to present (median 31 [151] days) than male patients (median 14 [84] days). Age, comorbidities, classification of MG, and severity of MG at onset did not affect time to presentation.

Factors Influencing Time to Neurologist Referral From the First Presentation to a Health Service

The median time taken to refer to a neurologist from initial presentation to a health service was 2 (34) days across inpatient and outpatient settings. However, patients presenting to an outpatient service were referred to a neurology service later (median 11 [48] days) than those presenting to the ED

(median 0 [9] days). Most patients were initially referred to ophthalmology (39%), neurology (29%), and neuro-ophthalmology (16%). Three patients were referred to ear, nose, and throat (ENT) surgeons; 8 to other specialists; and 6 were not referred on. Patients referred to ophthalmology after their first presentation had a longer delay in subsequent referral to neurology for a second opinion compared with those who were not referred to ophthalmology first (median 26 [106] days vs 0 [11] days), $p < 0.001$).

A longer time to referral occurred if patients had diplopia compared with those without diplopia (median 15 [52] days vs 0 [7] days, $p = 0.022$) or respiratory symptoms compared with those without respiratory symptoms (median 14 [60] days vs 0 [33] days, $p = 0.026$). Sex, working status, and other factors did not influence time to neurologist referral.

Factors That Prolong the Time Taken for Neurologist Review From Initial Referral

The median time for a neurologist review after a referral was made was 2 (20) days, combining inpatient and outpatient review times. Separating the 2 groups, the review was slower for outpatients than inpatients (median 11.4 [27] days vs 0 [1] days, $p < 0.001$). A review was also slower for patients with ocular myasthenia than generalized patients (median 5 [25] days vs 1 [13] days, $p = 0.035$). Neurologist review was fastest if the referral came from ED instead of another health service (median 0 [1] day vs 5 [23] days, $p < 0.001$). MG was usually suspected, and diagnostic tests were ordered on the same day as the review. MG was also suspected faster in patients with bilateral ptosis than those with unilateral or no ptosis ($p = 0.027$). Those who received an icepack test had a shorter time to MG diagnosis than those who did not (median 59 [111] days vs 89 [405] days).

Factors That Increase the Time Taken for Results to Return and to Be Reviewed

Anti-AChR antibody (Ab) median result time from ordering was 11 (12) days compared with anti-MuSK Ab which took a median of 28 (24) days. Electrophysiology tests could take up to 3 days to order. The median time taken to perform electrophysiology was longer for outpatients than inpatients (median 21 [35] days vs 2 [8] days, $p < 0.001$). The results of electrophysiology were usually available on the same day. Overall, 84% of patients had more than 2 diagnostic tests performed. Table 2 summarizes all test results.

Patients usually performed their serology tests on the same day as the request. For outpatients compared with inpatients, the first diagnostic test to return took longer (median 0 [14] days vs 0 [0] days, $p = 0.001$) and was reviewed later (median 7 [3]days] vs 0 [2] days, $p < 0.001$). No other factors affected result turnaround time and review.

Time to Treatment

The median overall time taken to commencing treatment from review of the first diagnostic test was 6 (43) days. Outpatients were started on treatment later than inpatients (median 17 [52] days vs 0 [3] days, $p < 0.001$). Five patients diagnosed by ophthalmology had a greater time to treatment commencement compared with other clinicians (median 8 [52] days vs 2 [31] days, $p = 0.011$). 74% (81/110) of patients were treated after definitive diagnosis, whereas 24% (26/110) were preemptively treated before diagnosis. Three patients who remained untreated throughout had mild ocular symptoms. Treatments, dosing, reason for cessation, and side effects are available in eTable 1 (links.lww.com/CPJ/A491).

Time to Diagnosis of MG and Clinical Outcomes

There was no association between time to diagnosis and frequency of CSR, PR, and MM at years 2–5 and 10 years after diagnosis. Seven patients were treated as refractory MG within 2 years of diagnosis, and overall mortality was 3.6% (4/110).

The median number of follow-up appointments was 10,[7] and the median number of hospitalizations for MG flares was 1 (2) at 2 years postdiagnosis, with no trends associated with time to diagnosis. There was also no association between time to diagnosis and the prevalence of administration of prednisolone, immunosuppression, IVIg or PLEX, and ICU admissions over the first 5 years and at 10 years after MG diagnosis.

