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Epidemiology, management and patient needs in myasthenia gravis: an Italian multistakeholder consensus based on Delphi methodology

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ABSTRACT

Objectives To provide comprehensive information on the burden of myasthenia gravis (MG) in Italy, including the unmet needs of patients and several other aspects related to the disease, based on skilled viewpoints of MG experts.

Design Iterative analysis conducted in accordance with the best practices of the Delphi method, including anonymity, controlled feedback, and statistical stability of consensus.

Setting and participants 24 clinicians, 18 public health experts and 4 patient associations experts completed all the Delphi iterations between 18 April and 3 July 2023, for a total of 46 participants from several Italian Regions.

Outcome measures Five areas of investigation related to MG were examined: epidemiology in Italy and characteristics of disease; diagnostic issues and Italian patient journey; unmet needs during the acute and chronic phases of MG; quality of life; public health management of MG. Consensus in the Delphi iterations was defined by both the percentage level of agreement between panellists or the median value of the responses.

Results We reported a high level of agreement (ie, >66.7% of panellists) on the prevalence and incidence of disease in Italy and on several management issues. A strong impact of MG on the quality of life of patients also emerged. Cross-agreement was achieved among different subgroups of panellists (ie, clinicians, public health experts and patient associations representatives) for most items proposed.

Conclusions This study provided guidance for educational and practical aspects of MG in Italy, highlighted disease severity and its role on patients' quality of life. A few gaps related to the handling of MG in Italy also emerged.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The analysis was conducted in accordance with the best practices for Delphi studies (including anonymity, iteration, controlled feedback and statistical stability of consensus).
⇒ The Delphi panel was particularly large and different expert groups were represented (28 clinicians, 21 public health experts and 4 representatives of myasthenia gravis patient associations in the first round).
⇒ Participation was satisfactory (more than 85% of the experts involved in the first round completed the Delphi iterations).
⇒ This study was conducted through a Delphi methodology and thus relies on expert opinions rather than on evidence-based data.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder targeting the neuromuscular junction. While generally presenting with a common symptom, that is, fatigable muscle weakness, the disease is particularly heterogeneous across patients in terms of age at presentation, serology and clinical characteristics and patterns over time.[1]

Several studies reported recent changes in the epidemiology of MG, with a trend towards an increase in prevalence.[2–4] This was explained through improvements in disease diagnosis, treatment and survival and according to the ageing populations.[3] It is not clear whether the total incidence of MG is increasing, too.[5] Varying patterns of age at diagnosis have been reported, with an increase in the occurrence of late-onset (ie, after 50 years) cases,[6] and a distinct pattern between men and women, with the latter experiencing more frequently an early disease onset.[7] Overall, epidemiological data are heterogeneous across studies and geographical areas, even within single countries, in the absence of obvious explanations and after considering the role of different methods of investigation.[4] In Italy, prevalence and incidence of MG varied widely, ranging respectively from 4 to 65 cases per 100 000 and from 0.2 to 4.6 cases per 100 000 person-years across different studies.[8–12] One study from northeastern Italy reported increasing

prevalence and incidence of MG over time, particularly in elderly men.[3] For these reasons, it is hard to understand the current burden of disease.

MG severity is variable and difficult to predict. Patients subject to potentially life-threatening myasthenic crises are a minority, but many others—particularly those refractory to treatment—are highly affected in their quality of life, being often afflicted by fatigue and fatigability.[1 13 14] These patients experience a high burden of disease and present major unmet needs.

Disease control has improved much in the last decades through the availability of new treatments, but full and stable remission remains infrequent.[5] Similarly, clinical management of MG took advantage from the publication of international consensus guidelines of experts.[15 16] In Italy, recommendations for the diagnosis and treatment of MG were released in 2019[17] and more recent reports from disease experts are also available,[18 19] but gaps in MG care remain—particularly at a local/regional level—due to the lack of shared documents at a public health level.

Furthermore, the need for consensus on approaches in the diagnostic pathway and the central, but still puzzling, role of quality of life of the patient have been recently highlighted.[20 21] In such a context of limited and inconsistent data, a consensus exercise through the Delphi method can gather the personal expertise of specialists and provide critical information on the disease.[22]

Therefore, with the aim to provide a comprehensive overview of qualitative information on the burden of MG at a national level, considering the unmet needs of patients and several other aspects related to the disease in Italy, based on skilled viewpoints of different professionals, we conducted an online Delphi consensus involving clinical and public health experts and representatives of MG patient associations.

