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Immunization in Patients With Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammatory demyelination and some axonal damage. An overactive or dysfunctional immune response to self-antigen is believed to be the pathogenic mechanism and therefore the treatment of MS often involves immunosuppressive therapy. Because of altered immune function in patients with MS, questions arise about risk of infections in this population and the safety and efficacy of common immunizations. The risk of MS exacerbation with common infections and safety and efficacy of immunization are reviewed along with the available guidelines for use of vaccines in patients with MS.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammation mediated demyelination and also some axonal damage. An overactive or dysfunctional immune response to self-antigen is the presumed pathogenic mechanism, much like any other autoimmune disorder. Therefore, treatment of MS often involves immunosuppressive therapy. Because of altered immune function in patients with MS, questions arise about risk of infection in this population and the safety and efficacy of common immunizations.

Are Infections More Common in MS?

The traditional concepts of the pathophysiol-

ogy of MS include T-lymphocyte activation by an inciting antigen.¹ These activated T-cells induce an inflammatory cascade and cell-mediated attack of central nervous system myelin. More recent studies exploring the immunology of MS have found abnormalities in both T-lymphocytes and B-lymphocytes. Since abnormal cell-mediated and humoral immunity play a role in the pathogenesis of disease, there may be higher susceptibility to infections in MS patients. However, despite the immune dysregulation evident in patients with MS, immunity against common viral and bacterial infections appears to be preserved. The incidence of commonly occurring infectious diseases is not increased among MS patients.²⁻³ Howev-

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er, infection can trigger a relapse and it has been observed that there is increased incidence of clinical relapse in MS patients associated with infections.⁴⁻⁵ Therefore, immunization is important for MS patients not only to prevent an infectious illness, but also to potentially prevent MS relapses.

Can Vaccines Exacerbate MS Relapses?

There is a longstanding concern that immunization may trigger MS activity in much the same way that vaccines reportedly trigger other autoimmune diseases such as Guillain-Barre syndrome.⁶⁻⁸ Theoretically, by inducing a heightened immune response against live attenuated viruses (e.g. measles and varicella), inactive viruses (e.g. seasonal influenza and hepatitis A), or portions of viruses or bacteria (e.g. hepatitis B, HPV, and pneumococcus); vaccines might also induce an abnormal immune response against self-antigens. Hepatitis-B vaccine has been of particular concern and both new cases and relapses of MS have been reported following its administration.⁹ However, several epidemiologic studies have shown no relationship between the hepatitis B vaccine and either development of MS or MS relapses.¹⁰⁻¹² Another inactive virus vaccine with potential implications for MS patients, because of its widespread use, is the seasonal influenza vaccine. As with hepatitis B, there is no definite increase of either occurrence of MS or MS relapse following the flu vaccination. One randomized, double-blind, placebo controlled trial of influenza vaccine in MS patients found no significant differences in rates of relapse between those vaccinated and those receiving placebo.¹³ Another case-control study found no association between MS relapses and recent vaccinations for influenza, hepatitis B, or tetanus.¹⁴ The evidence is sparse regarding the risk of MS or MS relapse following immunization with live

attenuated viruses, such as varicella, measles, smallpox, yellow fever, polio, BCG, or intranasal influenza vaccine. Overall there does not appear to be a heightened risk, but there are no large controlled studies to support this observation.¹⁵⁻¹⁶

Are Vaccines Effective in MS?

Apart from the risk of MS or MS relapse from vaccination is the issue of vaccine efficacy in MS patients due to inherent immune system dysfunction. Few studies have investigated this question and there is insufficient evidence to make a determination.^{13,17} The antibody levels to viruses following vaccination are present in MS patients at similar levels to healthy subjects.¹⁵ This suggests that vaccination is likely as effective in MS patients.

How Does Immunosuppressive Therapy Affect Immunization in MS?

Since the advent of effective therapies in the last two decades, most MS patients are now treated with immunomodulatory agents such as interferon-beta or glatiramer acetate. A significant proportion of patients also receives one of the immunosuppressant medications such as corticosteroids, mitoxantrone, cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate. Some may also be treated with monoclonal antibodies such as natalizumab, alemtuzumab, or rituximab that are targeted against specific T-lymphocyte or B-lymphocyte antigens. There is a concern that immunosuppression or modulation induced by these therapies may potentially increase the risk of infection following the administration of a vaccine particularly a live vaccine. In general, all inactivated virus vaccines are considered safe and effective for patients receiving any of these therapies (see Table 1); however, the vaccine might need to be readministered after im-

Table 1 is compiled and adapted from the Centers for Disease Control website and the National MS Society website. Vaccine common brand names obtained from MICROMEDEX.

Vaccine & Common Brand Name(s)	Vaccine Type	Safe for MS patients on immunosuppressive therapy?*
MMR (measles/mumps/rubella)	Live attenuated	No
Oral Polio (OPV)	Live attenuated	No
Varicella (Zostavax [®] , Varivax [®])	Live attenuated	No
Inactive Polio Vaccine	Inactivated	YES
Inactive Influenza Vaccine (Fluarix [®])	Inactivated	YES
Influenza Nasal Vaccine (FluMist [®])	Live attenuated	No
Influenza A H1N1 2009 Monovalent Vaccine	Inactivated	YES
Influenza A H1N1 2009 Monovalent Vaccine, Live Intranasal	Live attenuated	No
Diphtheria/Tetanus/Pertussis (DTP, DTaP or dT, Tdap) (Adacel [®] , Boostrix [®] , Pediarix [®] , Daptacel [®] , Tripedia [®] , Infarix [®] , Pentacel [®] , Daptacel [®])	Toxoid	YES
Haemophilus influenza type B Hib (Hibirix [®] , ActHib [®] , PedVaxHib [®])	Component	YES
Hepatitis B (Recombivax-HB [®] , Engerix-B [®] , Twinrix [®])	Component	YES
Hepatitis A (Havrix [®] , Vaqta [®] , Twinrix [®])	Inactivated	YES
Pneumococcal vaccine (Pneumovax 23 [®] , Prevnar [®])	Component	YES
Meningococcal vaccine (Menactra [®] , Menveo [®])	Toxoid Conjugate	YES
Yellow Fever vaccine (Yf-Vax [®])	Live attenuated	No
Typhoid vaccine (Vivotif [®])	Live attenuated	No
Human Papilloma Virus (HPV) (Gardasil [®])	Component	YES
Tetanus Toxoid	Toxoid	YES
Rotavirus (Rotateq [®])	Live attenuated	No