Discussion

Most patients with MG in this study were diagnosed in less than 1 year, with the median time to diagnosis approximately 3.5 months. This is similar to one other Australian study[10] but substantially shorter than other publications which state delays on average >2 years. It is worth noting that these latter studies used mean rather than median which would overestimate diagnosis times with nonparametric data.[11,12] Furthermore, while the median time to diagnosis for this study is within the reported beneficial threshold for better remission outcomes of 1 year,[6] this still constitutes a significant delay, particularly when considering that patients with MG prediagnosis likely have untreated and fluctuating symptoms that can lead to a poorer quality of life from disruption to employment,[13] concurrent generalized fatigue associated with depression,[14] social anxiety, and social isolation.[15] Given that time taken to diagnose is tantamount to time taken to start treatment, it is important to recognize and address factors that contribute to prolonged time to diagnosis.

While this study did not identify a correlation with clinical outcomes (likely limited by study power), it has identified a combination of patient-related factors (sex, working status, MG phenotype) and institutional-related factors (diagnosis location, clinician uncertainty, delayed diagnostic results) that can contribute to the time taken to diagnose MG.

Female patients with MG had a more protracted time to diagnosis compared with male patients. This has also been reported by a Finnish study of 154 patients.[16] This MG cohort demonstrated that female patients also often presented later than male patients. There are no specific reports on factors influencing health-seeking practices of female patients with MG, but it has been reported as being multifactorial in other conditions.[17] This study is limited because of its retrospective nature and lack of marital, financial, and educational status information as potential variables. Severity of MG, working status, ocular, or generalized phenotype did not influence the time taken for female patients to present to a health service. There were no other discrepancies in sex at other time points of MG diagnosis.

Patients in this study who were not working demonstrated a longer time to presentation to an initial health service after symptom onset. Frequencies of sex, functional status score (mRS), and proportion of patients older than 50 years were similar in both groups; thus, these are unlikely to be confounders. This study did not look at potential health care accessibility issues from home such as distance to the health service which may delay health-seeking,[18] but a greater number of people who were not working did not drive which could be a contributing factor to delay in initial presentation because they are unable transport themselves to seek help.

In this cohort, patients with pure ocular symptoms or respiratory symptoms at presentation demonstrated a longer time to diagnosis. Referral to a neurologist or neuro-ophthalmologist was delayed in patients with diplopia, particularly for those who were referred to an ophthalmologist first. Diplopia can occur from multiple pathologies and can be difficult to diagnose.[19] As a result, patients with MG with ocular symptoms often see multiple clinicians before their final diagnosis. Patients with MG presenting with respiratory symptoms alone also experienced a delay in referral to a neurologist. This may be due to the subacute and variable nature of respiratory symptoms in MG[20] and concurrent disease such as asthma,[21] which could confuse the overall presentation.

In regard to diagnosis location, two-thirds of patients in this cohort were diagnosed in the outpatient setting. The median time to be seen by a neurologist as an outpatient was longer than an inpatient but was much shorter at 11 days compared with the national median across all specialties of 5.9 months.[22] However, it is noted that neurology review in this cohort could be delayed up to 10.2 months and more delayed if the referral came from a GP or ophthalmologist. It also took longer for results to be reviewed as an outpatient and for treatment to commence. The delay associated with outpatient management has been found in other diseases and is usually multifactorial, involving patient factors and institutional factors.[23,24] Delayed appointment bookings are not uncommon, particularly in overstrained public hospitals. One can only speculate that this may be due to lost communication, strict triaging criteria, or long waiting lists. This study did not explore patient nonattendance and rebooking requests, which could contribute to long initial and review neurology appointment wait times.

Clinician diagnostic uncertainty can be an important component of diagnostic delay. In this study, a longer time to neurology referral occurred if a patient presented to a GP or optometrist first or if they were subsequently referred to an ophthalmologist rather than a neurologist. MG often mimics other muscular, ocular, and neurologic disorders,[25] which can delay diagnosis for even the most experienced clinician.

A study of 583 physician-reported errors identified using the Diagnostic Error Evaluation and Research taxonomy tool[26] found that errors in clinical assessment involved failure or delay in recognizing the diagnosis (the most frequent), failure in recognizing urgency or complications, or failure/delay in ordering appropriate tests. MG is a rare disease, and although briefly explored in medical school, not all specialists have the ongoing exposure and experience to diagnose and manage these patients. There is abundant information about MG available, but no easily accessible framework to assist non-neurology clinicians in the early recognition and investigation of possible MG patients in clinical practice, especially those presenting with ocular, bulbar, and respiratory complaints.