METHODS

We conducted an expert-based online consensus on several topics related to MG. The project started in November 2022, and was led by an expert in Delphi methodology (PM) and a biostatistician (CG). The iterative analysis followed the guidelines for defining consensus in Delphi studies[23] and we reported the process and results of the investigation by following the recent ACcurate COnsensus Reporting Document (ACCORD) guidelines.[22] The ACCORD checklist is reported in the online supplemental table 1. The project was conducted in accordance with the best practices for Delphi studies, including anonymity, iteration, controlled feedback and statistical stability of consensus.[24] The study protocol was not prospectively registered. Figure 1 shows in detail the subsequent phases and the overall process of the project.

Bibliographic review and identification of gaps of knowledge

The first phase of the project involved a bibliographic, critical review of both Italian and international studies of MG. The aim of the review was to identify topics related to the disease that were controversial or had gaps in knowledge, and thus warranted inclusion in the Delphi survey. Three separate search strategies were defined. The first one, on the epidemiology of MG in Italy, was conducted in a systematic manner on 17 November 2022. We explored epidemiological data, with no restrictions according to date nor language, using PubMed/Medline, the Cochrane Library and EMBASE. The inclusion criteria was the presence of quantitative data on incidence and/or prevalence of MG in Italy. The search string used in PubMed/Medline was '(myasthenia gravis OR myasthenia gravis[MeSH Terms]) AND (epidemiol* OR prevalence OR incidence) AND (italy OR italian)'. The same logic combination of terms was applied in the Cochrane Library and EMBASE. The selection process of retrieved studies was conducted

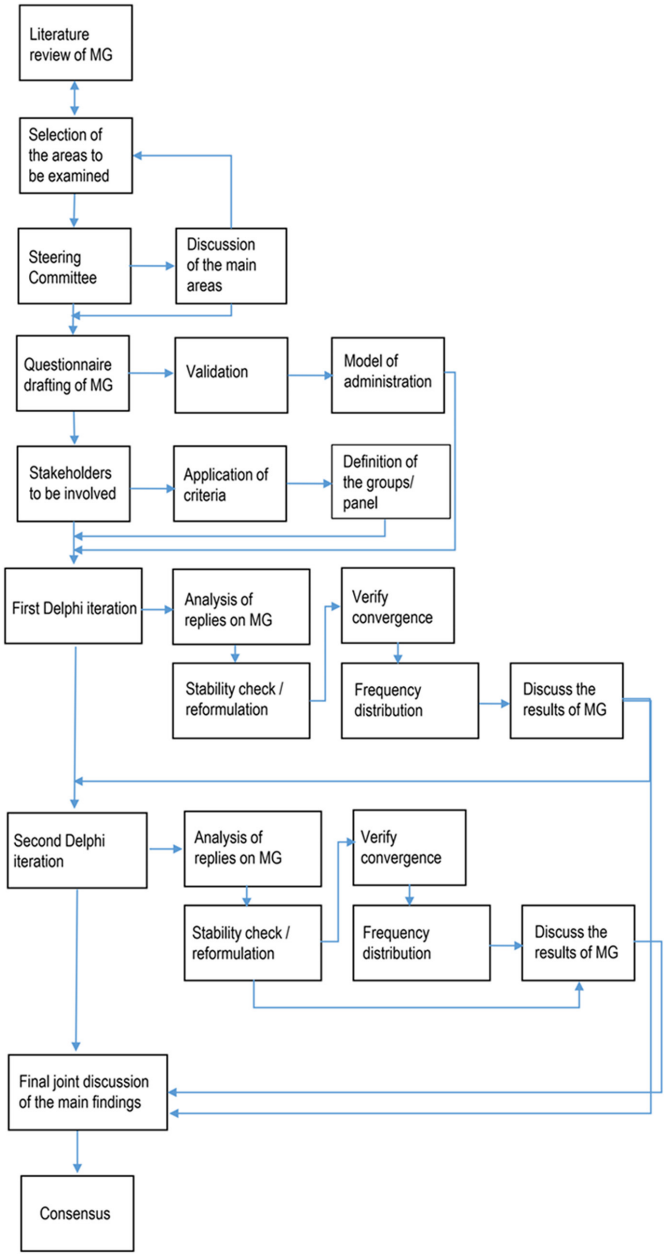

Figure 1 Subsequent phases and overall process of the Delphi consensus project.

