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Management of Multiple Sclerosis Patients in Special Conditions

Özel Durumlarda Multipl Skleroz'lu Hastaya Yaklaşım

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Summary

Multiple sclerosis (MS) is an immune mediated chronic inflammatory disease characterized by neuroinflammation and neurodegeneration of the central nervous system (CNS). The course and treatment of the disease are the most common questions asked by patients with MS. Questions concerning the relationship of MS with pregnancy and the postpartum period, assisted reproduction technology, pre and post-operative problems and vaccines are also frequently asked, and some of the answers are still controversial. It is known that MS has no harmful effect on pregnancy or the fetus. The presence of MS is not an indication to terminate pregnancy, and disease progression is not found to be related with pregnancy. The relapses during pregnancy are known to have a mild course but on the contrary, the relapses during the postpartum period tend to be particularly severe. It is suggested to stop taking disease modifying therapies (DMT) at least one month prior to the pregnancy planning period. There is no contraindication for the use of conventional contraceptives; however it is known that oral contraceptives increase the risk of venous thromboembolism in MS patients with impaired mobility. Patients with decreased fertility and who are candidates for assisted reproduction technologies (ART) should be informed about the increased risk of relapse. It is also shown that procedures under spinal anesthesia increase the risk of relapse, so general anesthesia may be an alternative in MS patients. Cautious titration of anesthetic drugs, continuous monitoring and using the lowest possible effective dose are the treatment principles. Except for hepatitis B there are no adequate published data about vaccines that cause CNS demyelination. In this paper, we discuss how to approach the above mentioned particular issues in MS patients. *(Turkish Journal of Neurology 2013; 19:77-84)*

Key Words: Multiple sclerosis, pregnancy, fertilization, anesthetics, vaccines

Özet

Multipl skleroz (MS) santral sinir sisteminde (SSS) nöroinflamasyon ve nörodejenerasyonla giden, immün kökenli, kronik inflamatuvar bir hastalıktır. Multipl skleroz'lu hastaların en sık sorduğu sorular hastalığın seyri ve tedavisiyle ilgilidir. Bu iki ana sorunun dışında, MS'de gebeliğin ve postpartum dönemin hastalıkla ilişkisi, yardımcı üreme teknikleri, pre-postoperatif sorunlar ve aşıların kullanımı gibi sık karşılaşılan ve bazılarının cevabı hala tartışmalı olan konular bulunmaktadır. Multipl skleroz'un gebelik ve fetus üzerinde zararlı etkisinin olmadığı, MS nedeniyle gebeliği sonlandırmanın gerekmediği ve gebeliğin hastalık progresyonunu etkilemediği düşünülmektedir. Gebelik süresince olan atakların daha hafif seyrettiği, postpartum dönemde oluşan atakların ise daha ciddi olduğu bildirilmiştir. Hastalık düzenleyici tedaviler ile ilgili olarak günümüzde önerilen; gebelik planlama sürecinde en az bir ay öncesinde ilaçların kesilmesi yönündedir. Konvansiyonel kontraseptiflerin kullanımına ait kontrendikasyon bulunmamakla birlikte, oral kontraseptiflerin MS'li ve mobilitesi azalmış hastalarda venöz tromboemboli riskini arttırdığı bilinmelidir. Yardımcı üreme tekniklerine (YÜT) aday MS hastaları; YÜT'ün atak riskinde olası artışa neden olabileceği konusunda bilgilendirilmelidir. Spinal anestezi ile yapılan işlemler sonrasında hastalarda atak sıklığının arttığı gösterilmiştir, bu nedenle MS'li hastalarda spinal anesteziden ziyade genel anestezi tercih edilmelidir. Dikkatli anestetik madde titrasyonu, sürekli monitorizasyon ve en düşük gerekli dozu kullanmak tedavi prensipleridir. Hepatit B dışında santral sinir sistemi demiyelinizasyonunda risk faktörü olabilecek diğer aşılar için yayınlanmış araştırma sayısı çok azdır. Bu yazıda yukarda sözü edilen özel durumlarda MS'li hastalara yaklaşımı ve halen tartışmalı olan ve cevap bekleyen bazı soruları ele aldık. *(Türk Nöroloji Dergisi 2013; 19:77-84)*

