Vaccinations in autoimmune myasthenia gravis

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Chapter 7

General discussion and future perspectives

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GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Within the neurological field there is a broad spectrum of autoimmune diseases that affect the central or the peripheral nervous system. This range includes disorders like autoimmune encephalitis up to autoimmune-mediated myopathies. In the case of an autoimmune disease, two problems can arise in the context of a vaccination: 1) The vaccine stimulates the immune system and thereby aggravates the pre-existing autoimmune disease. 2) The vaccine is less effective due to the often (necessary) use of immunosuppressive medication or due to the underlying immune dysregulation underlying the autoimmune disease. Another association between vaccination and autoimmune diseases is the occurrence of autoimmunity de novo after vaccination, such as Guillain-Barré syndrome or narcolepsy [1, 2]. This latter possibility is not a topic of this thesis and will not be discussed here.

Treatment with immunosuppressive medication makes patients more prone to infections. Therefore, they are eligible for prophylactic vaccinations, such as influenza vaccination. It is also known that infections can (temporarily) aggravate the symptoms of autoimmune diseases such as myasthenia gravis (MG) and multiple sclerosis (MS)[3, 4]. On the other hand, an adequate immune response to vaccination could be hampered by the dysregulation of the immune system which is evident from the development of autoimmunity or by the effect of the immunosuppressive medication on the immune system. This thesis discusses autoimmune mediated MG and the indication, effectiveness and safety of vaccinations for this condition.

Autoimmune mediated MG is the most well-known neuromuscular junction disorder [5]. It is the first neurological disorder that has been identified as an antibody-mediated disease [6]. The initial trigger for making the pathogenic acetylcholine receptor (AChR) antibodies, which cause MG, still has to be elucidated. AChR antibodies can be present long before clinical onset, as we described in chapter 2 of this thesis. This supports the idea that development of autoimmunity takes time and becomes evident when titres reach a critical threshold. Which triggers facilitate the increase of autoantibody titres are not known. As described in chapter 2, a possible contributing trigger for onset of clinical symptoms can be pregnancy. Vaccinations could also be a trigger, that was why we investigated two frequently used vaccines and found no immunological, neither humoral nor cellular, or clinical exacerbations.
Treatment of MG consists of symptomatic treatment with cholinesterase inhibitors, but immunosuppressants are also often required to adequately control the symptoms. A disadvantage of treatment with immunosuppressive medication is the increased risk of infections and a more serious course of infections. This is because of a decrease in the number of B and T cells or an immune system malfunction due to this medication (7, 8). Therefore, due to immunosuppressants the desired immune response, following a vaccination, can be elicited less efficiently. This applies to a greater extent for a primary immune response after a first vaccination than for a secondary response after a revaccination / booster. Corticosteroids, as well as azathioprine, or a combination thereof are widely used for the treatment of

MG. To illustrate the effect of immunosuppressive medication: from a daily dose of prednisolone of ≥10 mg, a person should be considered as immune compromised [8]. From a daily dose at 20 mg, a person can be classified as seriously immune compromised [7]. Eculizumab, a recent addition to the treatment options of MG, inhibits the formation of the terminal complement complex. The recommendation is to vaccinate for Neisseria meningitidis prior to the start of treatment, because the complement system is especially important for the immune response to this specific bacteria. In case of rituximab, another recently added treatment option for MG, a patient needs to complete any vaccination that is needed, 4 weeks prior to the treatment. This is because of the depletion of CD20+ B-cells by rituximab. Patients can't be vaccinated with live vaccines during, or in the months after treatment with rituximab. In chapters 4 and 6 we saw a clear effect of treatment with immunosuppressive medication, azathioprine in particular. In chapter 4 we describe that patients with immunosuppressive medication had a significantly lower pre and post titre compared to healthy controls, but their humoral response was still significant. In chapter 6, a significant effect on both the proliferative response as well as the number of B-cell subsets and NK cells was described. However, this azathioprine associated decrease in B-cell numbers had no impact on the IgG anti-tetanus response upon vaccination in our cohort.