Suspecting and ordering diagnostic tests for MG was generally fast once seen by a neurologist. Although, it seems from this study that clinicians (including neurologists) are not using bedside tests frequently. Clinicians only tested 56% of ptotic patients with the ice test, and only 21% of ptotic patients were tested for Cogan lid twitch. Both these bedside tests have been found to be reliable signs of MG.[27,28] Some patients had undergone eyelid surgery before diagnosis of MG with no improvement. Current paraclinical diagnostic tests are not 100% sensitive for ocular MG,[29] and there is a need for more sensitive diagnostic tests[30]; thus, bedside tests are a useful adjunct until these are found and may prevent patients undergoing unnecessary procedures. Similarly, patients with bulbar symptoms in this study were often seen by gastroenterologists and ENT surgeons and underwent scopes and imaging with contrast before diagnosis. Suspecting MG earlier may prevent the need for invasive tests and allow an earlier trial of treatment.

A delay in diagnostic results and result review time may contribute to greater MG diagnostic time. This study explored the result turnaround time of both serology (Anti-AChR Ab and anti-MuSK Ab) and electrophysiology (SFEMG and RNS). There is a median 2-week result return time for anti-AChR Ab and median 1-month wait time for anti-MuSK Ab, with no difference between outpatient or inpatient status services. Anti-AChR Ab is processed in the same external laboratory for all hospitals in this study, and the delay is likely related to limited fortnightly laboratory availability for running the assay.[31] Anti-MuSK Ab takes much longer because it has to be transported interstate for processing, although the laboratory also has

fortnightly availability. These result return times are fixed for patients and would be difficult to improve unless there is significant infrastructure change. However, it must be noted that these time frames here apply for Australia only and may vary between countries.

Electrophysiology was performed faster as inpatients rather than outpatients likely because of prioritization for inpatients. There were only 6 neurologists who have the highly specialized training to perform SFEMG in this study. Electrophysiology is a scarce resource.

The results were also reviewed faster in the inpatient setting likely because of easier accessibility. In the outpatient setting, there is no specific alert system for the return of results, and clinicians often have to book a follow-up appointment with the patient around the estimated time at which they believe results will return; however, this may be delayed by patient or clinic factors. This may hinder formal diagnosis and commencement of treatment resulting in prolonged symptoms and ongoing impact on quality of life.

Addressing patient and institutional factors identified in this study is important to optimize the diagnosis of MG and prevent further morbidity. This study revealed that a delayed presentation to an initial health service occurred more in female patients and those who were not working. Further psychosocial studies of patients with MG who are female patients and those who are not working with MG will need to be performed in future to determine what factors contribute to a more delayed time to present. Increasing public health awareness campaigns about MG may educate more patients about different phenotypes of MG and when to seek help. However, this may be logistically difficult because funding is a limiting factor and usually more common, preventable diseases take precedence.

With regard to clinician factors, ongoing MG education in the workplace is important to reduce diagnostic errors and serve as a reminder about current clinical and paraclinical tests used in MG diagnosis. The provision of an easily accessible and actionable protocol for a clinical diagnosis of possible MG in the outpatient setting may be useful to suspect MG in patients with mild ocular signs. Initial investigations can be sent before a neurology appointment, reducing the delay in diagnosis overall. Ocular myasthenia still poses a diagnostic dilemma, and current diagnostic tests are not sensitive or have scarce availability because of highly specialized skill set. Adjunctive tests using orthoptic measurements,[32] oculography, and pupillometry[30] have been previously explored but not yet powered enough to assist in the diagnosis of patients with MG. There is an ongoing need for further studies in this area to be performed.

To address institutional factors, a separate evaluation of neurologist appointment bookings, including method of receipt and processing time of referrals, triaging criteria, and clinic availabilities, is required to pinpoint specific areas of improvement, particularly in the outpatient setting. This would need to be conducted on an individual hospital basis. An alert system for results would also be useful to reduce long review waiting times.

Myasthenia gravis is a condition with phenotypic variability, posing a diagnostic challenge to many clinicians worldwide. This study is the first to explore specific factors leading to a more prolonged time to diagnosis in MG; however, it is based on an Australian cohort and may not be generalizable. Several patient, clinician, and institutional factors all contribute to the time to MG diagnosis. Reducing the time to MG diagnosis will likely improve physical and psychosocial morbidity and overall quality of life by reducing the duration of uncertainty and also duration to appropriate treatment. Improved patient and clinician education remains a key player in reducing time to diagnosis. More resources and cost analysis studies are required for improved laboratory result times, and institutional clinic flow studies are needed to improve appointment waiting periods.