independently by two reviewers. A total of 13 full articles and 4 conference abstracts with data on incidence and/or prevalence of MG in Italy were finally identified (full list in the online supplemental table 2). The main findings of these studies were extracted and synthesised in summary tables, that were subsequently presented and discussed with the Steering Committee (as reported below). The second and third search strategies were focused on clinical management and on disease burden (unmet needs, quality of life), respectively, and were not systematic. For the latter searches, the terms used in the search strings included 'myasthenia gravis' combined to specific terms such as, in turn, 'clinical outcomes' or 'patient-reported outcomes', 'unmet needs', 'quality of life', and so on. Potentially relevant national grey literature materials on MG were also searched by exploring the websites of various Italian agencies, institutions and rare diseases, patient and medical associations related to neuromuscular disorders. Following the revision of the available literature, a set of five broad areas of investigation to be included in the Delphi survey were defined: (1) disease epidemiology (focused on Italy) and main characteristics of MG; (2) diagnostic issues and Italian patient journey; (3) unmet needs of patients and caregivers during the acute and chronic phases of MG; (4) quality of life and MG measurement scales/scores; and (5) public health management of MG, plus a few other mixed aspects. Broader areas were investigated among all expert groups (eg, diagnostic delay, quality of life), while specific areas were posed to only one group of experts (eg, epidemiology was asked to clinical experts alone).

Composition of the Steering Committee and definition of the questionnaires

The second phase of the project was focused on the discussion of the specific topics to be considered, with the final aim to prepare (separate) survey questionnaires destined to physicians, healthcare and patient associations experts. We adopted an iterative approach to finalise the research questions. A Steering Committee of the project, which included three clinician experts in MG (FH, RI, RM), two public health managers (GA, GL), one Chair of a European MG Patient Advocacy Committee (EuMGA) (MBU) and two experts of the Delphi method (PM, CG) met on 22 February 2023. During this meeting, the results for each specific topic of the bibliographic review were presented and discussed, and the questionnaires (in Italian language) were assessed. These were partially overlapping across expert groups, with a number of common questions on cross topics, and were designed to achieve a high level of consensus among the expert panellists.[25] They included three to seven items for each predefined area of investigation, generally a mix of open-ended and multiple-choice questions, some of which were statements on specific topics. For the latter, the panellists were asked to indicate their agreement with each statement, using a 4-level Likert scale, that is, 'fully disagree', 'partially disagree', 'partially agree' and 'fully agree'. Then, responses of 'full' or 'partial' agreement, as well as 'full' or 'partial' disagreement, were counted together in the analysis of results, in order to obtain binary responses and evaluate their consensus level. For some questions/statements, a subsequent open-ended field allowed the panellists to provide any comment or explanation of their responses. Validation of the survey questionnaires was performed after qualitative checking and assessment of both its facade and contents.[26] Facade validity was evaluated through a superficial examination of the elements of the questionnaire, to understand whether the tool was applicable to non-experts, too. Contents validity was evaluated through an expert analysis of the elements of the questionnaire, to understand whether the tool was adequately comprehensive for each area of investigation. The questionnaires also included preliminary questions to assess the panellists' expertise and eligibility. In particular, after expert discussion within the Steering Committee, clinicians were required to diagnose and treat at least 20 patients with MG per year to be eligible for the Delphi project. Pilot testing of the questionnaires was performed by a member of the Steering Committee (CG). The final questionnaires were sent to the Steering Committee on 12 April 2023, for a last revision and definitive approval. Members of the Steering Committee did not participate in the voting rounds of the Delphi.

Definition of the panel of experts

A third part of the project was focused on the identification and recruitment of a panel of specialists, including clinicians, public health and patient associations experts. Panellists were mainly selected by the members of the Steering Committee, with no specific rationale on the total number of invitations but taking care to include experts distributed in various areas (northern, central and southern) of the country. Clinicians were neurologists with known expertise in the diagnosis and management of MG, and patient associations experts were members of MG advocacy groups or were involved in patient empowerment activities. On the other hand, public health experts were not required to have specific expertise on MG, but rather were local or regional managers and professionals of Italian hospitals, rare diseases networks, Local Health Units or Regions, with expertise in the public health management of (mainly rare) diseases. Those public health experts with a specific knowledge of MG also answered an additional, MG-oriented, section of the questionnaire.

An initial contact email was sent to all potential Delphi panellists on 13 April 2023, introducing the project and inviting them to participate. A few days later, we sent an email with a link to the questionnaire of the first e-Delphi round, that was active from 18 April 2023 to 3 May 2023, and was conducted through the SurveyMonkey platform.[27] No fees nor reimbursements were given to the panellists for participation, and no information on sociodemographic characteristics of panellists was collected. Out of a total of 101 invited panellists, 53 (52%) met the

required criteria and completed the first Delphi round. Among these were 28 clinicians (out of 38 invited, 74%), 21 public health experts (out of 59 invited, 36%) and 4 representatives of MG patient associations (out of 4 invited, 100%).

