Specific aspects of modern life for people with multiple sclerosis: considerations for the practitioner

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Abstract: Multiple sclerosis (MS) is a chronic, debilitating, neurodegenerative disease that has a high impact on patients' quality of life. Individuals are often diagnosed in early adulthood and are faced with the difficulty of managing their lifestyle within the context of this chronic illness. Here we review factors that influence the disease course and the challenges that might be encountered when managing patients with MS.

The majority of diagnosed patients are women of childbearing age, making pregnancy-related issues a key concern. MS typically stabilizes during pregnancy and evidence suggests that the disease has no impact on the risk of complications or outcomes. However, the effect of disease-modifying therapies on outcomes is less clear, and discontinuation of treatment prior to pregnancy or when breastfeeding is recommended. Awareness of genetic risk factors is important for patients planning a family, as several genes increase the risk of MS.

Further aspects that require consideration include infections, vaccinations, environmental factors, surgery and the emergence of osteoporosis. Vaccinations are generally not a risk factor for MS and may be beneficial in terms of protection against infection and reducing the number of relapses. Environmental factors such as vitamin D deficiency, low exposure to sunlight, smoking and Epstein–Barr virus infection can all negatively influence the disease course. Furthermore, osteoporosis is generally higher in patients with MS than the general population, and the risk is increased by the environmental and genetic factors associated with the disease; bone mineral density should be assessed and smoking cessation and correction of serum vitamin D levels are recommended. Finally, as patients with MS are typically young, they are at low risk of surgery-related complications, although they should be carefully monitored postoperatively. Awareness of, and planning around, these factors may minimize the impact of the disease on patients' lifestyle.

Keywords: disease-modifying therapies, Epstein–Barr virus infections, genetic risk factors, multiple sclerosis, osteoporosis, pregnancy, vaccination, vitamin D

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Introduction

Multiple sclerosis (MS) is a complex, neurodegenerative disease with a heterogeneous disease course. It is associated with an array of symptoms that vary both over time and among individuals. For patients with relapsing–remitting MS, the reduction of the frequency of relapses is a key therapeutic goal. As such, research attention in recent years has focused on the development of pharmacological strategies to reduce this relapse risk. However, it must also be recognized that individuals are often diagnosed in early adulthood and therefore encounter a variety of common experiences that must be managed within the context of their chronic illness.

Recognition of factors that might impact on the MS disease course is an important component of the ongoing care plan for patients with MS. Implementing effective strategies to mitigate health

risks for patients with MS will empower individuals with this debilitating disease to pursue their life goals, with adequate knowledge and minimized disruption. Although these factors are essential considerations with respect to intended or continued treatment with disease-modifying therapies (DMTs), healthcare professionals are also ideally placed to offer broader lifestyle support in addition to symptomatic management of the disease.

The majority of individuals diagnosed with MS are women of childbearing age and hence family planning and pregnancy-related questions are a common concern [Orton *et al.* 2006]. In this article we review the genetic risk factors for MS as well as pregnancy-related issues. We also consider a number of other factors that require careful consideration and planning for patients with MS, including the management of infections, vaccinations, surgery and the emergence of osteoporosis.

Methods

We conducted an extensive MEDLINE search covering publications on all topics that are dealt with in this article combined with the term 'multiple sclerosis', during the period 1985–2012.

Genetic risk factors

The concept of genetic inheritance and family risk is of considerable importance to patients with MS, particularly if they are planning a family, to help them make the necessary informed medical and personal decisions. Both a predisposing set of genes and certain, yet unidentified, environmental triggers are required for a person to develop MS [Ascherio and Munger, 2007a, 2007b; Baranzini, 2009]. The disease is most common among people of northern European origin, and a female:male ratio of approximately 2.5:1 has been noted [Pugliatti *et al.* 2002]. Approximately 15% of patients with MS have a positive family history of the disease, and the overall age-adjusted risk in the general population is approximately 0.3% [Dwosh *et al.* 2003]. Recurrence among monozygotic twins is approximately 35%, which reflects the degree of genetic contribution. The estimated risk to the siblings of a proband is 3–5%, increasing to 29.5% if one or both parents have MS. Risk to the offspring of a patient with MS is 2–3% and higher if both parents have MS (20%) [Dwosh *et al.* 2003].