Anahtar Kelimeler: Multipl Skleroz, gebelik, fertilizasyon, anestezi, aşılar

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Introduction

Multiple sclerosis (MS) is an immune mediated chronic inflammatory disease characterized by neuroinflammation and neurodegeneration of the central nervous system (CNS). The disease is characterized by focal inflamatory-demyelinating lesions affecting the cortex, deep gray matter and especially white matter. The demyelinization due to the disease and the subsequent axonal degeneration accounts for the neurological impairment associated with MS (1). In this paper we reviewed the commonly discussed and controversial issues regarding the relationship between the disease to pregnancy and postpartum stage, assisted reproduction techniques (ART), pre-postoperative issues and the use of injections.

Pregnancy and Multiple Sclerosis

The fact that two in every three patients with MS are fertile women of childbearing age and that the disease starting in pregnancy in 10% of the cases motivated years of research and debate on the effects of pregnancy on MS. Through the end of 1950's, based solely on case reports and limited retrospective studies, the patients were advised against pregnancy due to the belief that the prognosis of the disease will worsen. A meta-analysis of case reports made by Douglas and Jorgensen in 1948 showed for the first time that MS has no negative effects on pregnancy and fetus, and contrary to the previous beliefs, MS does not necessitate the termination of pregnancy (2). Similarly, a study by Tilman in 1950, which used 52 pregnant women showed that the number of attacks does not differ significantly between pregnant people with MS as compared to those who are not pregnant (3). Many others were conducted following these studies, but they failed to gain traction because they did not meet the newly established criteria for MS (2,4). The first study that used the established diagnostic criteria for the disease and the attacks was done by Lubetzki and his colleagues and compared the first three trimesters to 6 months postpartum in 338 female patients. This study showed that the frequency of attacks decreased in the third trimester while they increased in the postpartum stage (5).

The first multicenter prospective study on the progression of MS in pregnant women is PRIMS (The Pregnancy in Multiple Sclerosis study). Confavreux and his colleagues monitored 254 MS cases presenting with relapses between June 1993 and July 1995. The results showed a 70% decrease in attack frequency during the third trimester as compared to one year before pregnancy. During the first 3 months postpartum, however, the frequency increased by 70% as compared to the state before pregnancy. This result was attributed to immunosuppression during the third trimester and immune reactivation during the postpartum stage. Another important finding of this study stated that the disease progression is not affected by pregnancy, when the year before pregnancy, the pregnancy period and the year after pregnancy were considered altogether. After monitoring the patients in PRIMS study for 2 years Vukusic and colleagues showed that the patients who had a more severe disease activity before pregnancy and higher rates of attacks during pregnancy also had higher rates of attacks during postpartum. Breastfeeding and epidural anesthetics were not found to have significant effects on the disease prognosis in this group which was monitored for two years (6).

The Severity of Attacks during Pregnancy and Postpartum

There is a limited number of studies investigating the severity of attacks during pregnancy. Roullet and colleagues monitored 125 female patients for 10 years and made comparisons with a control group. It was reported that the attacks during pregnancy have a milder amplitude and inflict minimal damage while the ones during postpartum are more severe. An increase exceeding one point in the Expanded Disability Status Scale (EDSS) scale was considered as the criterion for attack severity in these patients. Eight patients in this ten-year-follow-up study converted to progressive phase (7).

Pathophysiology

Considering the immune mechanisms thought to be responsible for MS, it is possible to expect a positive influence from pregnancy. In a physiological context, there exists a balance between T helper cell subgroups in the organism. The Th1 response is a cellular immune component that is responsible from tissue rejection while Th2 responses drive the humeral immunity and the secretion of anti-inflammatory cytokines. During pregnancy, the cytokines produced by feto-placental structure cause a down-regulation of the cytokines mediating the cellular immune system, which are produced by the mother. As a result, pregnancy is characterized by reduced cellular immunity, increased humeral immunity and a shift of balance between Th1 and Th2 towards the latter. On the other hand, childbirth is associated with the reversal of this balance to a certain extent, meaning the Th1 response becoming more dominant. This view can potentially explain the decreased rate of attacks during pregnancy in patients with MS and the increased rate of attacks after the delivery (6).

