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

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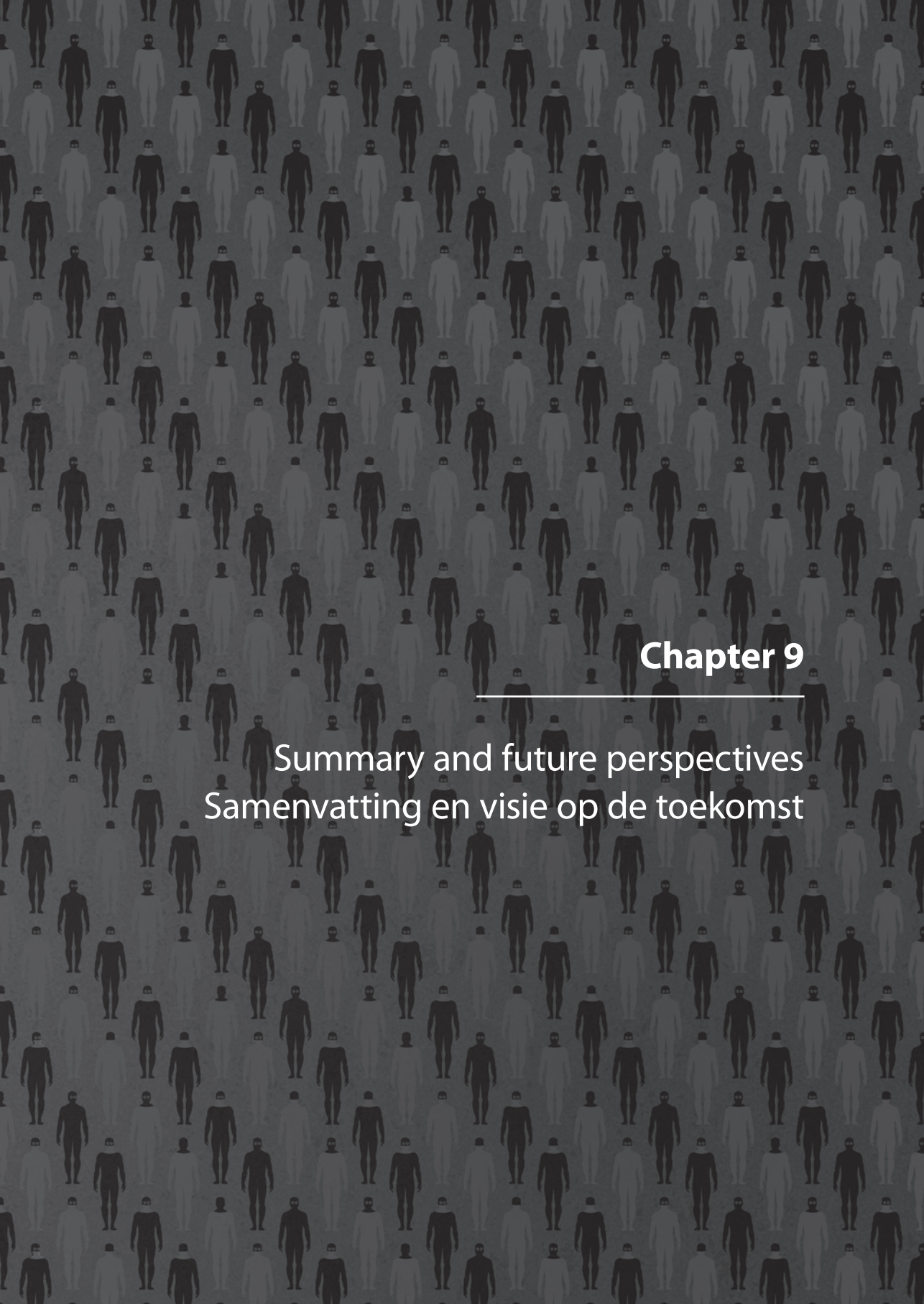
SUMMARY



Chapter 9

Summary and future perspectives
Samenvatting en visie op de toekomst

SUMMARY

Over the last years several advancements have been made in MG research. Additional antibodies against for example MuSK, LRP4 or agrin have been discovered, multiple outcome measures have been developed and new therapies have been tested. However, research has focused to a lesser extent on understanding the heterogenous muscle weakness that we encounter in MG and taking this heterogeneity into account in outcome measures and analyzing therapeutic effects. This thesis aimed to gain more insight in the phenomenology of MG and its reflection in current outcome measures and diagnostic tests.

In a cohort of 225 AChR MG patients, we found a high heterogeneity in the distribution of muscle weakness and a frequent occurrence of shifts between phenotypes in individual patients. In 12 patients (5%) MG was restricted to ocular weakness, whereas 15 other patients (7%) never had any form of ocular weakness throughout their disease course. These phenotypic extremes suggest that other factors aside from the AChR antibody mediated immune response, such as characteristics of individual muscles and their resistance against the antibody mediated attack, are of importance in determining the disease expression in MG. Ocular or bulbar weakness went into remission more frequently than neck/limbs/respiratory (NLR) weakness, suggesting that the latter form of weakness responds less well to therapy or that oculobulbar muscles are more capable of adapting to the autoimmune disorder. Clinical remission occurred more often in patients that did not have any form of NLR weakness in the first 6 months of disease. This suggests that the initial phenotype in AChR MG patients is of prognostic value. **(CHAPTER 2)**

Changes in the side of the ptosis or affected EOMs occur frequently in MG. In 83% of MG patients at least one other EOM was involved at the second visit. EOMs of both eyes were usually affected (75%) and double vision contained both a vertical and horizontal component in most cases (95%). In diagnostically challenging cases, we recommend testing ptosis and diplopia in all gaze directions for 60 seconds during at least two follow-up visits to maximize the chance of observing diplopia or changes in diplopia patterns observed earlier. **(CHAPTER 3)**

