Faces and fatigue in myasthenia gravis

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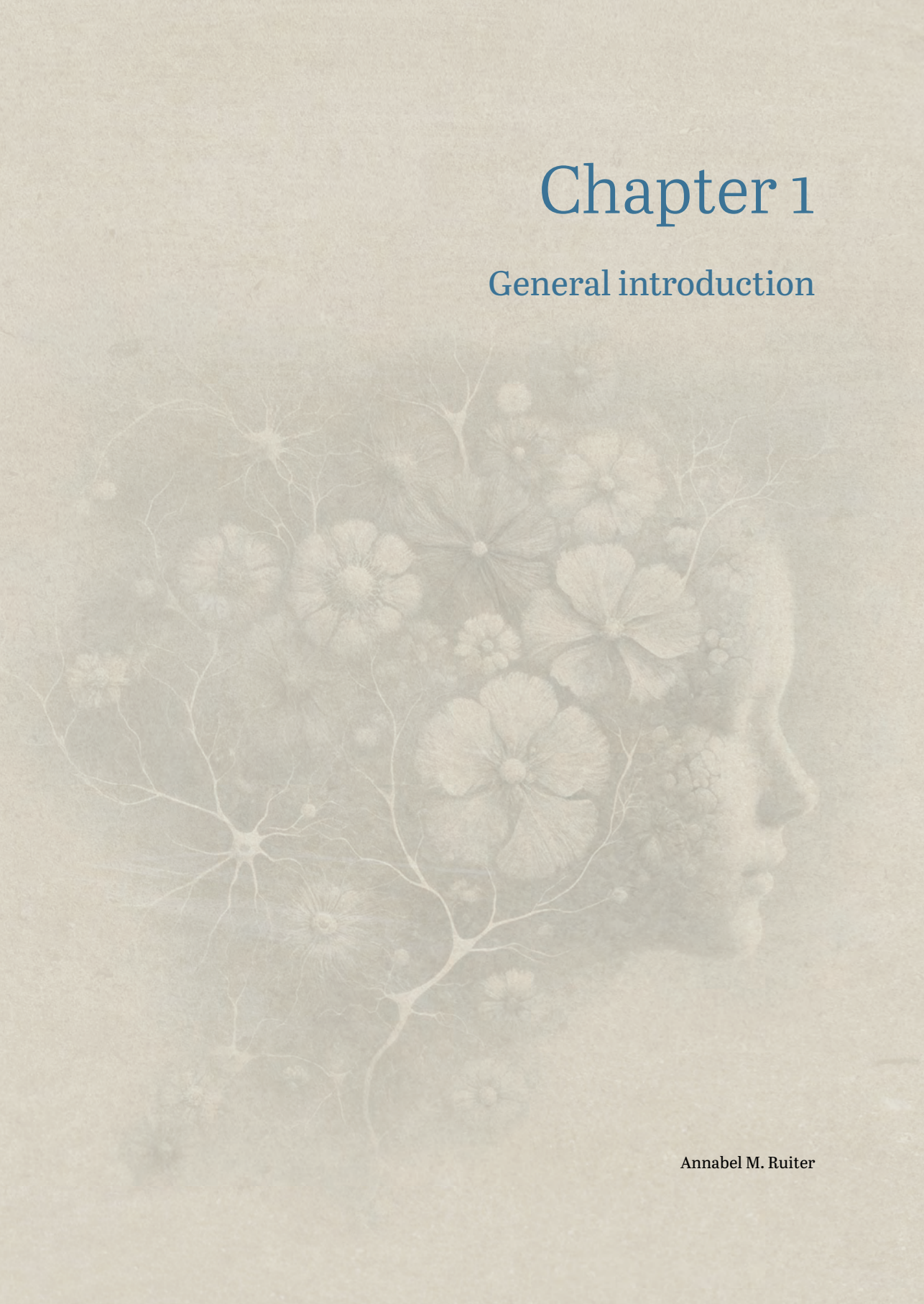
Chapter 1

General introduction



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General introduction and thesis outline

Introduction to myasthenia gravis: a clinical perspective

myasthenia gravis is one of the antibody-mediated autoimmune disorders of the neuromuscular junction (NMJ), the critical synapse where motor neurons communicate with skeletal muscle fibers. Dysfunction of this synaptic communication leads to the disease's hallmark symptoms: fluctuating and fatigable weakness of voluntary muscles. Although, the neuromuscular synapse occupies only 0.01% of the total surface area of a typical muscle fiber, the consequences of the autoimmune attack can be profound, affecting muscles throughout the body and significantly impacting a patient's quality of life.

