Autoimmune myasthenia gravis : the impact of heterogeneous patterns of muscle weakness on outcome measures and diagnosis

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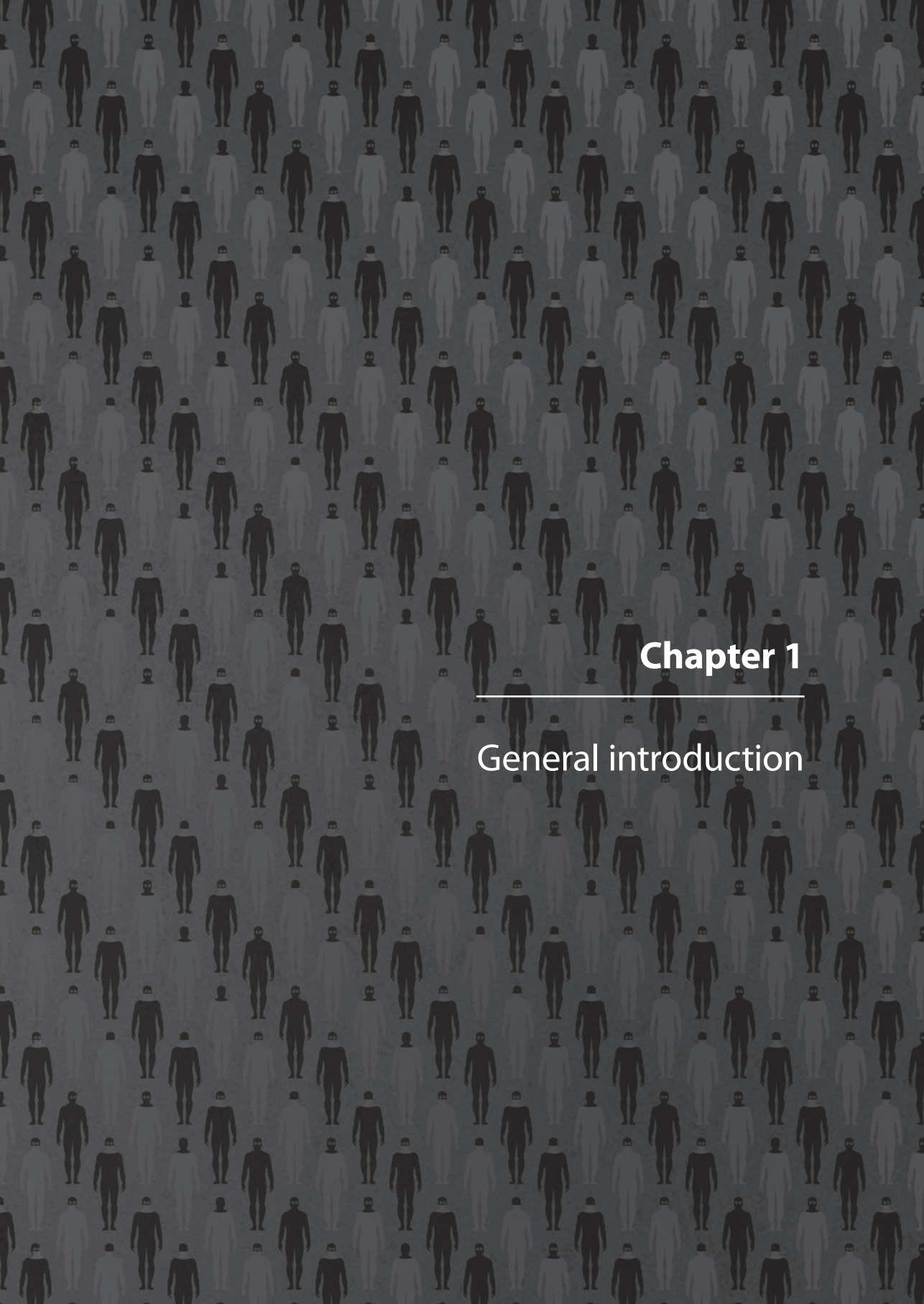
INTRODUCTION



Chapter 1

General introduction

HISTORY OF MYASTHENIA GRAVIS' CONCEPTION

The first descriptions of a myasthenia gravis (MG) patient were made in the 17th century. One side of the Atlantic Ocean claimed that the first described MG patient was native American Chief Opechancanough in 1644: "The excessive fatigue he encountered wrecked his constitution; his flesh became macerated; his sinews lost their tone and elasticity; and his eyelids were so heavy that he could not see unless they were lifted up by his attendants . . . he was unable to walk; but his spirit rising above the ruins of his body directed from the litter on which he was carried by his Indians".[1, 2] According to the other side of the Ocean, the first description of MG was made in England by Thomas Willis in 1672: "She speaks freely and readily enough for a while, but after a long period of speech … she is not able to speak a word and is as mute as a fish. Her voice does not return for one or two hours".[3, 4] Interestingly, the first two descriptions of MG patients express two different patterns of muscle weakness. The former description highlights ocular and generalized muscle weakness but gives no mention of bulbar muscle weakness, whilst for the latter description the reverse is true. Heterogeneous patterns of muscle weakness were observed from the start; however, the factors causing this heterogeneity are still largely unknown.

