

BMJ Open Clinical characteristics of ocular myasthenia gravis and outcomes of secondary generalisation: a systematic review protocol

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ABSTRACT

Objective We aim to systematically assess the clinical characteristics of ocular myasthenia gravis (OMG) and report on the proportion of patients who develop secondary generalised myasthenia gravis (SGMG).

Introduction OMG is an autoimmune neuromuscular junction disorder resulting in ptosis and diplopia. A proportion of patients with OMG develop weakness in their limbs, respiratory or bulbar muscles, that is, convert to SGMG. The proportion of patients converting to SGMG reported in the literature have been varied. We therefore aim to systematically assess the clinical characteristics of OMG and outcomes of SGMG reported in the literature to date.

Inclusion criteria Studies describing a population of adults with OMG, that is, MG with ocular symptoms and signs only, seen consecutively through a clinical service, reporting on patient characteristics and the outcome of SGMG. Studies on paediatric and congenital myasthenia gravis will be excluded.

Methods We will conduct an electronic database search for randomised controlled trials, prospective non-randomised studies, observational studies and retrospective studies in MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Web of Science. Exploratory database search was conducted on 1 December 2021. Eligibility criteria will include quantitative and qualitative articles written in any language and containing data on OMG. Additional studies will be identified by reviewing bibliographies of retrieved articles. Two independent reviewers will screen titles and abstracts and extract data from full texts, reporting outcomes according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Data extraction of key characteristics will be completed using customised forms. Methodological quality will be assessed using the Joanna Briggs Institute critical appraisal forms.

Ethics and dissemination Ethical approval is not required for this review, as it will only include published data. Findings will be published in a peer-reviewed journal and disseminated across ophthalmic networks.

PROSPERO registration number CRD42021285257.

INTRODUCTION

Ocular myasthenia gravis (OMG) is an autoimmune neuromuscular junction disorder

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols.
- ⇒ The review will comprehensively assess all relevant studies on ocular myasthenia gravis identified by the literature search.
- ⇒ A potential limitation might be the paucity of high-quality trials.
- ⇒ Due to the expected heterogeneity in study methods, it is unlikely that a meta-analysis will be possible.

resulting in ptosis and diplopia. A proportion of patients with OMG develop weakness in their limbs, respiratory or bulbar muscles, that is, convert to secondary generalised myasthenia gravis (SGMG).¹ The outcomes reported in the literature have been varied, with the proportion of people with OMG converting to SGMG ranging between 30% and 80%, usually within the first 2 years of symptom onset.²

Approximately 50% of people with OMG have antibodies against the neuromuscular junction receptors, predominantly against the acetylcholine receptors (AChR), and a smaller proportion against the muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4.¹ Treatment options include symptomatic measures, with pyridostigmine, ptosis props or eye patches; or immunosuppression with corticosteroids and/or other immunosuppressive medications.

The thymus gland is implicated in the autoimmune pathogenesis of myasthenia gravis.³ The Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX) trial, a randomised control trial of thymic surgery in people with non-thymomatous generalised myasthenia gravis showed improved clinical outcomes over a 3-year period in those who receive thymic surgery, requiring less immunosuppression

with azathioprine or hospitalisation for exacerbations.⁴ However, the MGTX trial excluded people with OMG. Some centres offer thymic surgery for OMG, but the role of thymic surgery for non-thymomatous OMG is not clear.¹ There is also controversy about whether early treatment with immunosuppression or thymic surgery can alter the risk of SGMG.¹

In recent years, an increasing number of papers have been published on the outcome of SGMG in patients who present with OMG.^{5–7} Additionally, a new gold standard has been set for reporting on predictive outcomes, that is, the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD).⁸ It is therefore timely now for a systematic review in this area. A better understanding is important to guide the development of future clinical trials in OMG.⁹ We aim to systematically assess the clinical characteristics of OMG and outcomes of SGMG reported in the literature to date.

REVIEW QUESTION

We aim to systematically assess the clinical characteristics of patients with OMG and report on the proportion of patients who develop SGMG. OMG is defined as MG limited to ocular symptoms and signs only. Generalised myasthenia gravis is defined as MG causing weakness of limbs, bulbar or respiratory muscles.

INCLUSION CRITERIA

Participants

This review will consider studies on adults with OMG, reported consecutively through a clinical setting or through a population-based study. OMG is defined by MG causing only ocular symptoms of ptosis or diplopia.¹⁰ We will exclude studies that select patients based on interventions only (eg, a retrospective series of all patients who had thymectomy). There are no restrictions on geographical location, setting or demographic factors. Studies reporting on paediatric and congenital myasthenia gravis will be excluded.

In line with the recommendations for systematic reviews reporting on prevalence and incidence by Munn *et al*,¹¹ inclusion criteria are set as follows;

Condition: OMG.

Context: data from clinical setting or population registries.

Population: adults with myasthenia gravis of ocular symptoms and signs only at onset.

OUTCOMES

This review will consider studies that include the following outcomes:

Primary outcome

Proportion of patients with OMG who convert to SGMG. SGMG is defined as the development of neuromuscular

weakness that may involve limb, bulbar or respiratory muscles after initial onset with ocular symptoms only.¹²

Clinical characteristics

- ▶ Patient demographics: age, sex and ethnicity.
- ▶ Antibody status (AChR, MuSK or low-density lipoprotein-related receptor 4 antibodies), seronegative status.
- ▶ Thymic abnormality (thymus imaging).
- ▶ Electrophysiology tests including repetitive nerve stimulation and single-fibre electromyography.