A complex multifactorial aetiology, including interactions of genetic and environmental factors is likely. Similar aetiology to several other common diseases is typical, for example, rheumatoid arthritis or diabetes mellitus type I [Baranzini, 2009]. Large-scale genome-wide association studies have helped to identify several genes associated with disease susceptibility, the most important of which include HLA-DRB1, IL7R (CD127), IL2R and SOCS1 [Gregory *et al.* 2007; Hafler *et al.* 2007; Oksenberg *et al.* 2004; Vandenbroeck *et al.* 2012; Zhang *et al.* 2011; Sawcer *et al.* 2011]. These polymorphic genes may work independently and/or interact with each other, and will exert a minor or moderate effect on the development of MS [Burrell *et al.* 2011; Mkhikian *et al.* 2011].

Pregnancy and multiple sclerosis

Pregnancy is typically a stabilizing period in the clinical course of MS. During the third trimester, the MS relapse rate can be up to 70% lower compared with prepregnancy, but aggravation of the disease is commonly seen during the first 3 months after delivery [Confavreux *et al.* 1998]. A high frequency of attacks before pregnancy, relapses during pregnancy and a high level of physical disability at pregnancy onset have been identified as predictors of postpartum attacks [Vukusic *et al.* 2004].

Currently, there is no evidence that patients with MS are more susceptible to pregnancy or delivery-related complications, such as ectopic pregnancy, pre-eclampsia, gestational diabetes mellitus, prolonged labour or miscarriage, than women in general, nor are their infants more likely to be delivered preterm, to be of low birth weight, have malformations or experience an early death [Dahl *et al.* 2005; Mueller *et al.* 2002; Sadovnick *et al.* 1994; Worthington *et al.* 1994; Jalkanen *et al.* 2010]. Fertility problems are also uncommon in women with MS. However, compared with healthy pregnant women, there is a higher frequency of operative deliveries among pregnant women with MS. This may be due to MS-related symptoms, such as neuromuscular perineal weakness and spasticity, in addition to fatigue and exhaustion [Dahl *et al.* 2005; Kelly *et al.* 2009]. Delivery anaesthesia should be chosen based on normal obstetric indications. Epidural analgesia during delivery is not known to be associated with an increased risk of postpartum flares or disability in women with MS [Confavreux *et al.* 1998]. Although the number of studies addressing the potential impact of

immune-modulating agents on pregnancy and neonatal outcomes is increasing, there is not yet sufficient information to draw any reasonable conclusions. A significant proportion of women with MS may be exposed to DMTs during pregnancy [De Las Heras *et al*. 2007]. In one small prospective study, interferon β was associated with an increased risk of spontaneous abortion and lower birth weight of the newborn [Boskovic *et al*. 2005], but other investigators considered the drug to have an acceptable safety profile in terms of pregnancy outcome [Sandberg-Wollheim *et al*. 2005; Patti *et al*. 2008; Amato *et al*. 2010; De Las Heras *et al*. 2007]. A retrospective study among 311 women with unintentional DMT exposure during early pregnancy identified a trend towards a greater risk of assisted vaginal delivery but failed to identify any remarkable perinatal outcomes [Lu *et al.* 2012]. As the study samples are small, the safety of these medications has not been fully established and thus discontinuation of DMTs prior to pregnancy must still be recommended. Due to adverse events in animal studies (increased abortion rate), interferon β and glatiramer acetate have been given a US Food and Drug Administration (FDA) pregnancy category B or C rating. It is generally considered sensible to discontinue interferon β and glatiramer acetate treatment 1–2 months (in line with label recommendations) before the discontinuation of contraception in order to allow the woman's immune system to recover from the effects of DMT before conception. In the case of an unplanned pregnancy, the drug should be discontinued when the pregnancy is confirmed, and there is no need for termination of the pregnancy. Natalizumab treatment should be discontinued 3 months before cessation of contraception (type U recommendation), and fingolimod treatment should be discontinued at least 2 months before cessation of contraception, as experience from exposure to these drugs during pregnancy is still limited and they may well be harmful to the fetus [Cree, 2013; Cristiano *et al*. 2012; Novartis Pharma GmbH, 2012]. A disabling relapse during pregnancy may be safely treated with a course of intravenous immunoglobulin or, after the first trimester, with high-dose methylprednisolone, or with plasmapheresis in a more severe clinical situation.