Definition of consensus

With reference to the analysis of responses, consensus in the Delphi iterations was defined by both the percentage level of agreement between panellists or the median value of the responses. Responses were examined on aggregate to guarantee anonymity, first overall, and second by subgroup of expert panellists (ie, clinicians, public health specialists, representatives of MG patient associations). The convergence criterium for consensus was prespecified and defined according to the stability of results, to a threshold, equal to two-thirds of the response frequency. For each questionnaire item, the evidence was classified through the following focus level[28]:

Focus level 'A' → Substantial agreement among the respondents (ie, ≥67%); in the subsequent Delphi round, there is no need to reconsider the item.

Focus level 'B' → Moderate-to-high variability in responses; in the subsequent Delphi round, it is required to reconsider the item.

Focus level 'C' → Frequent (ie, >33%) 'I do not know' answers; in the subsequent Delphi round, it is required to reconsider the item.

With reference to focus level 'A', an agreement of 67%–99% of panellists was defined as 'majority' and an agreement of 100% of panellists was defined as 'consensus'. Items with high agreement, that is, that met the prespecified definition of focus Level 'A', were instantaneously accepted and did not need to be included in the subsequent voting round.[29]

Iterations

Aim of the iterations step was to arrive to an agreement between experts on the topics proposed. After the analysis of responses of the first iteration, a second iteration for the representatives of patient associations was not necessary and, therefore, the second Delphi round was restricted to clinicians and public health experts only. This was conducted from 22 June 2023 to 3 July 2023, and was based on the same methods and criteria described above for round 1. Before each question/statement proposed in round 2, quantitative results of round 1 (mostly presented through summary graphs and/or tables) were reported for the corresponding item. A total of 42 (86%) out of 49 clinicians and public health experts involved in the first Delphi iteration completed the second round (24/28 clinicians, 86%, and 18/21 public health experts, 86%). Consistency of answers between the two iterations was generally high, thus indicating satisfactory accuracy in the definition of the statements. Focus level 'A' was achieved for all the questionnaire items of the second round, iterations were therefore stopped and the Delphi was concluded.

Patient and public involvement

No data or information derived from patient experiences were involved, and no sensitive data were collected. In order to inform the participants on the main findings and to have an immediate impact—no matter how limited—on the national public health, a final virtual event was organised on 1 December 2023 to disseminate the results of the Delphi to any interested panellist.

RESULTS

Table 1 reports the key results of the Delphi method on various topics examined. An in-depth description of the main findings of the project is also given below, area-by-area.

Epidemiology and main characteristics of MG

Epidemiology of MG was investigated among clinicians alone. Most of them (25 out of 28, 89%) agreed with two separate statements reporting that in Italy: (1) the current prevalence of MG is between 15 and 35 cases per 100 000 inhabitants; and (2) the current incidence of MG is between 1 and 3 new cases per 100 000 person-years. During the first round, two separate questions were focused on age at diagnosis of MG in males and females. A different distribution of age at diagnosis emerged across gender (figure 2). In the second round, two statements were proposed on the basis of these results and experts concurred that the proportions of diagnoses at age <40, 40–60 and >60 are 10%–20% in young, 25%–40% in middle-aged and 40%–60% in elderly males, respectively, whereas in females they are similar in the three age groups, ranging between about 20% and 40%. A question was focused on mortality: the majority of panellists (21/28, 75%) agreed that myasthenic crises lead to an increased mortality of patients with MG as compared with the general population. The definition of refractory MG was also explored. In the first round, 89% of clinicians evaluated that 'failure to respond adequately to conventional therapies' is an appropriate definition of refractory MG. The corresponding proportions were 68% for 'inability to reduce immunosuppressive therapy without clinical relapse or a need for ongoing rescue therapy', 54% for 'frequent myasthenic crises even while on therapy', and 32% each for 'severe or intolerable adverse effects from immunosuppressive therapy' and 'comorbid conditions that restrict the use of conventional therapies'. In the second round, when we asked to indicate the most appropriate definition of refractory MG, 'failure to respond adequately to conventional therapies' was confirmed as the most relevant one by 71% of panellists.