Another important point is the sex steroids. Sex steroid (estrogen or progesterone) levels are elevated during pregnancy and they decrease markedly during childbirth (8). Sex steroids were found to be protective against or restorative for experimental allergic encephalomyelitis in animal experiments (9). In addition, sex steroids were shown to have a positive effect on Th1-Th2 balance in in-vitro studies on and that progesterone increases remyelination and protects myelin sheaths in at least the peripheral nervous system. Progesterone's role in central nervous system is still largely unknown (10).

Treatment of Multiple Sclerosis during Pregnancy

Disease Modifying Therapies (DMT)

It is advised that disease modifying therapies which decrease the attack frequency by 30% (interferon β [IFNβ] or glatiramer acetate) should be stopped before the pregnancy in the cases of relapsing-remitting multiple sclerosis (RRMS). There is limited data on the use of interferon β and glatiramer acetate over the course of pregnancy. Animal models and the findings from 13 RRMS patients in the literature suggest no adverse effects associated with glatiramer acetate use during pregnancy (11). Even though the long-term effects were not reported, IFN also had no significant adverse effects during the early months of pregnancy. In a retrospective study patients who used IFNβ1a during the first two weeks of pregnancy were compared to those who stopped using before pregnancy and the rate of miscarriage was found to be higher in the group that uses the treatment (12). However, it should be noted that this difference was not statistically significant and that the study was not randomized. In another study, a group that stopped treatment 4 weeks before the pregnancy was compared to a group that consisted of 388 MS patients who used IFNβ1b for the first four weeks of pregnancy and no significant difference was found between the two groups in terms of fetal anomalies and risk of miscarriage (13). The same study also reported lower average birth weight, a higher rate of premature births and an increased rate of Caesarian section, even though these differences were not statistically significant.

Contemporary approaches to disease modifying therapies encourage the cessation of treatment during the planning process (at least one month before) for the pregnancy (14). Even though there is insufficient evidence for the risks of DMT during early pregnancy, many physicians in clinical practice debate the risks of recurrence when the treatment is stopped. This debate carries more weight especially for the patients who have a history of frequent attacks and those who are still in active stages of the disease (Table 1).

Table 1. The risk categories of Disease Modifying Therapies (DMT) during pregnancy

	A	B	C	D	X
Avonex			+		
Betaferon			+		
Rebif			+		
Copaxone		+			

Category A: Controlled studies showed no harmful effects of the drug on the fetus during the first trimester. There is no data for the safety of the drug after that time. These are the safest drugs during pregnancy.

Category B: Pregnant women can use them when necessary.

Category C: Insufficient clinical experience with pregnant populations. Treating physician should recommend use only if he/she concludes the potential benefits outweigh the potential harms on the fetus.

Category D: The harmful effect of the drug on the fetus has been shown. The drug should only be used if the mother and the fetus will experience a more serious harm without the drug. The pros and cons should be assessed carefully and the mother should be thoroughly informed about the potential risks.

Category X: Animal experiments and studies with pregnant women documented the harmful effects of the drug on the fetus. Further, the benefits of this drug on the mother's health are insignificant compared to its harm on the fetus. The drugs in the Category X are contraindicated for pregnant women.

Another option for the patients who are irresponsive to disease modifying treatments or those who have aggressive cases of MS is the natalizumab, which is an 4 integrin antagonist. Due to the insufficiency of the evidence for the safety of natalizumab's use in pregnancy, the patients who undergo this treatment were advice to use contraception during the course of treatment, and termination of the treatment 3 months before the planned pregnancy. In a study that included 35 women who were unaware of their pregnancy while they were still using natalizumab, 5 patients had miscarriage (5/35; 14.3%), one patient chose termination of pregnancy, 5 patients had vaginal births and 14 patients had C-sections. Twenty-eight babies were born healthy and one baby was born with hexadactyly. The group that received natalizumab treatment did not differ significantly from the control group in terms of attack frequencies during pregnancy and the postpartum stage (15).

The suggested course of action for Fingolimod, the primary oral agent in MS treatment, is the termination of use at 2 months before conception. Azathioprine was not found to be associated with increased congenital malformation and it is relatively safe during pregnancy. Methotrexate, on the other hand, should never be used during pregnancy due to the risks of miscarriage and congenital malformation (14).

