Faces and fatigue in myasthenia gravis

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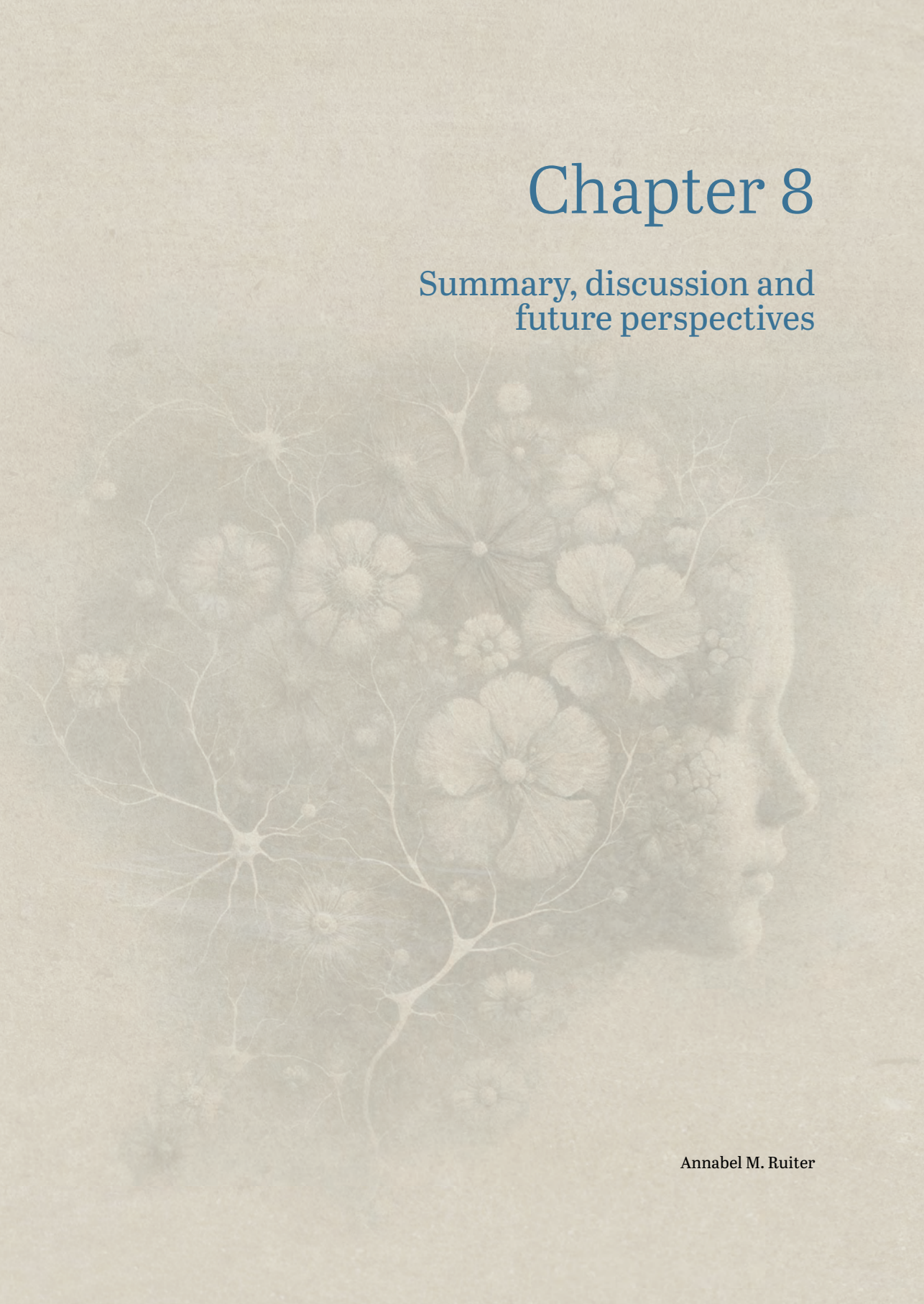
Part three

Epilogue

Chapter 8

Summary, discussion and future perspectives



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Summary, discussion and future perspectives

Myasthenia gravis (MG) is an antibody-mediated autoimmune disease affecting the neuromuscular junction (NMJ) of the peripheral nervous system, leading to fatigable muscle weakness. MG with acetylcholine receptor antibodies is the most prevalent form of MG. Its most typical hallmark a fluctuating asymmetric weakness of the eyelids and diplopia[1].
This thesis consisted of two parts. The first part covers the subject of central fatigue in MG: its prevalence, pathophysiology and burden for patients. The second part focusses on artificial intelligence for diagnosis and disease monitoring of MG through automated assessment of facial weakness.