The prevalence of breastfeeding was very high (90%) in a cohort of German mothers with MS [Hellwig *et al.* 2008]. This observation is in stark contrast to a southern European MS population, where only 28.6% of mothers with MS chose to breastfeed their babies [De Las Heras *et al*. 2007]. Breastfeeding is considered beneficial for the mother–baby relationship and it reduces the incidence of infections and allergies experienced by the baby [Oddy, 2004]. Moreover, women with MS who breastfeed their babies tend to have a lower relapse rate than women who do not breastfeed [Confavreux *et al*. 1998; Langer-Gould *et al*. 2009]. However, this does not necessarily mean that breastfeeding mothers experience fewer relapses due to a biological impact of breastfeeding on MS disease activity. It might rather imply a selection bias: mothers with nonactive prepregnancy disease choose to breastfeed, and the pattern of low disease activity continues after the delivery [Airas *et al.* 2010; Amato *et al*. 2010]

The postpartum period is a more challenging time regarding controlling the disease activity, as treatment with azathioprine, fingolimod, glatiramer acetate, interferon β, mitoxantrone or natalizumab is not recommended during breastfeeding (type U recommendation). One therapeutic option is intravenous immunoglobulin, which is not contraindicated to use during breastfeeding and which has been suggested to reduce disease activity in patients with relapsing–remitting MS [Fazekas *et al*. 1997], although in a later study no benefit could be demonstrated [Fazekas *et al*. 2008]. A retrospective study suggested that intravenous immunoglobulin may be efficient in preventing postpartum relapses [Achiron *et al*. 2004], a finding subsequently confirmed in a more recent observational study [Hellwig *et al.* 2009]. However, randomized, placebo-controlled study data are still lacking.

Vaccinations

A small number of case reports have suggested a relationship between vaccination and MS relapses or early disease onset [Gout *et al.* 1997; Tartaglino *et al*. 1995; Stewart *et al*. 1999]. A large case–crossover study in France conducted to assess whether vaccination increased the risk of relapse in MS failed to demonstrate any increase in the short-term risk of relapse in MS following vaccination [Confavreux *et al*. 2001]. A number of additional studies have also failed to demonstrate vaccination as a causative agent for MS [DeStefano *et al.* 2003; Sievers and Heyneman, 2002].

Many patients with MS receive immunosuppressive or immunomodulatory therapy, which could

render them more susceptible to infections and may affect their ability to respond to immunization [Löbermann *et al*. 2012]. Inactivated vaccines are generally considered safe for patients with MS, including those who are taking interferon, glatiramer acetate, mitoxantrone or natalizumab. However, readministration of the vaccines is recommended, once immune competence has been restored [Cahill *et al*. 2010]. The use of live attenuated vaccines may carry a risk of infections and complications in patients receiving immunosuppressants, including steroids, and should therefore be avoided [Cahill *et al*. 2010]. While live attenuated vaccines are considered safe for patients receiving an immunomodulator such as glatiramer acetate or interferon [Goldman *et al.* 2006], physicians should refer to specific guidelines before administering vaccines in patients with MS. For the more recently approved agents (natalizumab, fingolimod and teriflunomide), there are relatively few data on the concomitant use of live attenuated vaccines and current guidance is summarized here. The administration of live attenuated vaccines in patients receiving fingolimod should be avoided due to a possible risk of severe infections [Novartis Pharma GmbH, 2012] and is also not recommended for patients receiving teriflunomide [Genzyme, 2012]. The long half life of teriflunomide should be considered when contemplating the use of a live attenuated vaccine after discontinuation of this compound [Genzyme, 2012]. Live attenuated vaccines should be avoided for patients currently taking immunosuppressant medications and for a period of 3 months after discontinuation of treatment [Cahill *et al*. 2010].

The consensus of the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines, based on available research data, is that 'patients with multiple sclerosis should not be denied access to health-preserving and potentially life-saving vaccines' [Multiple Sclerosis Council for Clinical Practice Guidelines; Paralyzed Veterans of America, 2001]. The panel noted that 'vaccination for patients experiencing a relapse of multiple sclerosis should be delayed until the patient has stabilized clinically, generally 4 to 6 weeks after onset of relapse' [Multiple Sclerosis Council for Clinical Practice Guidelines; Paralyzed Veterans of America, 2001].