Disease management: diagnostic issues and patient journey

Experts agreed that a delay in diagnosis occurs sometimes or often (37 out of 43 respondents, 86%), with an expected median delay in diagnosis since the first visit—according to their expertise—of 4 months. In the second Delphi round, 79% of clinicians agreed that most symptomatic

Table 1 Key topics examined through the Delphi methodology, and their consensus results

Main topic Question/statement	Experts involved	Consensus at round	Reply*	Agreement level
Epidemiology and main characteristics of MG				
A prevalence of MG between 15 and 35 cases per 100 000 inhabitants is currently a reliable estimate in Italy	CE	1	–	Majority, 89%
An incidence of MG between 1 and 3 new cases per 100 000 person-years is currently a reliable estimate in Italy	CE	1	–	Majority, 89%
In men, 10%–20% of new diagnoses of MG occur before age 40, 25%–40% at age 40–60 and 40%–60% after age 60	CE	2	–	Majority, 96%
In women, 20%–50% of new diagnoses of MG occur before age 40, 25%–40% at age 40–60 and 20%–40% after age 60	CE	2	–	Consensus, 100%
In your opinion, myasthenic crises lead to an increased mortality of patients with MG as compared with the general population?	CE	1	Yes	Majority, 75%
In your opinion, which is the most appropriate definition of refractory MG?	CE	2	Failure to respond adequately to conventional therapies	Majority, 71%
Disease management: diagnosis and patient journey				
In your experience, after the first visit of a patient with symptoms, are there delays in the diagnosis of MG?	CE, PHE, PE	1	Yes, sometimes or often	Majority, 86%
In your opinion, is there a significant problem of MG underdiagnosis in Italy?	CE, PHE	1	Yes	Majority, 72%
In your opinion, is there a significant problem of MG overdiagnosis in Italy?	CE, PHE	1	No	Majority, 89%
General practitioners and ophthalmologists are the physicians most frequently involved in the first contact with patients with MG	CE, PE	2	–	Majority, 81%
After the first patient visit, which specialist is involved?	CE, PE	1	Neurologist	Majority, 94%
Which physician(s) diagnose MG?	CE, PE	1	Neurologist	Consensus, 100%
Which physician(s) set up the treatment for MG?	CE, PE	1	Neurologist	Consensus, 100%
Specialists most frequently involved in the multidisciplinary management of patients with MG are neurologists, thoracic surgeons and pneumologists	CE, PE	2	–	Majority, 81%
Unmet needs				
In your experience, which are the main unmet needs of patients with MG during the acute phase of disease?	CE†	2	Rapidity—in the diagnosis, therapy initiation and/or recovery	Majority, 87%
Control of adverse events of therapy, control of symptoms/avoidance of clinical relapse and management of daily activities/patient independence are the main unmet needs of patients with MG during the chronic phase of disease	CE†	2	–	Majority, 96%
Quality of life				
In your opinion, which areas of quality of life are affected in a relevant manner by MG?	CE, PHE, PE	1	1. Psychological area 2. Functional area 3. Physical area 4. Economic/ occupational area	Majority, 88% Majority, 88% Majority, 78% Majority, 73%
Patient-reported outcomes are crucial to correctly evaluate the severity of MG	CE, PHE, PE	1	–	Majority, 92%

Continued

Table 1 Continued

Main topic Question/statement	Experts involved	Consensus at round	Reply*	Agreement level
Public health management of MG and other mixed aspects				
In your opinion, a correctly implemented organisational Hub & Spoke model would be useful to improve the management of patients with MG?	CE, PHE, PE	1	Yes	Majority, 86%
How would you rate the availability of regional PDTA documents (ie, Diagnostic-Therapeutic-Healthcare Pathways) to manage rare diseases?	PHE	1	Useful/essential	Consensus, 100%
How would you rate the availability of regional Clinical/Healthcare Disease Networks to improve the management of rare diseases?	PHE	1	Useful/essential	Consensus, 100%
In your experience, do patients and their caregivers get in contact with any MG patient association?	CE, PE	1	Rarely/sometimes	Majority, 80%
A referral centre for MG should ensure the presence of a multidisciplinary team, access to new therapies, expertise in the management of patients with MG and availability of advanced diagnostic tools	CE, PHE	2	–	Majority, 98%

*The main reply is reported for multiple choice or open-ended questions, while statements did not require any reply.
†Open-ended questions alone were also asked to public health and patient experts, to collect their description of patient unmet needs.
CE, clinical experts; MG, myasthenia gravis; PE, patient associations experts; PHE, public health experts.

patients achieve a diagnosis of MG within 6 months from the first visit. A scarce knowledge of the disease by non-expert physicians was reported as a major cause of delayed diagnosis by 77% of panellists. MG was deemed underdiagnosed in Italy by 72% of experts overall, with some heterogeneity between expert subgroups (ie, 64% among clinicians, 91% among public health experts). On the other hand, clinical and public health experts agreed that overdiagnosis of MG is not a significant issue in Italy (89% overall; 88% in clinicians and 91% in public health experts).