Study Funding

Graduate research scholarship from Monash University and a Women in Neurology fellowship grant.

Disclosure

M. Nguyen is supported by a Monash University Graduate Scholarship from Monash University and Women in Neurology Fellowship grant. B. Cruse has no disclosures relevant to this manuscript but has received speaker honoraria from CSL Behring and Allergan Australia. A. van der Walt has no disclosures relevant to this manuscript but has served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche. She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia. J. Fielding receives funding from Genzyme and Biogen and has received honorarium from Novartis. M. Clough and O. White report no disclosures relevant to this manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology: Clinical Practice* March 27, 2023. Accepted in final form December 5, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Belinda Savage-Edwards, MD, FAAN.

Appendix Authors

Name	Location	Contribution
Minh Nguyen, FRACP, MBBS, BBSci	Department of Neuroscience, Monash Health; Department of Neurology, Alfred Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Meaghan Clough, PhD, PGDip, BA	Department of Neuroscience, Monash Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Belinda Cruse, FRACP, MBBS, BSc	Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Anneke van der Walt, FRACP, AFRACMA, PhD, MBChB	Department of Neuroscience, Monash Health; Department of Neurology, Alfred Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Joanne Fielding, PhD, BSc (Hons), BA	Department of Neuroscience, Monash Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content
Owen B. White, FRACP, PhD, MD, MSc, MBBS	Department of Neuroscience, Monash Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content