Treatment of Attacks During Pregnancy

The first choice in the treatment of attacks in MS is high doses of corticosteroids. Even though it is known that corticosteroids permeate placenta, large portions of prednisolone and hydrocortisone are converted to more active metabolites by the placental syncytiotrophoblasts, which decreases the fetal steroid concentration to 10% of the mother's (16). There are no reports of prematurity or low birth weight due to steroid use. However, it should be noted that steroids may cause neonatal orofacial malformations and, to a lesser extent, fetal adrenal suppression during the first hours after birth (16, 17).

Treatment of Postpartum Attacks

While postpartum stage attacks are more frequently seen in 1/3rd of MS patients, the treatment protocol is not clearly defined. The populations that are under relatively increased risk for postpartum attacks, namely the patients that high disease activity before or during pregnancy, can be started on IFNβ, glatiramer acetate or natalizumab treatment during the postpartum stage. Another approach is to start on high dosage steroid administration for 3-5 days to alleviate the increased attack frequency manifested during the first 4 postpartum weeks (5). The strategy that we employ in our daily practice is based on close monitoring of the patient.

Breastfeeding

The effect of breastfeeding on postpartum effects is still a matter of debate. It was shown that breastfeeding stabilizes IFNβ-producing CD4+ T cells in patients with RRMS, which showed, hypothetically, that proinflammatory response diminishes in RRMS during the nursing period and thus the attack frequency may decrease (18). Two studies done in 2009 showed that women with MS who breastfed at least for 2 months had a decreased frequency of attacks (18,19). A large-scale prospective study done in 2010 showed that the attack frequency increased in women who breastfed for less than 2 months during postpartum stage or did not breastfeed at all, although the difference failed to reach statistical significance.

The mothers are generally advised to breastfeed based on the current evidence with the exception of women with high disease activity before pregnancy who are required to start DMT right after the birth, making them unable to breastfeed (20).

Contraception, Preconception and Inheritance

There are no known contraindications for the use of conventional contraceptive methods in patients with MS. Even though it is difficult to show any possible benefits of estrogen and progesterone contained in combined oral contraceptives using cohort studies, it is possible to argue that they are both beneficial for MS in theory. It was shown that estrogen is associated with Th-2 type immune response and reduces microglial activity (21). Clinicians should be reminded that the agents used in MS and those that induce P450 decreases the activity of contraceptives (e.g. carbamazepine which is used in pain and spasticity). In addition, it was known that oral contraceptives may increase the risk of thromboembolism in MS patients with decreased mobility (15).

Even though MS does not affect fertility, symptoms like sexual dysfunction and decreased libido are seen in 50-90% of the patients with MS and may affect conception (22).

The most common question asked by MS patients planning pregnancy is the hereditary properties of the disease. There are currently no prenatal tests for inheritance of MS. Multiple sclerosis is possibly an epigenetic condition described by over 70 genetic loci. Inheritance is a function of many genetic and environmental factors. Among such factors are the month of birth, which determines the exposure to sunlight in infancy, the mother's MS type, the gene responding to vitamin D, certain infective agents and the gender of the patient. The likelihood of MS in a child given birth by a mother with MS is reported as 3-5%. This number indicates a risk 10 times higher than the general population (23). The risk of developing MS is 28.4% in monozygotic twins whereas it is 5.6% in dizygotic twins (24).

Multiple Sclerosis and Assisted Reproduction Technologies

The failure in conceiving after practicing unprotected sex regularly for a year is called "infertility". There has been many methods for treatment. Many factors such as the patient's age, etiology and the duration of the infertility should guide the selection of best treatment.

The incidence rate of infertility is at the same level as the healthy population. However, it is known that the MS patients are often willing to seek assisted reproduction technologies (ART) due to a failure in conceiving (25).

Endometriosis, bilateral tube occlusion or sperm deficiency are among many causes of infertility in patients with MS. Assisted reproduction technologies typically include hormone treatments such as gonadotropin releasing hormone (GnRH) agonists and antagonists, follicle stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (hCG) and progesterone (26).