In the second half of the 19th century, Erb and Goldflam gave a first detailed description of the disease that was then referred to as Erb's or Erb–Goldflam disease.[5, 6] In 1895, Jolly showed that during repeated stimulation of a nerve, decreased contraction of the innervated muscle is observed. This neurophysiological proof of fatigability in MG was in accordance with the first clinical observations of fatigable muscle weakness.[7] As MG could be distinguished from 'true' paralyses, Jolly coined the term 'myasthenia gravis pseudoparalytica' (myo, muscle; asthenia, weakness; gravis, severe). A possibly pathophysiological mechanism involving unknown intrinsic factors was first hypothesized by Buzzard In 1905: "the symptoms of the disease are best explained by assuming the presence of some toxic, possibly autotoxic, agent." Even though at the time, MG was already commonly believed to be a disease of the motor system, he argued that non-motor symptoms occur as well: "myasthenia gravis is a disease in which the symptoms are not always confined to the motor system, but may include other sensory, mental or other origin".[8] However, as later research would indicate the neuromuscular junction as the localization of the neurological deficit, MG to date is conceived as a disease with only motor symptoms.

In the 20th century, the auto-immune disorder underlying MG became apparent by observations such as the presence of lymphocyte aggregates in muscle biopsies and thymic abnormalities in a proportion of MG patients. In 1960, Simpson proposed the hypothesis that MG was caused by an antibody-mediated auto-immune disorder, mainly supported by the observation that neonates of mothers with MG had a transient form of myasthenia.[9] This hypothesis was further supported in 1976 by Pinching et al. who found that plasma exchange resulted in strong clinical improvement of MG patients.[10] The paradigm of the

pathophysiology in MG was set after the presence of antibodies directed towards the acetylcholine receptor (AChR), a postsynaptic protein playing a crucial role in neuromuscular transmission, was shown in 85% of MG patients by Lindstrom et al.[11] One of the major areas of research focused on the identification of additional antibody targets in the remaining 15% 'seronegative' MG patients. In the last two decades, several new antibodies to synaptic proteins were found, among which the voltage-gated calcium channel (VGCC), muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4) and agrin.[12-15] Interestingly, the pattern of muscle weakness in MuSK MG is different from that in AChR MG. In MuSK MG, bulbar and respiratory weakness is more predominant and ocular weakness often resolves early in the disease course. In AChR MG, on the other hand, ocular weakness is often the first symptom and frequently remains present to some extent during the disease course.[16, 17] It has been hypothesized that differences in the relative importance of the AChR and MuSK proteins in various muscles might explain the distinct muscle weakness patterns.[18] The predominant presence of proximal leg weakness and less frequent involvement of oculobulbar muscles in Lambert-Eaton Myasthenic Syndrome (LEMS), with the presynaptic Cav2.1 voltage-gated calcium channel (VGCC) as antigen, is another example of a strikingly different pattern of muscle weakness in an antibody mediated disease of the neuromuscular synapse. Several factors have been suggested to contribute to the distinct involvement of muscle groups in MG and other neuromuscular disorders: differences in embryological origin of muscles, adult or fetal AChR isoform expression, innervation patterns, the neuromuscular safety factor, the firing frequencies of motor neurons, the sensitivity to complement mediated membrane damage or differences in the mitochondrial content between extraocular and skeletal muscles. All these factors are proposed as explanations for the differences in involvement of extraocular, bulbar or limb-girdle muscles in MG.[19-21]

However, aside from the heterogeneity of muscle weakness patterns between AChR MG, MuSK MG and LEMS, there is also a remarkable variation *within* these disorders, such as ocular versus generalized AChR MG, rare occasions of distal weakness in AChR MG, or pure ocular weakness in LEMS.[19, 22]

HETEROGENEITY AND SHIFTS IN DISTRIBUTION OF MUSCLE WEAKNESS

Although the exposure of the target antigens to circulating serum antibodies theoretically should be similar for all muscles, different patterns of muscle weakness are observed within the group of AChR MG patients. Acknowledging different phenotypes in MG might be of importance in treatment choices and clinical trials as some studies show that ocular or generalized weakness responds distinctly to different therapies.[23-25] Moreover, the sensitivity of outcome scales for changes in muscle weakness could depend on the muscles involved.[26, 27]