References

1. Salari N, Fatahi B, Bartina Y, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. *J Transl Med.* 2021;19(1):516. doi:10.1186/s12967-021-03185-7
2. Mantegazza R, Baggi F, Antozzi C, et al. Myasthenia gravis (MG): epidemiological data and prognostic factors. *Ann N Y Acad Sci.* 2003;998:413-423. doi:10.1196/annals.1254.054
3. Serra A, Ruff RL, Leigh RJ. Neuromuscular transmission failure in myasthenia gravis: decrement of safety factor and susceptibility of extraocular muscles. *Ann N Y Acad Sci.* 2012;1275(1):129-135. doi:10.1111/j.1749-6632.2012.06841.x
4. Jeong A, Min JH, Kang YK, et al. Factors associated with quality of life of people with myasthenia gravis. *PLoS One.* 2018;13(11):e0206754. doi:10.1371/journal.pone.0206754
5. Beekman R, Kuks JBM, Oosterhuis HJGH. Myasthenia gravis: diagnosis and follow-up of 100 consecutive patients. *J Neurol.* 1997;244(2):112-118. doi:10.1007/s004150050059
6. Mao ZF, Mo XA, Qin C, Lai YR, Olde Hartman TC. Course and prognosis of myasthenia gravis: a systematic review. *Eur J Neurol.* 2010;17(7):913-921. doi:10.1111/j.1468-1331.2010.03017.x
7. Li M, Ge F, Guo R, et al. Do early prednisolone and other immunosuppressant therapies prevent generalization in ocular myasthenia gravis in Western populations: a systematic review and meta-analysis. *Ther Adv Neurol Disord.* 2019;12:1756286419876521. doi:10.1177/1756286419876521
8. Landfeldt E, Pogoryelova O, Sejersen T, Zethraeus N, Breiner A, Lochmüller H. Economic costs of myasthenia gravis: a systematic review. *Pharmacoeconomics* 2020;38(7):715-728. doi:10.1007/s40273-020-00912-8
9. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology.* 2000;55(1):16-23. doi:10.1212/wnl.55.1.16
10. Li V, Jasinarachchi M, Butler E. Epidemiology, symptomatology and treatment of patients with myasthenia gravis in an Australian hospital. *Intern Med J.* 2019;49(12):1537-1540. doi:10.1111/imj.14662
11. Lehnerer S, Jacobi J, Schilling R, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. *J Neurol.* 2022;269(6):3050-3063. doi:10.1007/s00415-021-10891-1
12. Cosi V, Romani A, Lombardi M, et al. Prognosis of myasthenia gravis: a retrospective study of 380 patients. *J Neurol.* 1997;244(9):548-555. doi:10.1007/s004150050142
13. Alekseeva TM, Gavrilov YV, Kreis OA, Valko PO, Weber KP, Valko Y. Fatigue in patients with myasthenia gravis. *J Neurol.* 2018;265(10):2312-2321. doi:10.1007/s00415-018-8995-4
14. Blum S, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci.* 2015;22(7):1164-1169. doi:10.1016/j.jocn.2015.01.022
15. Richards HS, Jenkinson E, Rumsey N, Harrad RA. The psychosocial impact of ptosis as a symptom of Myasthenia Gravis: a qualitative study. *Orbit* 2014;33(4):263-269. doi:10.3109/01676830.2014.904375
16. Myllenen C, Tuulasvaara A, Atula S, Laakso S. Effect of gender on symptoms at onset, diagnostic delay and response to thymectomy in patients with myasthenia gravis. [Presentation]. In press; 2022.
17. Saunders-Pullman R, Wang C, Stanley K, Bressman SB. Diagnosis and referral delay in women with Parkinson's disease. *Gend Med.* 2011;8(3):209-217. doi:10.1016/j.genm.2011.05.002
18. Farquharson RM, Fairley CK, Abraham E, et al. Time to healthcare seeking following the onset of symptoms among men and women attending a sexual health clinic in Melbourne, Australia. *Front Med (Lausanne).* 2022;9:915399. doi:10.3389/fmed.2022.915399
19. Danchaivijitr C, Kennard C. Diplopia and eye movement disorders. *J Neurol Neurosurg Psychiatry.* 2004;75(suppl 4):iv24-31. doi:10.1136/jnnp.2004.053413
20. Pfeffer G, Povitz M. Respiratory management of patients with neuromuscular disease: current perspectives. *Degener Neurol Neuromuscul Dis.* 2016;6:111-118. doi:10.2147/DNND.S87323
21. Santy L, Janssens W, Buyse B. A late diagnosis of myasthenia gravis at the respiratory practice: back to basics. *Breathe (Sheff).* 2022;18(2):210167. doi:10.1183/20734735.0167-2021
22. McIntyre D, Chow CK. Waiting time as an indicator for health services under strain: a narrative review. *Inquiry.* 2020;57:46958020910305. doi:10.1177/0046958020910305
23. Bosch X, Sanclemente-Ansó C, Escoda O, et al. Time to diagnosis and associated costs of an outpatient vs inpatient setting in the diagnosis of lymphoma: a retrospective study of a large cohort of major lymphoma subtypes in Spain. *BMC Cancer.* 2018;18(1):276. doi:10.1186/s12885-018-4187-y
24. Sandhu AT, Tisdale RL, Rodriguez F, et al. Disparity in the setting of incident heart failure diagnosis. *Circ Heart Fail.* 2021;14(8):e008538. doi:10.1161/CIRCHEARTFAILURE.121.008538
25. Engstrom JW. Myasthenia gravis: diagnostic mimics. *Semin Neurol.* 2004;24(2):141-147. doi:10.1055/s-2004-830903
26. Schiff GD, Seijeong K, Abrams R, et al. Diagnostic error in medicine: analysis of 583 physician-reported errors. *Arch Intern Med.* 2009;169(20):1881-1887. doi:10.1001/archinternmed.2009.333
27. Fakiri O, Tavy DLJ, Hama-Amin AD, Wirtz PW. Accuracy of the ice test in the diagnosis of myasthenia gravis in patients with ptosis. *Muscle Nerve.* 2013;48(6):902-904. doi:10.1002/mus.23857
28. Cogan DG. Myasthenia gravis a review of the disease and a description of lid twitch as a characteristic sign. *Arch Ophthalmol.* 1965;74(2):217-221. doi:10.1001/archopht.1965.00970040219016
29. Al-Haider M, Benatar M, Kaminski HJ. Ocular myasthenia. *Curr Clin Neurol.* 2018;26:241-251.
30. Nguyen M, van der Walt A, Fielding J, Clough M, White O. Tracking eye movements for diagnosis in myasthenia gravis: a comprehensive review. *J Neuroophthalmol.* 2022;42(4):428-441. doi:10.1097/WNO.0000000000001668
31. *Acetyl Choline Receptor Ab [Web Page].* The Royal Melbourne Hospital; 2023. thermh.org.au/health-professionals/pathology-handbook/acetyl-choline-receptor-ab
32. Keene KR, de Nie JM, Brink MJ, et al. Diagnosing myasthenia gravis using orthoptic measurements: assessing extraocular muscle fatiguability. *J Neurol Neurosurg Psychiatry.* 2023;94(2):151. doi:10.1136/jnnp-2022-329859

How to cite this article: Nguyen M, Clough M, Cruse B, van der Walt A, Fielding J, White OB. Exploring factors that prolong the diagnosis of myasthenia gravis. *Neurol Clin Pract.* 2024;14(1):e200244. doi: 10.1212/CPJ.0000000000200244.