In vitro fertilization (IVF) is the process of fusing the sperm and oocyte cells in a culture medium in order to form the embryos that will later be transferred to mother's womb. This technique is employed in cases where the infertility is due to severe sperm disorders, tube occlusions, or low egg count. Michel and colleagues conducted the largest cohort analysis to date on the risk of IVF induced relapse in 32 MS patients. This study reported a statistically significant increase in the relapse rate following IVF, and that this increase can partially be explained both by a failure in IVF and the use of GnRH agonists. It is known that gonadotropin releasing hormone agonists may exert a direct influence on the proliferation of B and T cells and trigger gene transcription, adhesion and chemotaxis. Jacobson and colleagues reported that GnRH causes an exacerbation of the disease in the mice that are susceptible for lupus and that GnRH antagonists provided a statistically significant beneficial outcome in survival. It is known that GnRH directly stimulates the immune system, which can partially account for the increased risk of relapse in patients who receive GnRH agonist treatment. On the other hand, the study by Michele and colleagues also emphasize that the group which received the GnRH antagonist treatment had shown lower rates of pregnancy and childbirth, and that this decrease can lead to an increased risk for relapse (25).

Hellwig and colleagues reported that duration between ART cycles and the type of hormone used had no meaningful effects on the relapse rate in MS patients using artificial insemination, ICSI or IVF (27,28). As the possible causes for the increase in attack rate, the same author highlighted the reduced estrogen levels during hormonal stimulation, temporary interruption of immunomodulatory treatments and the stressful state induced by ART (27).

The MS patients who have are affected with low fertility and who are candidates for ART should be advised for the increased risk

of attacks that ART may cause. The patients should be cognizant of the fact that the relapse risk of MS following IVF would be higher, especially if it fails.

Anesthesia in Pregnant women with Multiple Sclerosis

A study by National Multiple Sclerosis Society (NMSS) compared the attack frequencies of women who used epidural to those who had general anesthesia and did not find a meaningful difference. Following the spinal anesthesia, on the other hand, the patients had higher rates of attacks. Therefore spinal anesthesia should not be used in patients with MS (29).

Anesthesia and Multiple Sclerosis

Peri-operative stress and anesthesia usually increases the rate of attacks in patients with MS. In the pre-operative stage, the patients should be informed about the increased risk of attacks. It is possible to attribute the high rates of post-operative attacks to recent infections, emotional lability and hyperpyrexia rather than the anesthesia itself (30).

Pre-Operative Stage

Multiple sclerosis presents with demyelination in different places of the CNS. This demyelination causes sluggish transmission in the affected neural paths. Lesions involving medulla oblongata or cervical/thoraxic spinal cord may affect respiratory functions. Motor functioning is typically impaired and despite the total lung volume and the vital capacity remains normal, the maximal inspiratory and expiratory volumes are generally decreased. This decrease can be as high as 50% in some patients. This involvement highlights the importance of preoxygenation in the state of decreased functional residual capacity and during anesthesia induction. Cases with pulmonary findings caused by diaphragm paralysis due to cervical cord lesions have been reported. In such cases, the central control of ventilation and the response to increased CO2 pressure is impaired. Some views suggest the application of pulmonary function tests and artery blood gas test to assess the severity of this dysfunction in the pre-operative stage. Another view asserts that these tests are not necessary as long as the patient is capable of coughing out pulmonary secretions or perform deep inhalation. It should be noted that the cranial nervous involvement may lead to an increased risk for chronic aspiration due to impaired pharyngeal and laryngeal muscle control (30).

Upper thoracic spinal cord lesions may affect autonomic nervous system, leading to varying degrees of hemodynamic instability in the peri-operative stage. Serious cases of hypotension have been reported following local anesthesia by applying sympathetic blockage. The presence of syncope, impotence, sphincter-colon dysfunction, vasomotor instability and orthostatic hypotension should be clinically indicative of autonomic dysfunction in the peri-operative stage.

The patient's medicine use should be under close scrutiny and additional steroid treatment should be started in the peri-operative stage to prevent adrenal imbalance if steroids were recently being used. It should be noted that chronic use of steroids can cause muscle damage and osteoporosis, and therefore lead to positioning difficulties during surgery. Baclofen, used for spasticity, causes muscle weakness and increased sensitivity to non-depolarizing muscle relaxants. Cyclophosphamide users should be cautious of pancytopenia, pulmonary fibrosis and myocarditis (30,31).