Importantly, in the immunocompromised patient, the titre does not necessarily need to be as high as in healthy controls, as long as it falls within the range that is considered protective. It should be noted, however, that the height of the titre can influence the duration of the protection [8].

Vaccinations can prevent some infections or make the course less serious. The best known example is the annual influenza vaccination. This vaccination is recommended for a number of patient groups, including patients with an autoimmune disease or to patients with immunosuppressive medication. In addition, patients with immunosuppressive medication or an autoimmune disease also increasingly want to travel abroad, often also to regions for which vaccinations are recommended. Important points to consider, as a treating physician, are the effectiveness and safety of prophylactic vaccinations for this population. In this assessment, the indication and necessity of a vaccination also need to be taken into account. These can differ between vaccinations. Potential side effects, both local and a potential flare-up of the disease, must outweigh the benefits. There are currently no specific guidelines for vaccinations in patients with MG or other neurological autoimmune diseases.

Prior to the studies described in this thesis, little research on the effectiveness and safety of vaccinations in patients with autoimmune MG was performed. In the 60s and 70s, two studies on vaccinations in MG were reported. These studies were performed in light of the thymectomy that was introduced since recently at that time. The aim was to investigate the humoral response in thymectomized patients compared to healthy controls. Adner et al. included 48 MG patients and 21 healthy controls and used the vaccine for Pasteurella Pestis [9]. Kornfeld et al. included 38

MG patiens and 29 healthy controls and used the vaccine for typhus [10]. Both studies found an acceptable primary response, but Kornfeld et al. found a relatively less secondary response to a booster [9, 10]. They didn't investigate a possible effect of a vaccination on the disease symptoms. Nor did they obtain information on the effect of immunosuppressive medication, since this medication wasn't used yet in patients with MG. Furthermore, the influence of a vaccination on the pathological antibodies couldn't be investigated, as they weren't known at that time. In our studies in chapter 4 and 5 we do describe that there is no effect on the disease symptoms or pathological antibodies, but that there is an effect of immunosuppressive medication. A later conducted study investigated the titre of antibodies to diphtheria and tetanus in healthy controls, and in patients with SLE or MG [11]. No difference in the coverage ratio was found between these groups [11]. However, most of these patients were already vaccinated prior to onset of the disease. Neither effectiveness of the immune response to the vaccination nor the safety of a vaccination was studied prospectively. Usage of medication in the study population was not described.

Two other studies investigated the number of hospital admissions of MG patients in the period of the annual influenza vaccination [12, 13]. No increase of the number of admissions due to an exacerbation of the symptoms of MG was found [12, 13].

Aside from immunological and physician-reported clinical outcome measures, also patient-reported outcome measures are increasingly important tools. We validated a patient-reported questionnaire in Dutch during the tetanus study: the Dutch MG-QoL15 [14] (chapter 3). This makes it possible to monitor a patient, based on a patient-reported outcome score instead of a physician reported outcome score. This is important, because a physician can interpret good or improving scores on the QMG or MG composite (physician-reported), but this can differ from the health-related quality of life that a patient experience.

Tetanus revaccination in myasthenia gravis

As described in this thesis in chapter 4, we prospectively investigated the efficacy and safety of a tetanus revaccination in 50 AChR MG patients, 6 MuSK MG and 9 LEMS patients [15]. These patients had a 'stable disease' and used daily prednisolone dosages up to 30 milligrams, which could be combined with other immunosuppressive medication. Stable disease was defined as a stable dosage of immunosuppressive medication at least 3 months prior to the study and a maximum MGFA classification of 3 (mild severe MG). Our findings showed that the patients had an adequate humoral immune response, independently of the type of medication they used. Neither an increase of the pathological antibodies (AChR, MuSK, VGCC) nor a change of the clinical outcome measures was found.