Questions on patient journey were posed to clinicians and patient association representatives. First contact with an MG patient in Italy generally involves General Practitioners and ophthalmologists (according to 81% of panellists); thereafter, patients are generally visited by a neurologist (94% agreement), who is also in charge of the diagnosis (100% consensus) and treatment set up (100% consensus). Eighty-one percent of respondents agreed that the specialists most frequently involved in the multi-disciplinary management of MG patients are neurologists, thoracic surgeons and pneumologists.

Unmet needs of patients with MG

Unmet needs of patients were considered separately in the acute and chronic phases of disease. In the acute phase, rapidity—either in the diagnosis, the initiation of therapy and/or to achieve a fast and full recovery—was reported as the main unmet need of patients by most clinicians (87%) in two subsequent Delphi rounds (the first one proposed an open-ended question, the second one a multiple-choice question). Open-ended questions alone were asked to public health experts and patient association members. Public health experts reported rapidity of response, too, as well as prompt access to treatment as major needs in order to improve the prognosis of MG. Patient representatives mainly underlined the need for improved understanding by the physicians and psychological support to the patient. In the second round (again, after an exploratory, open-ended question in the first round), 96% of clinicians agreed with a statement reporting that control of adverse events of therapy, control of symptoms/avoidance of clinical relapse and management of daily activities/patient independence are the main patient needs during the chronic phase of MG. Physical support, dedicated centres and improved patient well-being were the main unmet needs of the chronic phase reported by public health experts, while the need for compassion/understanding of the patient status, as well as protection of patient rights were underlined by patient associations representatives.

Quality of life and MG measurement scales

The majority of panellists agreed that MG has a major impact on several aspects of quality of life of the patient, including the psychological/emotional (88%), functional (88%), physical (78%) and economic/occupational (73%) areas. Overall, 92% of respondents agreed that patient-reported outcomes are crucial to correctly evaluate the severity of MG. This result was broadly consistent in the subgroups of clinicians (89%), public health (100%) and patient associations experts (75%). Further, a few questions were posed to clinicians alone to collect exploratory information on the scales they know and use to monitor the severity of MG and the quality of life of their patients. The Quantitative Myasthenia Gravis (QMG, 100% of

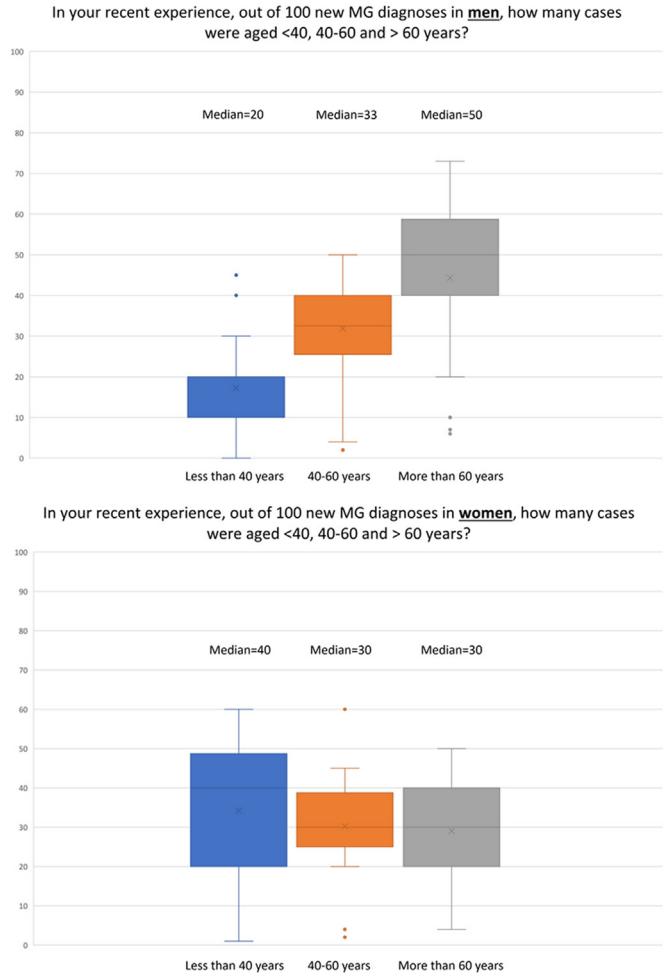

Figure 2 Distribution of age at MG diagnosis in men (first panel) and women (second panel), according to 28 Italian clinicians. MG, myasthenia gravis.

respondents), the MG Activities of Daily Living (ADL, 86%) and the MG Composite (MGC, 79%) scales/scores were most frequently reported among known clinical indexes to monitor MG severity, while the most frequently adopted scales/scores to monitor MG severity were the MG-ADL (64%) and the QMG (61%) (figure 3). Patient representatives did not feel that clinical scales used during the visits accurately reflected their perception of disease evolution (4/4, 100% consensus), with two of them highlighting that this is due to the extreme variability of the disease.

