Vaccination in multiple sclerosis - Challenging practices (Review)

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Abstract. Infections are an ever-present problem in the medical community, even more so for patients with multiple sclerosis (MS), for whom these infections have been linked to relapses and neurological disabilities. Even though it was believed that MS can be caused by an infection, research does not support this theory. MS is a chronic inflammatory disease considered to be autoimmune. Vaccination is proven to be one of the most effective means to prevent infections, but still it is surrounded by controversy in the general populations, as well as in the MS group. Vaccines are generally considered safe for MS patients. The exceptions from this, which turn into contraindications, are a medical history of allergic reactions to one of the vaccine components and immunosuppressed patients in the particular case of live vaccines. Given the presumed autoimmunity of the disease, some medication for MS is immunosuppressive and any live vaccine should be administered before starting treatment. Although there is still confusion regarding this subject, the current guidelines have clearer recommendations about vaccinations in MS patients and especially in treated MS patients.

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Contents

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Approximately 2.2 million people worldwide are living with MS (1). Its etiology is presumably autoimmune and by stimulating the immune system, vaccination in MS patients is still a controversial subject. In the present study we reviewed whether infections in patients with MS are more frequent or more severe, if these infections influence the development of the disease and whether vaccination is safe and effective in untreated MS patients as well as treated patients. An ongoing dilemma in the neurology community is if patients in treatment with disease-modifying treatments (DMTs) can be safely immunized and if the vaccine effectiveness in the MS group compares to the one in the general population.

2. Mechanisms of MS

Despite recent advances regarding the understanding of this disease, the triggers of the autoimmune mechanism are still unclear. MS is characterized by the infiltration of the CNS with immune cells that target myelin basic protein (MBP) possibly because of similarities between MBP and microbial antigens. It is believed that the pathological mechanisms of MS are initiated by the activation of autoreactive CD4 T cells

that migrate into the CNS (2). In the CNS, autoreactive CD4 T cells are reactivated by antigen-presenting cells (APC) and recruit CD8 T cells, which become the majority T cells in the inflammatory lesions (3). In the early years of the disease, most patients experience acute neurological symptoms defined as relapses, which are divided in time by periods of remission.

Inflammation in the CNS is the mechanism through which these relapses occur. Over time, multiple episodes of inflammation lead to axonal loss and the disease becomes progressive without a remission stage. MS relapses can lead to increased short and long-term neurological dysfunction (4). Relapsing MS involves the travel of immune cells as CD4 T cells from the periphery into the CNS, whereas progressive MS features a compartmentalized immune reaction in the CNS along with an immune-independent mechanism (5). Although the peripheral adaptive immune system (T cells) is responsible for the relapses of MS, the innate immune system (microglia, astrocytes) together with B cells are responsible for progressive MS (5).

It was theorized that MS can be caused by a specific infection, but no such link or the infection itself has been found. Some studies incriminate an altered sequence of infections as the initial event in the immunological network that enhances the risk of MS, especially the infection with Epstein-Barr virus (EBV) in adulthood instead of childhood (6). However, evidence proves that infections trigger MS exacerbations, and prolonged neurological deficit leading to disease progression (7). After urinary, pulmonary, or intestinal infections, MS patients are more likely to present clinical relapses and new active lesions on MRI (8). It was demonstrated that patients in an MS relapse had higher odds of varicella-zoster virus (VZV) viral DNA present in CSF compared to MS patients in remission (9). One study found a link between influenza infections and MS exacerbations (10). Although hospitalization rates for the MS population have declined in recent years, they are still higher than those of the general population, and specifically, admissions for influenza are double in the MS group (11). One study suggested that there is a higher likelihood of MS exacerbations linked to infections to cause neurological disability, in contrast to relapses not associated with infection (7). Decreasing the infection rate in MS patients reduces the risk of relapses and consecutively improves the quality of life (12). Vaccination in patients with MS can prevent infections known to increase the risk of relapses (13). Although scarce, some case-control studies suggest that vaccination can lead to MS relapses (14).

3. Types of vaccines

Vaccination is one of the most important tools we have in the fight against infectious diseases. Vaccines are biological products that, much like infections, determine immune responses against pathogens, which hopefully leads to lasting protection. This protection is constituted by a fast and effective immune response to each exposure to the same pathogen. After being activated by the antigen in the vaccine, the APC presents it to the B cells and TH cells, which then interact and the result is that B cells transform into plasma cells that produce antibodies and the TH1 and TH2 start secreting cytokines (15). While B cells and antibodies prevent infections, the CD4 and CD8 T cells control and clear out the infections (16).

Since their discovery, until the present time, four types of vaccines have been developed: live attenuated, inactivated (whole cell), purified proteins or polysaccharides, and genetically engineered (17). The live vaccines contain a live pathogen that has been attenuated most often through serial cultivation like the bacilli Calmette-Guérin (BCG) vaccine (18). Other vaccines developed through the same technique are polio (oral), measles, mumps, rubella, influenza (nasal). In immune depressed individuals live vaccines are contraindicated because even an attenuated pathogen can cause disseminated disease in the absence of a normal functioning immune system.