We also investigated the cellular immune response to tetanus vaccination and found a lower pre and post vaccination stimulation index in patient with immunosuppressive medication compared to those without IM (chapter 6). Despite this, both groups reached a significant post vaccination response. Tetanus revaccination did not affect

cell counts of lymphocyte subpopulations and B- and T-cell differentiation stages. A preceding thymectomy showed no effect on lymphocyte compartments. However, immunosuppression, azathioprine in particular, was associated with strongly decreased natural killer (NK) cell and B-cell counts, but did not affect levels of anti-tetanus antibodies before or after revaccination. Therefore, a tetanus revaccination seems to be safe in a patient with (stable) MG.

Influenza vaccination in myasthenia gravis

As mentioned above, the annual influenza vaccination is recommended for patients with an autoimmune disease like MG or patients who use immunosuppressive medication. In our own experience and as described by others, patients with MG are concerned that this vaccination can give a exacerbation of their disease and, therefore, don't take the annual influenza vaccination [12]. This is most likely unnecessary, as there are indications from previous research that influenza vaccination can be effective in reducing (laboratory confirmed) influenza disease, hospital admissions and the risk of death, especially in vulnerable and elderly patients [16, 17]. Furthermore, we already reported that tetanus revaccination, as described in chapter 4, is safe and effective, and decided that providing evidence for the safety and efficacy of the influenza vaccination would be practical for both patient and clinician. In order to investigate this, we conducted a double-blind, placebo-controlled, randomized study in 47 patients with MG in the 2016-2017 influenza season [18] (chapter 5). Our study demonstrated an effective response comparable to healthy controls. Also, no clinical or immunological (AChR antibodies) exacerbation was found 4 weeks after vaccination. It was striking that patients even reported less frequently adverse reactions to the influenza vaccination than healthy controls [18]. Thus, the results of the tetanus and influenza vaccinations studies were very comparable.

Since we found that relatively little research is conducted in neurological autoimmune diseases and vaccinations, except for MS, it is interesting to compare our results with other groups of autoimmune diseases, MS, Guillain-Barré syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or rheumatoid arthritis (RA).

Multiple sclerosis

MS is the only neurological autoimmune disease in which a lot of vaccination research has been conducted and for which guidelines are published. In MS there are studies focusing on safety of vaccination by looking at the frequency of relapses or radiological changes of scans [19-25]. Vaccination with a live weakened yellow fever vaccine resulted in an increased relapse in a small study of seven patients [26]. However, the clinical relevance of this finding is probably limited, since vaccination with live attenuated vaccine is not recommended in patients taking immunosuppressive drugs, due to an increased risk of infection. Furthermore, there are studies that investigated the efficacy (the specific increase in titre) of vaccinations, mostly of influenza vaccination, during the use of immunosuppressive or immunomodulating medication. Several studies show that the frequency of

relapse or the radiological image of MS does not change due to a vaccination [19-25]. No adverse effect of teriflunomide (an NF-κB inhibitor) or interferon treatment on increase of the titre following influenza vaccination is described [24, 27]. Findings for natalizumab (monoclonal antibody against α4-integrin) and fingolimod (causing internalization of S1P receptors) are varying and often involve small studies, making it difficult to draw conclusions [19, 20, 22, 23, 25]. For fingolimod a larger placebo-controlled, randomized study reported that there is a lesser increase of titre after influenza vaccination, 3 and 6 weeks after vaccination (vaccinated 6 weeks after starting fingolimod), compared to healthy controls. For tetanus revaccination this only applies at 3 weeks, not at 6 weeks [19, 20]. In a small study (23 patients with natalizumab), Natalizumab does not appear to have a significant influence on the response to influenza [25]. A study published in 2018 found lower titres in patients who used natalizumab. However, only 8 patients used natalizumab in this study [28]. For glatiramer (a myelin basic protein analogue) and mitoxantrone (type II topoisomerase inhibitor), an influence on the increase of titres after influenza vaccination has been described [21, 22]. A later, observational study, on the other hand, found a good response to influenza, despite glatiramer use [29].