In separate questions focused on the knowledge and use of scales to evaluate the quality of life of patients (rather than MG severity), the MG Quality of Life 15-item (MG-QoL15) was known by 79% of clinicians and was used by 73% of them.

Public health management of MG and other mixed aspects

Most respondents (86%) agreed that a correctly implemented organisational Hub & Spoke model[30] would be useful to improve the management of patients with MG. A strong agreement was achieved in all subgroups, including clinicians (81%), public health (90%) and patient associations experts (100%). There was 100% consensus among public health experts that the availability of regional PDTA (Percorsi Diagnostico Terapeutici Assistenziali, that is, Diagnostic-Therapeutic-Healthcare Pathways) guidelines to manage rare diseases is useful or essential. Similarly, all public health experts agreed (100% consensus) that the availability of regional Clinical/Healthcare Disease Networks would be useful/essential to improve the management of rare diseases in general.

Two questions were posed on MG patient associations. First, clinicians and patient advocacy experts concordantly replied (80% of respondents) that Italian patients and their caregivers only rarely-to-sometimes get in contact with MG patient associations. Second, an exploratory question was asked to understand which Italian MG patient associations (either national or regional/local) are known to the clinicians and public health experts. The 'Associazione Italiana Miastenia' (AIM—Italian Association Myasthenia) and the 'Associazione MIA Onlus' were most frequently indicated, by 52% and 34% of respondents, respectively.

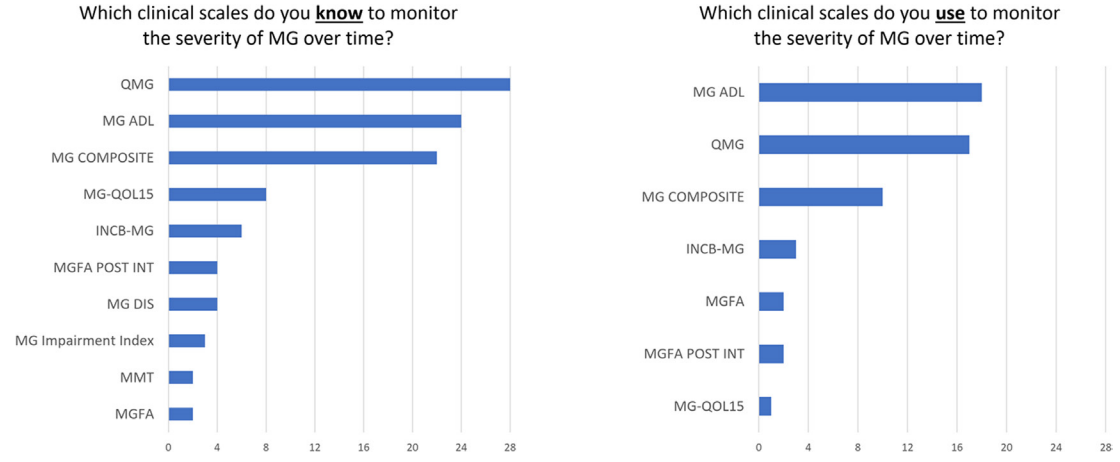

Figure 3 Descriptive information on the clinical scales known (left panel) and used (right panel) to monitor the severity of MG over time, according to 28 Italian clinicians. ADL, activities of daily living; MG, myasthenia gravis; QMG, quantitative myasthenia gravis.

After collecting indications in the first round on the main characteristics required by a referral centre for MG through an open-ended question, the following statement was proposed, and agreed on by almost all respondents (98%), during the second iteration: 'A referral centre for MG should ensure the presence of a multidisciplinary team, access to new therapies, expertise in the management of patients with MG, and availability of advanced diagnostic tools'. Eighty-three per cent of public health experts agreed that, at the moment, about 25 referral centres for MG are present in Italy.

DISCUSSION

This consensus of Italian experts of MG conducted through the Delphi method reported a high level of agreement on most of the topics considered, including epidemiological aspects such as prevalence and incidence of disease in Italy, several clinical and public health management issues, as well as the (strong) impact of MG on the quality of life of patients. More than 50 experts of the disease and public health managers were involved in the project and, for a large majority of items proposed, cross-agreement was achieved among different subgroups of panellists (ie, clinicians, public health experts and patient associations representatives), thus strengthening the value of the findings.