Hepatitis B vaccination

Concerns have been raised regarding a potential relationship between hepatitis B vaccination and MS relapses [Faure, 2005; Herroelen *et al*. 1991; Monteyne and André, 2000; Ozakbas *et al*. 2006; Salleras *et al*. 2006]. The concerns relate, in part, to a report from France in the mid 1990s of a possible increase in autoimmune diseases, including MS, after hepatitis B vaccination. However, efforts to confirm this report have been unsuccessful, and two separate studies have concluded that there is no evidence of an association between hepatitis B vaccination and the risk of either developing MS or MS relapse [Ascherio *et al.* 2001; Sadovnick and Scheifele, 2000; Zipp *et al.* 1999].

Influenza vaccination

An increase in the rate of MS relapses is known to be associated with influenza [De Keyser *et al.* 1998]. However, a study published by DeStefano and colleagues indicated that vaccinations for influenza, hepatitis B, tetanus, measles and rubella are safe for patients with MS and are not associated with an increased risk of the development of MS or optic neuritis [DeStefano *et al*. 2003]. A study by Cahill and colleagues recommends that patients with MS, and their physicians, should consider, unless there are specific contraindications, the influenza vaccine as a safe and effective prophylactic option in advance of the influenza season [Cahill *et al.* 2010]. The live attenuated influenza virus vaccine (nasal), however, is not recommended for people with MS [National Multiple Sclerosis Society, 2013a].

Tetanus vaccination

Vaccination against tetanus is associated with a lower risk of relapse [Confavreux *et al*. 2001]. A study that utilized data from the European database for MS (EDMUS) showed that the risk of MS was not increased after tetanus vaccination [Confavreux *et al*. 2001]. Hernán and colleagues also found that the risk of MS relapse was lower among people following tetanus vaccination than in people who had not received the vaccination [Hernán *et al.* 2006].

Human papillomavirus vaccination

Human papillomavirus (HPV) vaccination was approved in 2007 for the prevention of cervical cancer and vulvar and vaginal dysplasia in female patients aged 9–26 years. In 2009, six cases of demyelination syndrome were described following immunization with this vaccine [Sutton *et al.*

2009]. The aetiology of these observations is unclear. The immune modulators approved by the FDA for use in MS are not believed to contraindicate HPV vaccination; mitoxantrone, like other immunosuppressive agents, would likely interfere with effective immunization. The Centers for Disease Control and Prevention (CDC) stated that there is no contraindication for the use of this vaccine in patients with MS [CDC, 2002].

Measles, mumps and rubella

A recent cohort study in Sweden revealed no change in MS incidence associated with the introduction of the measles, mumps and rubella (MMR) vaccination [Ahlgren *et al.* 2009]. Other studies also showed no increased risk of MS with this vaccine [Confavreux *et al.* 2001; DeStefano *et al.* 2003]. However, it is possible that MMR vaccination could provoke severe adverse events among patients who are immunosuppressed.

Other vaccinations

There are no studies regarding the risk of diphtheria and MS. However, a European database study reported in 2001 suggested that the risk of an MS relapse was not increased following diphtheria vaccination [Confavreux *et al.* 2001]. The yellow fever vaccine (live vaccination) is not recommended for patients who are immunosuppressed, including those receiving immunosuppressive therapy, because of side effects and the risk of relapses [Farez and Correale, 2011]. For example, there have been reports of encephalitis after this vaccination [Löbermann *et al.* 2010; CDC, 2002]. Smallpox vaccination should be given only to patients with MS who have been directly exposed to the smallpox virus [Goldman *et al.* 2006].

Before initiating treatment with fingolimod, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with fingolimod, following which initiation of treatment with fingolimod should be postponed for 1 month to allow the full effect of vaccination to occur [Novartis Pharma GmbH, 2012].

Environmental considerations

The imbalanced distribution of MS across the world can be attributed to differences in genes and environment and their interaction. Ethnic origin plays a part in the development of MS: studies have shown a lower prevalence of MS in African American, Japanese and Chinese populations, and a higher prevalence in European and American populations [Ramagopalan *et al.* 2010]. An identical twin has approximately a 30% chance of developing MS if their twin already has the disease. Therefore, genes are needed for developing MS, but the environmental factors play an important role in determining MS risk.