Since the emotional state of the patient is another important factor that increases the attack frequency in MS, anxiolytic treatment is recommended prior to the operation for the patients who need surgery urgently (31).

The Operation Stage

Local anesthesia is not commonly preferred for patients with MS. Possibly due to the increased sensitivity of the demyelinated neurons to the neurotoxic effects of the local anesthetics, an increase in the attack rate during the post-operative stage has been reported in patients who were administered spinal anesthesia. Epidural anesthesia is seemingly less risky because the anesthetic matter permeates through the intrathecal area in smaller amounts compared to spinal anesthesia. The attacks reported following epidural anesthesia can be related to anesthetic agents of high concentration (such as bupivacaine). Due to the small number of case studies involving epidural anesthesia, it is not possible to reach a definitive conclusion for the reliability of these findings (30).

General anesthesia has been shown to be associated with exacerbations in MS. There is insufficient evidence for the preference for intravenous or inhaled anesthetics. On the other hand, caution must be taken when neuromuscular-blocking agents are being used. Succinylcholine causes hyperkalemia by increasing intracellular potassium secretion. Hyperkalemia, as a result, may lead to muscle denervation and cardiac arrest. The patients with lesions involving only the motor nucleus are under increased risk for hyperkalemia. For this reason, succinylcholine should not be used in patients with MS. The use of non-depolarizing muscle relaxants also present certain difficulties. The variety of their pharmacodynamics effects and their interaction with MS medicine may cause important problems in the use of anesthesia. Careful titration, close monitoring and the smallest necessary dose should constitute the principles of treatment (30).

It was seen that an increase in temperature decreases the speed of transmission in demyelinated nerve fibers. This is thought to be one of the leading causes for the attacks. The peri-operative hyperpyrexia is possibly responsible for the post-operative exacerbation (30,31).

Post-operative Problems

Patients with MS should be monitored closely in the post-operative stage. Increased body temperature should be treated promptly. Blood pressure fluctuations due to autonomic dysfunction

are possible due. The patients with bulbar and respiratory involvement are especially more susceptible to problems such as airway constriction, hypoventilation and atelectasis. In addition to these, residual neuromuscular blokage may present more severely in patients with MS compared to others.

Deep vein thrombosis is another problem that should be keep under close surveillance in patients with MS during post-operative stage. The incidence rate of venous thrombosis was recorded as 43.9% in 132 late stage MS patients. Anticoagulants, compression socks, periodic external compression and early ambulation following surgery are recommended for the deep vein thrombosis prophylaxis (32).

Multiple Sclerosis and Vaccinations

Even though the direct or indirect pathogenic roles of many infectious agents are still being debated, MS exacerbations during infection period have been shown and vaccination can prevent these infections. However, there have been many questions especially regarding the increased risk for attacks following vaccinations (33). In terms of case studies, there has been evidence suggesting a relationship between hepatitis B vaccination and the increased frequency of attacks (34). There are also some reports on influenza and other vaccinations (34). It may not be the right approach to draw conclusions based only on case studies since the temporal relationship between vaccinations and the attacks may be coincidental and not necessarily be causal (36). There has been a very small number of research on vaccinations what can cause central nervous system demyelination except for hepatitis B.

In the first comprehensive study by Confavreux and colleagues in 2001, tetanus, hepatitis B and influenza vaccinations were not found to be associated with an increased risk of attacks in the short term (37). DeStefano's study in 2003 showed no increased risk for the MS or optical neuritis in people who had vaccinations for hepatitis B, influenza, tetanus, measles and rubella (36). Farez and colleagues investigated the effect of yellow fever vaccination in MS patients and observed an increased risk of attacks in the vaccination group after the first 6 weeks of administration of the course of 2 years (38). There is insufficient evidence for the safety of pneumonia, meningitis, typhoid, polio, hepatitis A, human papilloma virus (HPV) and pertussis vaccinations for MS patients (39).

Special Vaccinations

Varicella vaccine: For the patients who are planned to undergo cellular immunity suppressing MS treatment (such as fingolimod treatment), those who did not have varicella previously or those who tested negative for VZV Ig G antibodies, varicella vaccination should be administered before the treatment.