*does not include patients taking monotherapy interferon-beta or glatiramer acetate who should be vaccinated as per CDC guidelines.

immune competence is restored. Live attenuated virus vaccines, on the other hand, portend a higher potential risk of infection and complication for patients on immunosuppressant medications including steroids.¹⁸ Therefore, in general, live attenuated vaccines are avoided in MS patients on chronic immunosuppressive therapy; however there is no

firm evidence to support this approach. Additionally, there is issue of effectiveness of common immunizations in MS patients receiving immunosuppressive therapy. The live attenuated virus vaccines are not as effective following periods of immunosuppression and should not be administered for three months following treatment with immuno-

suppressant medications. In contrast to concerns about decreased efficacy of live attenuated vaccines in immunosuppressed patients, immunomodulatory therapy with interferon or glatiramer acetate does not appear to interfere with efficacy of live vaccines and these vaccines are safe in patients on immunomodulatory therapy alone, without concomitant immunosuppressant medications.

Current Recommendations for Immunization in MS Patients

Based on available evidence, the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines has made some general recommendations. According to these, inactivated influenza vaccine, hepatitis B, varicella, tetanus, and other vaccines should be used per Centers for Disease Control (CDC) indication for these vaccines.¹⁹ The pneumococcal vaccine is indicated for patients with compromised pulmonary function, such as wheelchair-dependant or bed-bound patients, as these patients are more prone to pneumonia. There is a divided opinion regarding usefulness of influenza vaccine in patients with MS who otherwise do not meet the CDC indication criteria for flu vaccine. The panel recommends that the potential risks and benefits of vaccination in these cases should be discussed with the individual patient. However since the seasonal flu is quite common and can precipitate an exacerbation, it is appropriate to offer influenza immunization to all MS patients unless there are any contraindications. Similarly, deactivated H1N1 (Swine Flu) vaccine is generally indicated (per CDC guidelines) for persons aged 25-64 who have medical conditions that put them at higher risk for influenza-related complications. A person with advanced MS or someone with less severe disease with reduced pulmonary function is considered at risk for such complications and a good candidate for the de-activated H1N1

vaccine. For persons with less severe MS, the decision regarding H1N1 vaccine should be made in discussion with their physician and neurologist.

Conclusion

Overall, vaccines are safe and effective for patients with MS and should be offered to MS patient based on general CDC guidelines. For patients on immunosuppressant medications, live attenuated vaccines should be avoided while patients are on therapy and for three months after treatment. As the influenza season approaches, MS patients and their physicians should consider the influenza vaccine a safe and effective option unless there are specific contraindications.

References

1. Cohen JA. The future of multiple sclerosis treatment. *J Neurol Sci* 2009;277 Suppl 1:S55-S61.
2. Sibley WA, Foley JM. Infection and Immunization in Multiple Sclerosis. *Ann N Y Acad Sci* 1965;122:457-466.
3. Clinical viral infections and multiple sclerosis. *Lancet* 1985;2:165-66.
4. Andersen O, Lygner PE, Bergstrom T, Andersson M, Vahlne A. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. *J Neurol* 1993;240:417-422.
5. Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994;36 Suppl:S25-28.
6. Bakshi R, Graves MC. Guillain-Barre syndrome after combined tetanus-diphtheria toxoid vaccination. *J Neurol Sci* 1997;147:201-202.
7. Morris K, Rylance G. Guillain-Barre syndrome after measles, mumps, and rubella vaccine. *Lancet* 1994;343:60.
8. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome

- following vaccination in the National Influenza Immunization Program, United States, 1976--1977. *Am J Epidemiol* 1979;110:105-123.
9. Hernan MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004;63:838-842.
 10. Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344:327-332.
 11. DeStefano F, Verstraeten T, Chen RT. Hepatitis B vaccine and risk of multiple sclerosis. *Expert Rev Vaccines* 2002;1:461-466.
 12. Mikaeloff Y, Caridade G, Rossier M, Suissa S, Tardieu M. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Arch Pediatr Adolesc Med* 2007;161:1176-1182.
 13. Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology* 1997;48:312-314.
 14. Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. *N Engl J Med* 2001;344:319-326.
 15. Ross RT, Nicolle LE, Cheang M. The varicella zoster virus: a pilot trial of a potential therapeutic agent in multiple sclerosis. *J Clin Epidemiol* 1997;50:63-68.
 16. Ono F. Possible relation of small pox vaccination to multiple sclerosis-like disease. A personal note. *Med Hypotheses* 1986;20:339-340.
 17. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. *Mult Scler* 1997;3:243-247.
 18. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55:1-48.
 19. Rutschmann OT, McCrory DC, Matchar DB. Immunization and MS: a summary of published evidence and recommendations. *Neurology* 2002;59:1837-1843.
 20. MS Society website: <http://www.nationalmssociety.org/living-with-multiple-sclerosis/healthy-living/vaccinations/index.aspx>
 21. CDC website: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm> and <http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm>

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