Part one: Fatigue in myasthenia gravis

Chapter two describes the first results of the Dutch – Belgian Myasthenia Gravis registry. This registry uses a unique combination of patient-reported annual questionnaires together with physician-reported medical information, which is requested once at entry of the registry. Results of 565 MG patients and 38 Lambert-Eaton myasthenic syndrome patients provided insights on disease course which were in line with previously published data[2, 3]. We presented several novel insights regarding the Dutch MG cohort. One important finding was the high rate of potentially steroid-induced comorbidities, including hypertension and type 2 diabetes. This finding emphasizes the importance of starting non-steroid immune suppressive medication early. Besides longitudinal information on disease course, the registry also provided insights in disease burden. Surprisingly, the most limiting symptom reported by MG patients was not muscle weakness or diplopia, but fatigue. In neuromuscular diseases in general, a differentiation has been proposed between peripheral fatigue (muscle weakness and fatigability) and central fatigue (mental or cognitive fatigue)[4, 5]. Central fatigue is defined as an experienced lack of energy to sustain physical of mental tasks. A common hypothesis is that central fatigue serves to protect muscles from (further) damage by down-regulating activities, physically as well as mentally[4, 5]. Unfortunately, this patient-reported questionnaire did not refer to a specific type of fatigue. Along with other symptoms, patients were asked if they suffered from fatigue: 'yes', 'no' or 'I don't know'. Subsequently, they could indicate which symptom was experienced as the most limiting. In the following chapters we further focus on central fatigue.

Chapter three is a systematic review summarizing the MG-related literature on all aspects of central fatigue. Of 445 studies produced by the initial systematic search, 21 remained for final inclusion. Most studies were case control or case series. The sample sizes varied between 8 and 257 participants. In all studies, fatigue was assessed with the use of a variety of patient-reported questionnaires. The prevalence of fatigue in MG patients ranged between

44 and 82%. Secondly, fatigue was also highly prevalent in patients with a low disease severity, for example in patients in remission. In the control groups, the prevalence of fatigue was significantly lower and varied between 18-40%. The prevalence of fatigue in MG was in concordance with other chronic neuromuscular disorders, such as facioscapulohumeral muscular dystrophy (FSHD) and myotonic dystrophy, but also with other autoimmune diseases, like rheumatoid arthritis (RA) and inflammatory bowel disease (IBD)[6-8]. In MG, fatigue was strongly associated with disease severity, depressive symptoms and female gender, and correlated with a lower quality of life. Literature on the treatment of fatigue in MG is scarce. There is limited evidence on the benefits of a physical and psychological training program, however this was a very small study (n=9)[9]. To date, there is no evidence supporting the treatment of fatigue as a separate symptom besides muscle weakness. Previous studies found a significant improvement in patients treated with eculizumab as well as with intravenous immunoglobulins, plasma-exchange or prednisone[10, 11]. However, adjustment for disease severity was not applied, therefore the observed improvement of fatigue may have been the results of improvement of MG symptoms.

In **chapter four** we focussed on a large representative cohort of Dutch MG patients to assess the relationship between central fatigue and several factors, including disease severity and quality of life but also physical activities and coping strategies. A total of 420 MG patients participated in this study, making this the largest MG fatigue study so far. Severe fatigue was present in 62% of MG patients. We found that fatigue was positively correlated with disease severity, female gender, body mass index (BMI) and depressive symptoms. This was comparable with previous fatigue studies in MG, described in the systematic review but also with other autoimmune diseases, like rheumatoid arthritis (RA)[7]. These findings suggest a common pathophysiology for fatigue in chronic (autoimmune) disorders in contrast to a MG specific pathway. Next, we found that performing strenuous activities, such as running or cycling at an increased pace, was strongly correlated with lower fatigue scores. Although most patient (75%) did not perform any form of strenuous activities, this correlation was even found in patients performing this type of activity only once a week. One could suggest that patients with a low disease severity would probably be able to perform these type of activities due to better muscle condition, whereas a higher disease severity leads to a more inactive lifestyle. However, this correlation presented in **chapter four** is after adjustment for disease severity, BMI and age. This beneficial effect was not found for moderate physical activities, such as walking or cycling on a regular pace, even when these activities were carried out more than 150 minutes daily. This effect of moderate and strenuous physical activity on fatigue has not been systematically assessed in previous MG studies but comes as no surprise, since physical training programs are beneficial to fatigue in other neuromuscular disorders, including FSHD and chronic inflammatory