The severity and impact of MG emerged across various items considered in the Delphi project. First, three-fourths of clinicians agreed that myasthenic crises increase the mortality of patients with MG. In open-text comments, a number of panellists noted that this aspect is particularly relevant to frail patients (ie, elderly and/or with comorbidities) and that such crises are manageable when promptly identified and correctly treated. Literature data on the issue are inconsistent, with some studies showing a similar life expectancy in patients with MG as in the general population,[31] and others reporting increased MG-related mortality, particularly during the early years of disease when the risk of myasthenic crises is higher.[32] Second, and in connection with the first point, most clinicians highlighted that rapidity of action (both in the diagnosis and treatment of disease) is an essential unmet need of the patient during the acute phase of MG. In the chronic phase, the main unmet needs were rather controlling adverse events and symptoms, avoiding clinical relapse and improving the independence of patients in their everyday activities. Third, all groups of experts agreed that several areas of quality of life are affected by the disease, particularly the physical/functional (eg, fatigability, ability to perform daily activities), psychological/emotional and economic/occupational fields. With reference to the latter field, the finding is consistent with a meta-analysis of 19 studies showing that only half of patients with MG are employed—although a large fraction of them are at working life age.[33] Further, in this Delphi analysis, the point of view of representatives of MG patient associations was most critical on the strong effect of MG on quality of life, as all of them reported a relevant impact on—besides the fields already cited above—the familial, relational and medical/care areas. This is consistent with previous reports showing an unfavourable role of MG on several different aspects of patients' life, including for example family planning, increased presence and impact of comorbidities, decreased cognitive functions in at least part of MG cases, and frequent need to access medical resources.[34 35]

We proposed to the clinicians two statements with estimated ranges of prevalence—that is, 15–35 cases per 100 000 inhabitants—and incidence—that is, 1 and 3 new cases per 100 000 person-years—of disease in Italy. These estimates were deemed appropriate by almost 90% of experts and an agreement was reached as of the first Delphi round. Although the epidemiology of MG is still uncertain, such a large agreement of experts is reassuring of the figures that were proposed. Further, such prevalence and incidence estimates are in line with findings from selected Italian studies published during the last two decades,[3 8 12 36] as well as with OrphaNet data reporting a prevalence of 20 per 100 000 and an incidence of 1.7 per 100 000 from European studies.[37]

Diagnostic delay in MG is still an issue in Italy[38] although, according to the professionals involved in this Delphi consensus, most patients are correctly diagnosed within 6 months after the first visit related to the disease. Thus, the time to diagnosis is lower as compared with other rare diseases. Interestingly, various clinicians noticed that time to diagnosis is often related to different expertise of the physician involved with first contact/access (eg, General Practitioner or Emergency Department vs a centre with specific expertise in MG), whereas patient associations members attributed gaps in the time to diagnosis mainly to differences in territorial access (eg, northern vs southern Italy). There was full consensus across all groups that a neurologist should be in charge of the diagnosis and treatment of MG and general agreement on the optimal organisation of the patient journey and other aspects of public health management. Although all public health experts concurred that regional PDTA documents are important to manage rare diseases, such documents for MG are still scanty in Italy.[39] In fact, only 40% of panellists were aware of the existence of local/regional PDTA specific to MG. Therefore, territorial PDTA documents reporting uniform indications would be useful tools in Italy to guide the management of this fluctuating, heterogeneous disease.

Other relevant disease gaps that emerged from Italian experts include the need to assist caregivers of patients with MG[40] with several aspects, including education on the disease, psychological and practical support (including economic reimbursement and occupational issues), to improve patients empowerment by encouraging their access to influent patient associations, and to increase the role of regional Clinical/Healthcare Disease Networks specific for MG.

Limitations of this investigation are those typical of consensus methods,[41] that rely on expert opinions and

lack evidence-based data. Further, this Delphi analysis of MG was focused on the Italian scenario and included national experts only, thus its generalisability is limited. Still, this work can provide an important base helping to improve the paradigm for MG treatment and management in Italy and, possibly, in a few similar/neighbouring European countries. Among the strengths of this work, the analysis was conducted in accordance with the best practices for Delphi studies and results were reported following the indications of the ACCORD guidelines.[22] Further, the panel of experts was large, various groups of specialists were involved and participation and response rates during the iterations were satisfactory.

CONCLUSIONS

The project allowed to provide a thorough overview of MG in the Italian setting, bringing together the opinions of different expert groups and thus a variety of points of view. This notwithstanding, consensus was achieved on a large number of topics examined, granting solid guidance for educational and practical aspects of the disease. This may also stimulate new ideas and the design of future studies focused on MG. Lastly, a few gaps related to the handling of MG in Italy were highlighted, thus providing indications on which aspects should be ameliorated to improve the overall management and public healthcare of the disease.

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