The term myasthenia is derived from Greek, with *mys* meaning muscle and *astheneia* meaning weakness. *Gravis*, from Latin, means severe, reflecting the potentially life-threatening nature of the condition before the advent of modern therapies. The pathophysiology of myasthenia is rooted in an aberrant immune response. The body produces autoantibodies that target key proteins at the NMJ, disrupting neuromuscular transmission. Based on specific target antigens, the group of myasthenic disorders can be classified into several subtypes, each with distinct clinical and pathophysiological characteristics (table 1).

Table 1. Autoimmune myasthenic disorders.

Location	Name	Antibody target	Antibody frequency*
Presynaptic	LEMS	VGCC	85%
Synaptic	MG	agrin	<1%
Postsynaptic	MG	AChR	85%
Postsynaptic	MG	MuSK	1-10%
Postsynaptic	MG	Lrp4	~1%

Seronegative disorders are not included in table. *Frequencies are relative to either LEMS, or all forms of MG. Abbreviations: AChR = acetylcholine receptor; LEMS = Lambert Eaton myasthenic syndrome; Lrp4 = low-density lipoprotein receptor-related protein 4; MG = myasthenia gravis; MuSK = Muscle specific Kinase; VGCC = voltage-gated calcium channel

This thesis focused predominantly on the most common form of myasthenia gravis (MG), with antibodies against the acetylcholine receptor (AChR), and to a lesser extent on MG with antibodies against muscle-specific kinase (MuSK) and seronegative MG, where conventional antibodies are not detected.

Pathophysiological subtypes and their clinical correlates

approximately 85% of patients with generalized MG have detectable serum antibodies against the postsynaptic AChR[1, 2]. These polyclonal antibodies are predominantly of the IgG1 class. Some have IgG2 or IgG3 AChR antibodies, most often in combination with the presence of IgG1 antibodies[3]. IgM and IgA AChR antibodies have been detected in MG patients, but always in combination with IgG antibodies[3, 4].

These antibodies impair the neuromuscular transmission through three distinct mechanisms:

1. Steric hinderance of AChR functioning. By binding to the AChR, the antibodies directly block the binding of acetylcholine (ACh) or cause conformational changes in the AChR that hinder the activation of the AChR channel function.
2. Crosslinking of AChRs, leading to their internalization and degradation (antigenic modulation) and as a consequence a lower concentration of AChRs at the postsynaptic membrane.
3. Complement activation. The antibodies activate the complement cascade, causing destruction of the postsynaptic membrane and simplification of the junctional folds[5].

All three mechanism lead to a lower availability of well-functioning AChRs at the postsynaptic membrane.

The thymus gland plays a crucial role in the pathogenesis of AChR-MG; about 65% of patients exhibit thymic hyperplasia, and 10-15% have a thymoma (a tumour of the thymus)[5]. Thymectomy is therefore an important therapeutic consideration in AChR MG.

The second most common subtype, found in about 1-10% of MG patients (and up to 40% of those seronegative for AChR antibodies), is MuSK-MG[1, 2, 5]. MuSK is a receptor tyrosine kinase essential for the clustering and anchoring of AChRs at the NMJ during development and maintenance. The autoantibodies in MuSK-MG are typically of the IgG4 subclass[2]. Unlike IgG1, IgG4 does not activate complement but instead disrupts the interaction between MuSK and its co-activator, LRP4 (low-density lipoprotein receptor-related protein 4), which is critical for maintaining the structural integrity of the NMJ[1]. This leads to a reduction in AChR density and impaired synaptic function. Clinically, MuSK-MG often presents with more prominent bulbar (facial, pharyngeal, laryngeal) and respiratory muscle weakness, and muscle atrophy can be more common than in AChR-MG[2].

A small subset of patients has been found to have antibodies against LRP4[1]. These antibodies, similar to MuSK antibodies, interfere with the signaling that maintains AChR clustering. The clinical phenotype of LRP4-MG is generally milder than that of AChR- or MuSK-MG[6]. LRP4-Abs are more effective in inducing cellular FcR-mediated effector mechanisms, than

antibody-dependent complement activation. Their functional signature is likely to be different from AChR-specific antibodies[7].