Live vaccines are generally considered safe for untreated MS patients, but clinicians recommend against administering them to patients who receive immunosuppressive therapies (19). Inactivated vaccines like typhoid, cholera, hepatitis A, polio (injected), pertussis (whole cell), influenza (injected) contain the whole organism inactivated by heat or chemical treatment. The same process can be used for proteins like tetanus and diphtheria toxins and the resulted product is called a toxoid and is used in vaccines (20). The acellular pertussis vaccine contains proteins from the pertussis bacillus and has mostly replaced the whole-cell vaccine because of safety concerns. Haemophilus influenza type B, pneumococcal conjugate, and meningococcal conjugate vaccines contain purified capsule polysaccharides. The hepatitis B virus and human papillomavirus (HPV) vaccines are the most notable developed through genetic engineering. Live and attenuated vaccines are immunogenic and can activate antigen-presenting cells (APC), a characteristic that is missing for subcellular vaccines (21).

For an increased and sustained immune response vaccines contain adjuvants, which influence the titer, duration, isotype, and avidity of the antibodies, as well as mechanisms of cell-mediated immunity (22). The most commonly used adjuvants are aluminum salts, which are known activators of Th2 cells (23). Besides increasing immunogenicity, it is discussed that aluminum salts also induce autoimmunity (24). Although aluminum has known neurotoxic properties and in postmortem studies was found in high quantities in the brain and spinal cord of people with amyotrophic lateral sclerosis, the adverse reactions reported as provoked by the aluminum in vaccines are mild and local (25,26).

4. Safety of vaccination in patients with MS

In their analysis of the current literature, the French multiple sclerosis society found no evidence for an increased risk of MS after any vaccination (27). The American Academy of Neurology concluded in their 2019 practice guideline that there is not sufficient data to support or refute an association between the development of MS and a history of vaccination for diphtheria, hepatitis B, influenza, measles, mumps, measles-mumps-rubella, poliomyelitis, rubella, typhoid, yellow fever and VZV (19).

The controversy behind the hepatitis B vaccines in MS is based on the similarities between the S antigen and the MBP which could potentially induce autoimmunity through the mechanism of molecular mimicry (28). Despite this, the recombinant hepatitis B vaccine is considered one of the safest vaccines available and the evidence suggests that it does not play a role in the development of MS (29). A French paper that reported a causal link between hepatitis B vaccination and MS after the spike in MS cases following the mass vaccination

in 1994-1997 was criticized for the superficial analysis of the data from the French pharmacovigilance system (30). A couple of expert panels were assembled to review the same data, but could not find such a link (31,32). The HPV, Pertussis, and Tetanus vaccines are probably associated with a lower likelihood of developing MS (33,34). BCG vaccination is probably not associated with an increased likelihood of progression to MS in patients with the clinically isolated syndrome (35). There are reports on the effect of BCG vaccination in MS patients which suggests that the MRI disease activity decreased post-vaccination (36). Most studies regarding vaccination and MS were conducted on seasonal influenza, including a placebo-controlled randomized clinical trial which found no evidence of an increased risk of MS after the administration of the vaccine (37). Another study found that the number of autoreactive T cells against MPB did not increase consecutively to influenza vaccination (38). Although there are case reports of MS developing after vaccination, larger studies do not support this, including a case-control study with over 12,000 subjects determined that vaccination is not a risk factor for MS (39,40).

Regarding adjuvants, an investigation into autoimmune diseases following vaccination against influenza did not find a higher risk of autoimmune diseases following the administration of vaccines with adjuvants comparing to those without adjuvants (41). No study could prove any definitive long-term link between vaccines and MS, but a short-term link was suggested, within the first 30 days after immunization, given the fact that vaccines may accelerate the transition from subclinical to clinical disease (42).

The available evidence confirms that attenuated vaccines do not induce MS relapses (43). Although a link between most live vaccines and MS relapses does not exist, there is evidence that suggests that the yellow fever 17D vaccine strain may induce exacerbations in patients with MS (43,44). Thus, the yellow fever vaccine constitutes an exception and the vast majority of vaccines can be safely administered in untreated MS patients. As soon as MS is diagnosed, neurologists should get a complete history of vaccination from the patient and to update the vaccination schedule and administer the booster shots if needed before any DMT is administered (45).