Secondary outcomes

- ▶ Time from onset of OMG to secondary generalisation.
- ▶ Immunosuppression or thymic surgery for OMG.
- ▶ Where relevant, if the study fulfilled the TRIPOD criteria.

TYPES OF STUDIES

As randomised controlled trials (RCTs) with OMG are limited in the literature, we will evaluate the studies from a wide range of studies to have a complete overview and maintain generalisability without loss of validity. These include RCTs, prospective non-randomised studies, observational studies and retrospective studies. We will exclude case reports or small case series of less than 10 patients. We will include studies in all languages. We will only include full papers, that is, excluding conference abstracts.

METHODS AND ANALYSIS

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness evidence.^{11 13} The study start date is December 2021 and the anticipated end date is June 2022.

SEARCH STRATEGY

We will conduct a systematic electronic database search for RCTs, prospective non-randomised studies, observational studies and retrospective studies in MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Web of Science. The full search strategy with the keywords and index terms will be run on MEDLINE and Embase (see online supplemental appendix 1, searched in December 2021). The reference list of all studies selected will be screened for additional studies.

STUDY SELECTION

Following the search, all identified citations will be collated and uploaded into a reference management software (EndNote V.X9, Clarivate Analytics) and duplicates will be removed. Two review authors will independently screen search results by title, abstract and then by full text, against the eligibility criteria, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁴ Discrepancies between authors as

to whether studies meet inclusion criteria will be resolved by discussion. We will document the excluded studies and reasons for exclusion, and this will be presented in a PRISMA flow diagram.¹⁴

ASSESSMENT OF METHODOLOGICAL QUALITY

Eligible studies will be critically appraised by two independent reviewers at the study level using standardised critical appraisal instruments from the JBI.^{13 15 16} Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Two review authors will assess independently the risk of bias. Critical appraisal of study methodological rigour will be performed based on critical appraisal tools, depending on the experimental design of the study being assessed^{13 15 17} (eg, Cochrane risk of bias tool, Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) and Ottawa Newcastle scale). Any disagreements that arise between the reviewers will be resolved through discussion.

DATA EXTRACTION

Data will be extracted from included studies by two independent reviewers aligned to the standardised data extraction tool recommended by JBI.^{13 15 16} Variables to be extracted include

- ▶ Study characteristics such as country of origin, year of publication and sample size.
- ▶ Trial design.
- ▶ Participant characteristics such as age, sex and ethnicity.
- ▶ Number of patients withdrawn from study.
- ▶ Proportion of patients with OMG who convert to SGMG.
- ▶ Duration of follow-up.
- ▶ Time from onset of OMG to secondary generalisation
- ▶ Immunosuppression or thymic surgery for OMG.

To minimise errors, a data extraction form has been developed for specifically this review (see online supplemental appendix 2) Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of studies will be contacted to request additional or missing data, where required.

DATA SYNTHESIS

Studies where possible will be pooled for statistical meta-analysis. Statistical analyses will be performed using Stata V.17. Metaprop command in Stata V.17 will be used to pool the proportion of patients with secondary generalisation. Ninety-five percent CIs will be computed, and Freeman-Turkey double arcsine will be used transformation of proportions. If possible, effect sizes will be

expressed as either ORs or risk ratios and their 95% CIs will be calculated for analysis. Heterogeneity will be assessed statistically using the standard χ^2 and I^2 tests. If there is significant heterogeneity of the studies, we will categorise similar studies together and use best evidence synthesis for summarising the results. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures for data presentation, where appropriate. Where possible we will report the subgroup characteristics of those who develop SGMG and those who remained ocular, and subgroup characteristics of those who received immunosuppressive treatment or thymic surgery and those who did not.

ASSESSING CERTAINTY IN THE FINDINGS

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)¹⁸ approach for grading the certainty of evidence will be followed and a summary of findings (SoF)¹⁹ will be created using GRADEpro software (McMaster University, Ontario, Canada). We will grade the quality of evidence for each outcome by considering study limitations, indirectness, inconsistency, imprecision of effect estimates and risk of reporting bias. According to the software GRADEpro, we will assign four levels of quality of evidence: high, moderate, low and very low.

The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be presented in a tabular form.

PATIENT AND PUBLIC INVOLVEMENT

No patients were involved in this paper. The importance of putting this together was germinated from recurrent discussions with patients in clinic asking about the projected outcome of their condition.

STRENGTHS AND LIMITATIONS

The strength of this proposed work is a systematic review of the clinical characteristics and outcomes of published work on OMG, in a comprehensive inclusive way, representing the global experience. We anticipate this work to deepen our understanding of the condition, guiding next steps in research strategies. We anticipate this work to demonstrate the value and need for a global collaborative strategy among researchers for the benefit of our patients with OMG. A potential limitation of this work is the quality of research available to retrieve data for systematic analysis. We are also unable to assess the severity of OMG as there has not been any rating scales for OMG until recently.²⁰ Further strengths and limitations of this work

will become more apparent following data collection and analysis.

ETHICS AND DISSEMINATION

Ethics approval is not required for this review, as it will only include published data. Findings will be published in a peer-reviewed journal and disseminated across ophthalmic networks. We expect that the results of this review will be of interest to numerous stakeholders: clinicians in neurology, ophthalmology, neuro-ophthalmology, neuromuscular diseases and people with myasthenia gravis. It will also inform researchers to where there are gaps in evidence and identify areas for future research.

Contributors CEHF, DB and SHW contributed to the conception and design of the work and the acquisition of data, drafted the work and revised it critically for important intellectual content and had the final approval of the version to be published.

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Patient consent for publication Not applicable.

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