In a few MG patients agrin antibodies have been found. Agrin antibodies were almost always detected in combination with antibodies against MuSK, LRP4, or AChRs, indicating a high incidence of autoantibodies against several neuromuscular proteins in the agrin-positive MG cases[8, 9].

A significant portion of the remaining patients are classified as 'seronegative' MG (SNMG), as they lack detectable antibodies using the currently available assays[10]. It is likely that other, yet-to-be-identified, antigens account for the remaining seronegative cases[1].

The clinical spectrum of myasthenia gravis

The clinical presentation of MG is highly variable, but its defining characteristic is muscle fatigability and weakness that worsens with repeated or sustained muscle activity and improves with rest[1]. This fluctuation is a direct consequence of the reduced neuromuscular transmission; with fewer functional AChRs, the synapse cannot sustain the high rate of signalling required for continuous muscle contraction[1].

The distribution of muscle weakness determines the clinical subtype. In approximately 15% of patients, weakness remains confined to the extraocular muscles, a condition known as ocular MG[1]. These patients typically present with fluctuating, often asymmetrical, ptosis (eyelid drooping) and diplopia (double vision). Symptoms typically worsen towards the end of the day, after prolonged reading, or in bright sunlight, but some patients experience profound weakness early after rising. In the majority of patients, the weakness becomes generalized within the first two years of onset, a condition known as generalized MG (gMG)[11, 12]. The pattern of weakness is characteristic, with a preference for certain muscle groups[12]. Bulbar muscles are frequently involved, leading to significant morbidity[12]. Facial weakness can result in a 'myasthenic snarl' on attempting to smile and an inability to close the eyes tightly. Weakness of the muscles of mastication causes difficulty in chewing. Pharyngeal and laryngeal muscle involvement leads to dysphagia (difficulty swallowing) and dysarthria, where speech becomes nasal, slurred, and quiet with prolonged talking[12]. Limb weakness is typically proximal and symmetrical, affecting the shoulders and hips more than the hands and feet[12]. Patients may struggle with activities such as combing their hair, climbing stairs, or rising from a chair. Neck extensor and flexor weakness is also common, which can lead to a 'dropped head syndrome', a disabling symptom where the patient is unable to hold their head up. The most feared complication is weakness of the respiratory muscles, primarily the diaphragm and intercostal muscles. This can lead to a myasthenic crisis, a

life-threatening state of respiratory failure requiring mechanical ventilation[1]. Crises are often precipitated by infections, surgery, or certain medications.

MG is a rare disease, with a prevalence of approximately 15-20 per 100,000 and an incidence of about 1-2 per million person-years, which translates to an estimated 3,000 patients in the Netherlands[2, 13, 14].

Clinical assessment and the need for objective measures

The diagnosis of MG relies on a combination of clinical history, physical examination, serological testing for autoantibodies, and electrophysiological studies like repetitive nerve stimulation (RNS) and single-fibre electromyography (SFEMG). Once diagnosed, monitoring disease severity and treatment response is crucial. Clinicians traditionally rely on standardized quantitative scoring systems, such as the Quantitative Myasthenia Gravis (QMG) score and the Myasthenia Gravis Activities of Daily Living (MG-ADL) profile.

The QMG score is a physician-administered scale that measures muscle strength across 13 items, including eye closure, chewing, swallowing, and limb strength[15]. While valuable, it has limitations: it is subject to inter-rater variability, can be time-consuming to perform, and requires a trained examiner. The MG-ADL is a patient-reported outcome measure assessing eight common symptoms, providing a subjective snapshot of the disease's impact[16]. While useful, it lacks the objective refinement to detect subtle changes. The assessment of facial and bulbar weakness, in particular, relies heavily on the subjective clinical judgement of the examiner. This subjectivity presents a challenge for both clinical trials and routine practice, creating a clear need for more objective, sensitive, and automated methods for quantifying weakness. The development of such tools, as explored in the second part of this thesis, could revolutionize how we monitor disease progression and treatment efficacy, particularly for key symptoms like facial weakness.