To identify different MG phenotypes and to quantify the extent of heterogeneity between patients and shifts of muscle weakness pattern within patients, we systematically analyzed the distribution of muscle weakness in AChR MG patients on three points in time. **(CHAPTER 2)**

Ocular muscles are the most frequently involved muscles in MG.[28] The affected ocular muscles can be subdivided in muscles that move the eyeball (extraocular muscles; EOM), the muscle that elevates the upper eyelid (m. levator palpebrae superioris; LPS) and the muscle involved in closure of the eye (m. orbicularis oculi; OO). Although MG is a systemic disease, ptosis is reported to be typically asymmetric. In addition, the (more pronounced) ptosis has been reported to shift from one eye to the other during the disease course, but no quantitative data of this phenomenon are reported.[29] Detailed knowledge of the patterns and fluctuations of ocular weakness in MG could be helpful for neurologists treating patients with neuromuscular disorders: for diagnosis, to understand its pathophysiology and to establish the relevance of current commonly used outcome measures.[26, 30] To investigate patterns of ptosis, diplopia and eye closure weakness (ECW) in MG and the sensitivity of the most frequently used clinical MG outcome measures for EOM weakness, we systematically analyzed ocular weakness in a large prospective cohort of MG patients. **(CHAPTER 3)**

OUTCOME MEASURES IN MG

The clinical course of MG is highly variable, ranging from stable disease or remission to the occurrence of several exacerbations over time. Previous studies have mainly focused on prognostic factors for remission. However, prognostic factors for exacerbations, myasthenic crises and emergency treatments could also be useful to the clinician for predicting the course of the disease. These outcome measures can be used in order to better predict which patients are at risk for a more severe and debilitating disease course. We investigated the association between baseline clinical features and the risk of exacerbations and emergency treatments in 96 MG patients. **(CHAPTER 4)**

The Quantitative Myasthenia Gravis (QMG) score can be used to measure ocular, bulbar, and generalized muscle fatigability.[31] Several other measures have been developed to assess quality of life or impairments in activities of daily living (ADL) in patients with MG.[32-38]

However, impairments in ADL have never been compared between MG patients and patients with other NMD. The systematic use of a quantitative measure of activity limitations for different NMD may be useful to compare the burden they impose on ADL and establish clinically relevant outcome measures for future clinical trials. In addition, it is not known how fluctuations of the severity of muscle weakness affect the limitations that MG patients experience in ADL. The ACTIVLIM (acronym of 'ACTIVity LIMitations') questionnaire is a validated measure of daily activity limitations for patients with NMD in general focusing

on generalized weakness.[39] We measured the ACTIVLIM score in MG patients to estimate their ADL limitations. To identify which factors contribute to limitations in daily activities, we investigated the relationship between several clinical variables and the ACTIVLIM score. We also analyzed how changes in muscle strength and fatigability, as measured by the QMG, affected the ACTIVLIM score over a longer period of time. **(CHAPTER 5)**

MG-ADL (Myasthenia Gravis Activities of Daily Living) is a commonly used questionnaire in MG trials.[40-42] Of the 8 questions, only 3 query generalized weakness. These questions concern respiratory function, the ability to brush teeth or comb hair and the ability to rise from a chair. Alongside this ADL scale, the QMG score is often used in clinical trials as an objective physician-reported scale. The QMG, however, includes more items on generalized weakness (8 of 13). In general, the MG-ADL score correlates well with the QMG score,[38] but in a recently published trial on the effect of eculizumab in generalized MG patients, there was a non-significant change in MG-ADL whereas QMG improved significantly.[26, 41] This raises the question whether MG-ADL is equally sensitive to changes in generalized weakness and oculobulbar weakness and whether adding questions on generalized weakness would improve sensitivity. To investigate whether the sensitivity of MG-ADL for generalized weakness could be improved, we analyzed whether ACTIVLIM has an additional value on top of the MG-ADL in the prediction of the generalized domain of the QMG score in individual patients. **(CHAPTER 6)**

The studies described in chapter 6 indicated that MG-ADL had a lower sensitivity for changes in generalized weakness.[27] In addition, a prior study reported that patients considered limb weakness as most invalidating, further stressing the importance of a high sensitivity for generalized weakness.[43] The recently developed Myasthenia Gravis Impairment Index (MGII) is a promising measure as it has less floor effects and a higher relative efficiency in its responsiveness to treatment effect compared to other MG measures.[44, 45] Moreover, MGII has 10 out of 28 items reflecting generalized weakness. We validated the MGII in a Dutch cohort of MG patients and analyzed the sensitivity of the MGII for changes in generalized weakness. **(CHAPTER 7)**