demyelinating polyneuropathy[12, 13]. Another novel finding in this study was the difference in coping styles between fatigued and non-fatigued patients. Fatigued patients scored significantly higher on passive coping strategies compared to non-fatigued patients. Passive coping strategies are linked to expressing physical and mental distress, as well as denying the presence of stressful events, abandoning efforts to achieve goals in stressful situations, and intensifying feelings of stress[14]. To our knowledge, coping strategies have not been previously studied in relation to fatigue in MG or other chronic/ autoimmune diseases. There is very limited literature on coping strategies associated with fatigue. In a systematic review on breast cancer patients, among other things, subjective/ perceived stress was associated with higher levels of fatigue in different stages of breast cancer[15]. This is in line with our findings.

In **chapter five** we aimed to gain a better understanding on the pathophysiology of central fatigue in MG by searching for a potential circulating serum biomarker. One hypothesis is that central fatigue in autoimmune diseases is caused by systemic inflammatory cascades which are triggered by a local peripheral inflammatory process[5]. In case of MG, local inflammation at the NMJ might trigger these systemic cascades. In a cohort of 116 anti-acetylcholine receptor (AChR) positive patients, we found a robust positive correlation between fatigue and C-reactive protein (CRP), after adjustment for several pre-selected covariates like disease severity and cumulative prednisolone dosage and the use of non-steroid immune suppressive medication. This correlation continued to exist after post-hoc adjustment for BMI and strenuous physical activities. Our findings suggest that low grade inflammation is part of the pathogenesis of central fatigue and supports the hypothesis that local peripheral inflammation is a trigger for central fatigue. There is no previous literature on biomarkers for central fatigue in MG but the results of our study are in accordance with results on biomarkers for fatigue in other autoimmune diseases. Both in RA and IBD, a positive correlation between fatigue and CRP levels has been observed[16, 17]. In addition, this correlation has also been observed in very large general population cohort studies[18, 19], and there are even reports that CRP can be predictive for the development of future fatigue[20]. A repeated blood sample was collected in 88 MG patients (76% of the initial cohort), but unfortunately we could not reproduce our initial correlation between fatigue and CRP. This is most likely due to a lack of statistical power for the repeated measurement: the number of participants at the second visit was below the predetermined sample size. Secondly, the repeated measurement contained two apparent outliers with high CRP values and low fatigue scores, which due to the relatively small sample size had a substantial influence on the correlation. Longitudinal fatigue scores were collected in 104 MG patients (90% of the initial cohort). We could not replicate the predictive value of CRP for the development of future fatigue in this subgroup as demonstrated in a previous large general

cohort study of almost 3000 participants[20]. CRP production is mostly stimulated by interleukin 6 (IL-6). Previous research in different cohorts of non-MG patients, including a large general population cohort, cancer and chronic haemodyalisis[18, 21, 22], showed a correlation between fatigue and IL-6. Studies in RA even showed an improvement of fatigue in patients treated with IL-6 inhibitors[23, 24]. In addition, there is evidence that IL-6 plays a key role in the pathogenesis of MG[25-28]. This supports the relevance of our observed correlation between fatigue and CRP, which is a product of IL-6 stimulation. In **chapter four** we found that an active lifestyle including regular strenuous physical activities, was correlated with significant lower fatigue scores. Under normal circumstances, baseline IL-6 levels are higher in persons who have an inactive lifestyle compared to persons who frequently engage in physical activities[29, 30]. Although this has not been studied in MG or other diseases, we hypothesize that the beneficial effect of physical training programs on fatigue could at least partly be caused by a decrease in baseline levels of IL-6 as a result of these training programs.

Future perspectives

Central fatigue is an important and prevalent symptom in MG, that contributes to a lower quality of life. Consequently, its acknowledgement is of utmost importance. A significant amount of evidence points towards a role of physical activities for the improvement or even prevention of central fatigue. Therefore, a detailed clinical trial should be executed to study the effects of a strenuous training program in an adequately sized cohort. Due to different coping strategies in fatigued patients, it is essential to combine this with some sort of cognitive behavioral therapy, especially to provide tools to incorporate a more active lifestyle in their daily life after the trial has finished. During this trial repeated blood samples could provide more insights in the serum levels of CRP, IL-6 and others, before, during and after physical training sessions, and the effect of strenuous activity on baseline IL-6 levels in MG. Next, future research should explore the effect of immunosuppressive therapy, in severely fatigued patient, even when their condition is clinically stable or in (pharmacological) remission. While previous studies have demonstrated that improvements in disease severity often correlate with reduced fatigue, the question remains if it is appropriate to initiate or intensify treatment solely to address fatigue.