2010-2011 injectable seasonal flu vaccine (H1N1): This vaccine provides immunity for 3 different strains of flu virus. This includes H3N2 virus, influenza B virus, and H1N1 virus which effectively means protection from all of these viruses in one injection. Flu shot is an inactive vaccination and it is recommended for everyone older than 6 months. This vaccine has been shown to be safe using a large population of MS patients. This vaccination is safe to use for patients who are taking interferon, glatiramer acetate, mitoxantrone, natalizumab or fingolimod but the effectiveness is still not clearly evaluated. The patients who experience attacks severe enough to impair their daily activities should receive vaccination about 4-6 weeks after the attack (39).

FluMist is a live attenuated influenza vaccine that is delivered nasally. This live vaccine is not recommended for MS patients. Live attenuated vaccines, even though they are biologically weakened, are not completely inactivated.

High dose flu vaccine is used in patients over 65 years old. The safety of this vaccine with MS patients has not been investigated. It is not commonly recommended for the general population.

Hepatitis B vaccine: In 2002, National Academy of Sciences Institute of Medicine conducted a meta-analysis of the published studies on the subject, which concluded that hepatitis B vaccine is not associated with the onset of MS (39).

Human Papillomavirus vaccine (HPV): HPV vaccine is protective against HPV 6, 11, 16 and/or 18 associated with cervical cancer, cervical dysplasia, condyloma acuminatum, vulvar or vaginal dysplasia and is generally used by women between 9 and 26 years old. Recent studies in the literature include cases of demyelination following the vaccination. Waldemann and friends (HPV) showed the development of acute disseminated encephalomyelitis following the second HPV vaccine in a patient, while at the same time Sutton and colleagues observed multifocal or atypical demyelination in 5 patients within 21 days following the second or third administration of vaccine (40).

Since there is no conclusive evidence for the safety of HPV vaccine, the expected outcomes and risks should be discussed with the patient before a decision is made.

Smallpox: There has not been a study involving MS patients but it is not recommended for MS patients due to the severe potential adverse effects of the vaccine.

Shingles (herpes zoster): There is no consensus for shingles vaccine but since it involves demyleniation due to the fact that it is an active vaccine, the potential outcomes should be discussed with the patient before the administration.

The aforementioned suggestions regarding these 6 vaccines were formulated by NMSS. Additional information is limited except for sporadic case studies in the literature. While these studies showed that BCG does not affect the attack frequency, this information should be confirmed by larger scale studies (39).

Suggestions

Influenza is classified as Level A, varicella and tetanus are Level C and other vaccines are classified as Level U.

The vaccine should not be used during attacks but rather 4-6 weeks after attacks (Level U). If there is a risk of tetanus, he vaccine should be used immediately (Level U).

Pneumococcal vaccine can be used in wheelchair-confined and bedridden patients who have respiratory problems (Level U).

Evidence level B: Possible effectiveness, ineffectiveness or harm
Evidence level C: Likely effectiveness, ineffectiveness or harm
Evidence level U: Insufficient or incongruous evidence

Multiple Sclerosis and Dental Treatment

The mercury content in the amalgams has been one of the most debated topics in the dental treatment of MS treatments. The mercury in the amalgams around early 1980's has been thought to be responsible for attack frequency. This view was based mostly on anecdotal evidence where the patient's symptoms were alleviated after replacing the mercury-containing amalgam with mercury-free amalgams. Over time, however, this view was contested on the grounds that the link could be coincidental or caused by a placebo effect (41).

Another issue of debate in MS patients is the dental care. Even though the studies show impairment of dental care in MS patients compared to control group, the primary reason for this difference is the impaired motor functions of the affected patients, which would make them less likely to go to a dentist. Consequently, it would be more appropriate to consider impaired dental health as a result of fewer dentist visits, rather than a direct effect of the disease on dental care (42).

The opportunistic infections due to substances used in MS patients, such as xerostomia, gingival hyperplasia, mucositis/ ulcerative stomatitis and candida, and herpes should be reported to the dentist (43).

There is no known contraindication for dental treatment in MS patients. Due to the increased levels of anxiety compared to other patient groups, however, the use of IV sedation and general anesthesia is more likely in this population (44).

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