5. Recommendations for vaccination in patients with MS who receive DMT

The current guidelines recommend DMT in the treatment of MS. DMT can modulate or suppress the immune system and through it, they can increase the risk of infections and the risk of an insufficient immune response to vaccination. In MS, IFN-β acts by balancing the pro-inflammatory and anti-inflammatory cytokines in the CNS and reducing the crossing of inflammatory cells through the blood-brain barrier (BBB) (46). The glatiramer acetate molecule is similar to the MBP and competes with it for the MHC II molecule on the immune cells (47). Dimethyl fumarate modulates the immune responses by reducing the migration of inflammatory cells through the BBB and protects cells against oxidative damage (48). Teriflunomide is an immunosuppressive drug that has anti-inflammatory properties and inhibits the proliferation of B and T cells (49). Fingolimod prevents the migration of lymphocytes and blocks them in the lymph nodes (50). Mitoxantrone suppresses the proliferation of macrophages, B and T cells by disrupting the synthesis of DNA (51). Natalizumab is a humanized monoclonal antibody against α4-integrin, a cellular adhesion molecule (46). Ocrelizumab humanized monoclonal antibody against CD20, depletes B cells, and is the first medication approved for the primary progressive form of MS (52). Alemtuzumab, another humanized monoclonal antibody against CD52, causes long-lasting depletion of B and T cells (46).

It is still unclear if MS alone increases the risk for vaccine-preventable diseases, but there is evidence that supports the claim that patients who receive DMT are more likely to have a greater risk of infection, in part because some medication has leukopenia as an adverse reaction (5). Older DMTs like interferon β and glatiramer acetate are not considered to be associated with an increased risk of infection. There are no safety concerns regarding the vaccination of patients treated with these agents. However, dimethyl fumarate, fingolimod, teriflunomide, mitoxantrone, natalizumab, alemtuzumab, ocrelizumab have all been associated with severe cases of vaccine-preventable infections, such as HBV and VZV (53-55).

Taking into consideration the known risk of exacerbations caused by influenza infections and the lack of evidence linking vaccination to relapses, for most MS patients benefits of influenza vaccination outweigh the risks (19). The inactivated injectable influenza vaccine is preferred to the live one, because of the risk of the latter of producing influenza (19). It is recommended that patients with MS are vaccinated for their benefit, as well as for the benefit of their community through herd immunity (56). The present recommendations advise that after the diagnostic the patient should be screened for vaccine-preventable infections and that any necessary vaccines should be administered as soon as possible, including an annual influenza vaccine (19). In patients treated with fingolimod or alemtuzumab, there may be a higher risk of warts and cervical dysplasia and to these patients, the recommendation of HPV vaccination can be considered (57).

There are no special contraindications for vaccination for patients with MS, the only exception regards live-attenuated vaccines, the consensus being that they are contraindicated for MS patients who receive immunosuppressing or immunomodulating treatment unless the risk of infection is high (19). In VZV negative patients treated with fingolimod, varicella vaccine can be taken into consideration, since complications from the natural infection may outweigh the risk of postvaccination adverse reactions (16). MS relapses are not a contraindication, but a reason to delay vaccination until remission (19). The prescribing information for fingolimod recommends avoiding live vaccines during treatment and 3 months after discontinuation (58). Teriflunomide is recommended to avoid live vaccines during treatment and 6 months after stopping the treatment (59). The recommendations for prescribing alemtuzumab advise against the administration of live vaccines 6 weeks before, during, and after recent treatment (16). The producer of ocrelizumab recommends against the administration of live vaccines 4 weeks before beginning treatment, respectively 2 weeks for other types of vaccines, during and after treatment, until B cell depletion has occurred (60).

There is a higher likelihood of an insufficient response to influenza vaccination in MS patients compared to controls (38). Concerning vaccination when receiving DMT, it is probable that patients treated with Interferon β do not have a lowered

protection after influenza vaccination compared to people without MS (61). IFN-β also has antiviral properties which may have a beneficial effect against the influenza virus (62). In contrast, patients treated with glatiramer acetate, fingolimod, teriflunomide, natalizumab, and mitoxantrone are likely to have reduced protection in response to the influenza vaccination (61,63). In patients with ocrelizumab, the vaccine response was effective but decreased after 12 weeks for influenza, tetanus, pneumococcus compared with untreated and interferon-beta treated MS. Patients treated with fingolimod may have a lower immune response to a tetanus toxoid booster after 3 weeks.

Given that the etiology of MS remains obscure, there is no means to prevent the disease from occurring. There is nevertheless hope that based on the theory that the displacement of the EBV infection from childhood to adulthood can enhance the risk of MS, the development of an EBV vaccine for administration in early childhood may prove to be useful for lowering the risk of MS in individuals, in other words preventing MS (6).

6. Conclusions

The local epidemiological context and the patient's preferences must be taken into account when discussing vaccination with MS patients, but the recommendations of the international neurology community must be the first criteria considered when making a decision. In the past, the lack of guidelines used to lead to confusion amongst neurologists as well as patients. Nowadays the situation has improved with the appearance of recommendations from both national and international scientific organizations. The current guidelines encourage the administration of vaccines to MS patients, except for live vaccines to patients treated with newer DMTs. However, in the future, more clinical studies should be performed regarding vaccination of MS patients and especially vaccination of people undergoing treatments with DMTs.

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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