Part two: Faces of myasthenia gravis

Chapter six presents an image of the face of myasthenia gravis. Photos of 52 patients with MG and 38 healthy controls were averaged to compose one face expressing different facial expressions. The averaged images resulted in highly similar faces in which the MG face shows the typical clinical hallmarks of MG: ptosis and generalized facial weakness. This

averaged images formed the basis for **chapter seven**, in which we aimed to quantify and map patterns of facial weakness with facial expression recognition software. The second aim was to develop a deep learning (DL) computer model to classify diagnosis and disease severity. In this cross-sectional study we made video-recordings of 70 MG patients and 69 healthy controls (HC). A short video was recorded of each participant expressing a standardized set of 24 different facial expressions. An analysis of these videos with facial expression recognition software demonstrated a significantly decreased expression of anger, fear and happiness in MG patients compared to HC. This indicated that specific patterns of facial weakness are detectable in MG with facial analysis software. Impairments in facial expressions are also seen in other disorders affecting facial muscles, like facial palsies and facioscapulohumeral dystrophy and are associated with a lower quality of life due to their effects on social interactions[31-33]. Although we did not assess secondary outcomes such as quality of life or depressive symptoms, it is reasonable to assume that this decrease in facial expressiveness may significantly influence an individual's social well-being. A more recent study reported that MG patients performed worse on facial expression recognition compared to HC[34]. The authors hypothesize, speculatively, that MG patients might exhibit impairments in their ability to recognize emotions, potentially due to disruptions in the integration of bodily sensations and sensory inputs crucial for emotional processing. Our DL model was able to classify diagnosis and disease severity as a dichotomous outcome with considerable specificity and sensitivity. These results are promising and provide a first 'proof of concept', however further finetuning is required before this model can be used as a clinical tool.

Future perspectives

Chapter seven provides a 'proof of concept' that advanced computer technologies can be used for quantification and classifying diagnosis and disease severity of MG. Given the invasive and laborious nature of advanced diagnostic techniques now available for MG, including antibody testing and repetitive nerve stimulation, a user-friendly application for tracking disease fluctuations would be significantly more valuable. Such an application could contribute to better disease insights for patients, fewer unnecessary consultations and enhance the efficiency of MG care. Usual care typically involves outpatient consultations two or possibly three times a year, depending on the severity of the patient's disease and their response to treatment. A smartphone application could be used to conduct daily or weekly evaluations of disease severity, providing highly detailed information that is currently unavailable through standard care. This data may teach us more on the natural course of MG, potentially enabling us to predict exacerbations and tailor immunosuppressive therapy

more precisely to individual patients. Our study provides a first step, but further training and development of the model is necessary to result in more detailed information on disease severity. The model should incorporate an assessment of facial expressions, ideally focusing on a limited number of core-expressions. Additionally, future studies need to determine whether integrating patient-reported data and a brief strength assessment would enhance the model's effectiveness as an intuitive monitoring tool. Recent research demonstrated that an artificial intelligence model was able to successfully distinguish MG patients from healthy controls by analysing specific parts of the MG-core examination conducted via telemedicine[35]. This indicates that specific MG examinations could have added value for the effectiveness of our model as well.

Overall conclusion

The work presented in this thesis contributed to the knowledge of central fatigue in MG, which is a prevalent and important symptom leading to a diminished quality of life. A multifactorial origin is likely, due to the strong correlation with several factors, like disease severity, female gender and depressive symptoms, similar to fatigue in other autoimmune or neuromuscular diseases. In this multifactorial pathogenesis, low-grade inflammation plays a role of which the degree of contribution must be further determined. The results discussed in this thesis showed significant lower reported fatigue scores in patients who engaged in strenuous physical activities. This offers possibilities for a potential treatment of fatigue in MG and as a result of these findings, the MG research team of the LUMC is currently conducting a clinical trial to further study the effects of both a physical training program and cognitive behavioural therapy on central fatigue. This possible beneficial effect of training may be partially be explained by reduction of low-grade inflammation through physical activities, though this hypothesis requires further investigation.
In the second part of this thesis we demonstrated that typical patterns of facial weakness in MG can be captured visually in photos and videos. Novel in MG, we showed a 'proof of concept' of a DL model for classification of diagnosis and disease severity. The results of this study are promising for the development of a future (smartphone based) monitoring tool with an intuitive user interface, aligning with the broader trend of utilizing digital technologies to improve MG care.

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