UNMET DIAGNOSTIC NEED IN OCULAR MG

Early recognition and treatment is of great importance for patients' quality of life.[16] Currently, the diagnosis of MG is made by a combination of clinically confirmed fluctuating muscle weakness supported by either the presence of serum autoantibodies, abnormal findings during neurophysiological testing or a positive neostigmine test. Current neurophysiological tests have several limitations. The greatest limitation is that the most commonly affected muscles, the extra-ocular muscles, cannot be tested. Therefore, repetitive nerve stimulation (RNS) has a very low sensitivity (0.29) in ocular MG (OMG) patients. In this

group, antibodies are found in only 44% of patients and therefore there is a strong need for a test to support the diagnosis.[46] Single-fiber EMG (SFEMG) has been reported to have a relatively high sensitivity in OMG (62-97%), however it does not directly assess EOMs, requires a skilled neurophysiologist to reliably perform this test, and is time-consuming and operator-dependent. In summary, the lack of neurophysiological tests measuring the neuromuscular transmission of EOMs complicates the diagnosis in OMG patients.[47]

A possible solution to this problem was found by a recent study by Valko et al. that shows the possibility of measuring fatigability in the ocular muscles by using ocular vestibular evoked myogenic potentials (oVEMP).[48] The stimulation of the semicircular canals with bone vibrations administered to the skull cause a vestibulo-ocular reflex, currently used for diagnoses in vestibular disease. In vestibular disorders, a single oVEMP potential is elicited and analyzed. Valko et al. showed that NMJ function can be investigated by applying a train of ten repetitive oVEMPs. In MG patients, a decrement in the n2-p2 amplitude can be observed, analogous to the decrement observed in RNS. We will refer to this this technique as the Repetitive oVEMP (RoVEMP) test. To further investigate the diagnostic value of the RoVEMP test, we investigated its diagnostic yield compared to a control group of patients with a neuromuscular disorder other than MG. We also analyzed the effect of pyridostigmine use on RoVEMP results. Furthermore, we included a larger cohort of MG patients in order to further analyze the sensitivity and specificity of the RoVEMP in diagnostically challenging subgroups (OMG and seronegative MG patients). **(CHAPTER 8)**

SCOPE OF THE THESIS

Before the discovery of the auto-immune dysfunction underlying the manifestations of MG, the phenomenological description of MG was the starting point for understanding the disease. Both the heterogeneity in the patterns of muscle weakness and the possible minor involvement of non-motor systems were disease manifestations being closely described to find clues for the pathophysiology underlying this disease. The name Jolly coined for this disease, 'myasthenia gravis pseudoparalytica,' indicates the open and broad clinical and scientific approach towards this disorder. After the discovery of antibodies against the components of the neuromuscular junction, the pathophysiological paradigm of auto-antibodies causing the disease became the starting point for further MG research. Different MG antibody subgroups were found to have different distributions of muscle weakness. Several hypotheses were formed to explain why ocular muscles showed weakness more often than other muscles. However, changes in weakness patterns within patients and differences in weakness patterns between patients with the same antibody status were not considered to be 'challenges' to the paradigm that disease expression in MG is solely explained by the systemic autoimmune disorder underlying it. The focus on antibody status

over phenomenological disease expression was also found in inclusion criteria of clinical trials. Antibody status often formed a hard criterion, whereas the expression of disease was only subdivided between 'isolated ocular' and 'generalized'. Even though outcome measures take into account different forms of muscle weakness, the 'unidimensional' score following from these scales shows that there is no regard for the possibly different responses of ocular, bulbar or limb-girdle muscle weakness to the intervention that is studied in therapy trials.

The main scope of this thesis is to elucidate the heterogeneity of muscle weakness patterns found in MG and to investigate how outcome measures and diagnostic tests cope with different distributions of muscle weakness.

The specific main objectives of the different parts (I-II) and chapters (2-8) in this thesis are:

I. To describe heterogeneity and fluctuations in muscle weakness patterns
   2. To identify different phenotypes in AChR MG and to quantify the extent of heterogeneity and the frequency of shifts in muscle weakness pattern
   3. To investigate patterns of ptosis, diplopia and eye closure weakness in MG and to analyze the sensitivity of QMG for EOM weakness

II. To analyze the quantification of distinct forms of myasthenic weakness in outcome measures and a new diagnostic test
   4. To investigate the association between baseline clinical features and the risk of exacerbations and emergency treatments
   5. To identify factors contributing to limitations in daily activities and to analyze how changes in muscle weakness affected the ACTIVLIM score
   6. To investigate the sensitivity of MG-ADL for generalized weakness
   7. To validate the MGII in a Dutch cohort of MG patients and to analyze the sensitivity of the MGII for changes in generalized weakness
   8. To investigate the diagnostic value of the RoVEMP test in diagnostically challenging subgroups.

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