Hepatitis B, BCG, tetanus and varicella vaccinations do not seem to give an increased relapse rate [30, 31]. Vaccinations are recommended in a stable phase of the disease and preferably 4-6 weeks after a relapse. Tetanus vaccination is indicated in case of a wound after an outdoor accident. The influenza vaccination is recommended, because it is assumed that an influenza infection itself has greater adverse effects than the possible side effect of the vaccination itself [29]. A smaller increase of titre can still offer sufficient protection. An option is to determine the height of the titre. If the titre is too low, one can consider repeating the influenza vaccination. This principle can also be applied to other vaccinations.

Guillain-Barré syndrome and CIDP

Studies on vaccination in the Guillain-Barré syndrome (GBS) mostly investigate the incidence of a primary episode of GBS following a vaccination. There are two retrospective studies that investigated by questionnaires whether a new episode of GBS or an increase of symptoms occurred in CIDP patients after vaccinations. One of these studies found no relapse in the group with GBS-patients (n=106) after one or more influenza vaccinations (total 775 vaccinations in GBS-group) in the years after diagnosis. In the CIDP-group, 5 out of 24 patients who got an influenza vaccination after the diagnosis, reported an increase of symptoms after influenza vaccination [32]. The other study investigated the occurrence of relapse or an increase of symptoms by questionnaires and found a risk of 3.5% for the GBS patients and of 8% for the CIDP patients [30]. Overall, both studies reported a relative low risk. It is important to take a possible recall bias in account for both studies.

Inflammatory rheumatic conditions and vaccinations

For the group of inflammatory rheumatic disorders, more research on the efficacy and safety of vaccinations is conducted. The European League against Rheumatism

(EULAR) published recommendations for this group of patients [33]. They recommend to vaccinate patients in a stable phase of their disease. There are some small studies that included patients with mild to severe disease (activity), which found no increased risk for side effects or flares of the disease. However, based on a theoretical higher risk of flares, they recommend to vaccinate during stable disease. A distinction is made for the type of vaccination. Life-attenuated vaccines are discouraged in patients with immunosuppressive medication, because of the increased risk of conversion to an active infection. The question remains to what extent the dosage of the immunosuppressive medication relates to a higher risk. Based on the conducted studies, also it was stated that it can be necessary to repeat a vaccination in order to reach an adequate immune response [34]. The EULAR strongly advices to vaccinate patients for influenza, based on the increased risk of morbidity and mortality in case of an actual influenza infection or pneumonia in this population [33]. Finally, they conclude that it remains necessary to make the assessment per individual patient, based on the indication and necessity of the vaccination [33].

Conclusions and recommendations

Patients with AChR MG can make an effective immune response to tetanus revaccination and influenza vaccination, irrespective of their immunosuppressive medication. Immunosuppressive medication does cause a lower anti-tetanus pre and post titre in patients, compared to healthy controls. In case of influenza vaccination, immunosuppressive medication only influences the pre vaccination titre. Influenza vaccination and tetanus revaccination do neither result in an immunological exacerbation nor in any clinically significant exacerbation of symptoms of AChR MG. In case patients experience an increase of their MG symptoms, this increase is mild and of short duration.

Generalization of these results to other vaccinations can't be done with certainty. A tetanus vaccine can differ from other vaccines in immunogenicity. Also, a primary immune response to a vaccination can differ from a boost of the immune response with a recall antigen for which a patient already has memory B-cells [8]. However, an influenza or tetanus (re)vaccination in patients with MG neither cause an exacerbation of clinical symptoms nor an immunological exacerbation in patients with MG.

We suggest to provide an advice on vaccinations for the individual patient, based on the indication and necessity of a vaccination. Preferably vaccinate in a stable phase of the disease and advise against live attenuated vaccines in the immune compromised patient. Consider checking the efficacy of the immune response after vaccination, by measuring antibody titres. If necessary, the vaccination can be repeated in order to achieve an adequate, protective titre. At last, we recommend the influenza vaccine to all patients with an autoimmune disease or who use immunosuppressive medication, given the increased risk of morbidity and mortality in infections.

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