Disease burden beyond muscle weakness: the enigma of central fatigue

The primary therapeutic goal in MG is to manage muscle weakness and prevent life-threatening crises. This is achieved through a combination of symptomatic treatment with acetylcholinesterase inhibitors (e.g., pyridostigmine) and long-term immunomodulation with corticosteroids, steroid-sparing immunosuppressants (e.g., azathioprine, mycophenolate mofetil), and newer biologic agents targeting specific immune pathways.

Many patients, even those in pharmacological remission with minimal objective muscle weakness, continue to report a debilitating sense of fatigue. This fatigue is conceptually different from the peripheral, activity-induced muscle fatigability that defines MG[17, 18].

Patients describe it as a profound lack of energy, an overwhelming exhaustion, or a 'brain fog' that impairs their ability to sustain both physical and mental activities. This type of fatigue, termed central fatigue, is believed to originate from processes within the central nervous system, but the exact pathophysiology remains unknown[17, 19].

Central fatigue is a major contributor to the overall disease burden in MG, strongly associated with reduced quality of life, unemployment, and depressive symptoms[19]. Its prevalence is significantly higher in MG patients than in the general population, yet its pathophysiology remains poorly understood. Several hypotheses have been proposed, suggesting it may be a protective mechanism to prevent muscular overexertion or as a consequence of chronic systemic inflammation[17, 18].

Understanding the multifactorial nature of central fatigue is a critical frontier in MG research. It requires a comprehensive approach that considers not only disease severity but also psychosocial factors, sleep quality, physical activity levels, and potential biological underpinnings. This necessitates the use of large-scale patient cohorts and registries, such as the Dutch-Belgian myasthenia patient registry described in **Chapter 2**, to capture the full spectrum of the patient experience. Investigating the covariates, potential treatments, and underlying biomarkers of central fatigue, as undertaken in the first part of this thesis, is essential to address this profound unmet need and improve the care of individuals living with myasthenia gravis.

Thesis outlines

In **Chapter two** data is presented from the Dutch-Belgian myasthenia patient registry, 'het Nederlands-Belgisch Myasthenie Register'. It described the results of this patient-reported registry, complemented with physician-reported medical information. It provides an overview on the natural course of MG but also disease burden and comorbidity. Secondly, the accuracy of patient-reported data is discussed. This chapter gives a first glance on the magnitude of the impact of fatigue. **Chapter three** is a systematic review on central fatigue in MG. The aim of this study was to provide a complete overview of fatigue in MG. With a thorough literature search we attempted to summarize all aspects of fatigue. Apart from the strong relationship with disease severity, gender and depressive symptoms, it also provides evidence suggesting that fatigue may be treatable with psychological and/ or physical training programs. In **Chapter four** the aim was to study central fatigue in a large representative cohort of Dutch MG patients. For this study, an extensive online questionnaire was completed by 420 Dutch MG patients. In this cohort study we focused on several covariates with a potential influence on fatigue, including disease severity, gender, depressive symptoms, sleep quality and MG specific medication. Studies in other neuromuscular disorders found a beneficial effect of physical training on central fatigue[20, 21]. Therefore, we explored the relationship between the amount and degree of physical activities and central fatigue, as this has not been studied to this extent before in MG. Secondly, different coping styles and the influence on quality of life were assessed. In the final chapter of the first part of this thesis, **Chapter five**, the serum of 116 anti-AChR positive MG patients was examined in search of a potential circulating biomarker for fatigue. Due to the possible muscular origin of this potential biomarker, we studied 38 candidate serum biomarkers, including several myokines. In the discussion, a model for the pathophysiology of fatigue in myasthenia is proposed.

The second part of this thesis starts with **Chapter six**, in which we show averaged images of 52 patients with MG and 38 healthy controls while portraying several typical facial expressions. With these images we aimed to show that typical hallmarks of MG could be made visible and potentially detectable for automated quantification. **Chapter seven** is a cross-sectional study in which videos of 70 MG patients and 69 healthy controls were assessed by two different advanced computer techniques. For this study, all participants expressed an extensive set of standard facial expressions. The aims of this study were to 1) detect patterns of facial weakness, 2) to differentiate MG patients from controls without facial weakness and 3) to classify disease severity in MG patients. In this study two different techniques were used: facial recognition software and a 3D convolutional neural network (deep learning computer model).

Finally, **Chapter 8** provides a summary, general discussion and proposed future perspectives on central fatigue in MG and the use of advanced computer techniques for assessing facial weakness in MG.

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