Late-onset of symptoms and the presence of additional autoimmune diseases were shown to be prognostic factors for exacerbations and the necessity of emergency treatments in MG. The higher occurrence of exacerbations in these subgroups might reflect distinct underlying pathophysiological mechanisms. Future immunological research on interindividual differences in complement activity and antibody-specificity might provide new clues for understanding the disease fluctuations observed in MG. Besides remission, exacerbations and emergency treatments should also be considered as endpoints in future studies. **(CHAPTER 4)**

Both oculobulbar and generalized MG patients had changes in activity limitations that were most clearly associated with changes in the generalized items of the QMG score. This

finding suggests that we might underestimate the effect of subclinical generalized muscle weakness in patients who are clinically diagnosed with pure oculobulbar MG. This is in line with a previous study that described subclinical generalized weakness in ocular MG patients. Future studies on isolated ocular MG should take into account possible subclinical generalized weakness that might bias the study results. **(CHAPTER 5)**

In the eculizumab study a discrepancy was found between the primary (MG-ADL) and secondary (QMG) outcome measures. The former did not show a significant treatment response whereas the latter did. We suggested that difference in quantitative representation of different muscle groups in QMG and MG-ADL might provide an answer to the mismatch between the outcome measures. It was proposed that discrepancies between QMG and MG-ADL in the eculizumab trial may be explained by a preferential effect of eculizumab on generalized weakness, which would explain the better response on QMG as compared to MG-ADL. To test our hypothesis, we advised reporting the subscores of the oculobulbar and generalized items on both QMG and MG-ADL.

Subsequently, we further investigated MG-ADL and found that it has a lower sensitivity for generalized weakness than for oculobulbar weakness. ACTIVLIM had a significant additional value on top of MG-ADL in the prediction of the generalized items of the QMG, suggesting that adding questions on generalized weakness could improve the sensitivity of the MG-ADL for generalized weakness. This additional value was even higher for changes in generalized weakness over time. **(CHAPTER 6)**

The MGII score was cross-culturally validated in a Dutch cohort of MG patients. Compared to the MG-ADL, the MGII had much lower floor effects. As hypothesized in the previous chapter, increasing the number of generalized items leads to a higher sensitivity generalized weakness: MGII (with 10 generalized items) had a markedly higher sensitivity for generalized weakness than MG-ADL (with 3 generalized items). **(CHAPTER 7)**

The RoVEMP test is a new neurophysiological test that, in contrast to RNS and single-fiber EMG, directly measures neuromuscular transmission of extra-ocular muscles. We were able to show that RoVEMP decrement is not a measure for extra-ocular muscle weakness or diplopia in general as decrement was rarely found in the neuromuscular control group, notwithstanding the similar frequencies of diplopia found in neuromuscular controls and MG patients. In addition, we found a significant correlation between magnitude of decrement and the time since the last intake of pyridostigmine. These findings support that RoVEMP decrement reflects reversible neuromuscular transmission failure, probably analogous to RNS decrement. Especially in diagnostically challenging patients, with isolated ocular muscle weakness, negative antibody tests and negative RNS results, the RoVEMP test might be very helpful for establishing the diagnosis of MG. **(CHAPTER 8)**

FUTURE PERSPECTIVES

Novel assays testing individual differences at the level of epitope specificity, complement function or genes important for immune or muscle function will provide a deeper understanding of the heterogeneity in the distribution of muscle weakness observed in MG. Comparison of the phenotypic extremes described in chapter 2 (isolated ocular versus no ocular weakness at all during the disease course) could be a fruitful approach to explore underlying pathophysiological differences leading to these distinct patterns of muscle weakness.

The great heterogeneity of muscle weakness patterns observed in this thesis and the different response of ocular or generalized weakness to various types of therapies suggest that both inclusion criteria and outcome measures should take into account the different muscle groups that can be affected (e.g. ocular, bulbar and limb-girdle). New outcome measures, such as the MGII, will enable a more detailed analysis of the treatment response in different muscle groups. Moreover, including phenotypic criteria for the inclusion of patients in future trials will increase the success of those trials. If a therapy has a preferential effect on limb-girdle muscles, it may be more adequate to include patients with pronounced limb-girdle weakness than to include patients with a certain total QMG score or MGFA class. The former does not distinguish between ocular, bulbar or limb-girdle weakness and the latter gives only a rough indication whether limb-girdle weakness ('a') or bulbar weakness ('b') is dominant.

The RoVEMP test may become a routine neurophysiological test in patients with the suspicion of MG. It is quick, non-invasive and has a good diagnostic yield. Especially in the diagnostically challenging subgroups of ocular and seronegative MG patients, the RoVEMP test was found to have a higher diagnostic yield than the current neurophysiological standard (repetitive nerve stimulation). Our study suggested that the RoVEMP test might also be useful in LEMS and CMS patients. Future studies on the RoVEMP test will provide further insights in the diagnostic or prognostic value of this test in MG, LEMS and CMS patients.

In conclusion, future research should analyze heterogeneity of disease expression in more detail as it can be used to better understand the pathophysiology of MG. Limiting categorization of MG patients by antibody status, QMG score, MGFA class or ambiguous terms such as 'generalized disease' could impede uncovering one of the most intriguing questions in the field of MG and many other neuromuscular diseases: the differences within and between neuromuscular disorders in the patterns of muscle weakness. Subgroup-specific therapies, better diagnostic strategies and higher success rates of trials could be the rewards of putting effort in solving the puzzle why systemic (autoimmune) muscle diseases affect some muscles more than others.