The identification of environmental risk factors is difficult because no single factor in isolation appears to be responsible for the development of the disease [Koch *et al.* 2013].

The most involved environmental factors in the development of MS are vitamin D deficiency and low exposure to sunlight, cigarette smoking and Epstein–Barr virus (EBV) infection. Some of these factors not only increase the risk of MS, but also impact on the MS disease course.

Vitamin D

For many years, the existence of a latitude gradient has been described, with a lower MS incidence for populations closer to the equator [Kurtzke, 1995], and a higher MS incidence linked to populations nearer to the North or South Poles. Exposure to sunlight may explain the strong latitudinal gradient in Australia and New Zealand, mediated by skin production of vitamin D3. Later studies have confirmed, however, that the previously reported latitudinal gradient of incidence of MS in Europe and North America does not seem to be preserved [Wallin *et al.* 2004; Koch-Henriksen and Sorensen, 2011]. A contributory explanation for the missing latitudinal gradient for incidence may be changes in environmental factors (smoking, viruses, nutrition), and changes to lifestyle across Europe and North America.

The ultraviolet B radiation of sunlight converts cutaneous 7-dehydrocholesterol to vitamin D3, via two hydroxilation steps to the active form of vitamin D (1,25–dihydroxyvitamin D3) [Ramagopalan *et al.* 2011]. The consumption of fatty seafood and cod liver oil, both rich sources of vitamin D, has been noted to provide protection against the risk of MS [Ramagopalan *et al.* 2010]. Vitamin D has multiple immune-regulating functions, such as decrease or inhibition of

the production of proinflammatory cytokines, stimulation of regulatory T-cell activity and blocking of the production of nitric oxide by microglia [Döring *et al.* 2013]. The HLA-DRB1*1501 allele associated with MS is upregulated by 1,25 (OH)2D via vitamin D responsive elements [Ramagopalan *et al.* 2009].

Epidemiological data support a potential relationship between vitamin D deficiency and an increased risk of developing MS. Some retrospective and prospective studies have shown that vitamin D has a protective effect against MS. In a large case–control study of US military personnel it was observed that vitamin D levels were related to the risk of developing MS [Munger *et al.* 2006].

There is also a lot of evidence towards the notion that vitamin D influences the disease course of MS. Evidence for an association between vitamin D and relapses and disability comes from some studies that found a decrease of relapses and less disability in patients with MS with higher serum vitamin D levels [Smolders *et al.* 2008; Simpson *et al.* 2010]. A prospective study found that the intake of more than 400 IU/day of vitamin D reduces the risk of developing MS by 40% [Munger *et al.* 2004].

Nonetheless, although clinical transversal studies also support a beneficial role of vitamin D in preventing relapse and disease progression, prospective randomized controlled studies are necessary to confirm these results and to determine the adequate dose. Assessing the level of vitamin D in patients with MS in order to maintain normal accepted values (75–200 nmol/litre) should be recommended [Mehta *et al.* 2011; Pierrot-Deseilligny and Souberbielle, 2013].

Epstein–Barr virus

Some viruses (herpes simplex virus types 1 and 2, human herpes virus 6, EBV, measles) have been described as MS risk factors; evidence is greatest for EBV infection. It is not clear whether the EBV infection could be the cause or consequence of MS or whether these observations are merely a coincidence, as more than 90% of the healthy adult population are infected by EBV and it is a leading candidate trigger for several other autoimmune diseases [Giovannoni *et al.* 2006]. People with high titres of anti-EBV have a higher risk of developing MS compared with those with low titres [Sundström *et al.* 2004]. Seronegativity for EBV is associated with a very low risk of MS. A retrospective study including 1779 patients with MS and 2526 non-MS controls showed an odds ratio (OR) of 0.06 [95% confidence interval (CI): 0.03–0.13] for developing MS in seronegative individuals compared with seropositive ones [Ascherio and Munger, 2007a]. Some recent studies indicate that adults with a history of an infectious mononucleosis carry a moderately higher risk of developing MS compared with the general population [Thacker *et al.* 2006].

Studies on the association of EBV infection with the disease course of MS have shown conflicting results. Two studies showed an association between an increase in gadolinium-enhancing lesions [observed using magnetic resonance imaging (MRI)] and serum antibody EBV titres in patients with MS, but no relation with disability or relapses was reported [Koch *et al.* 2013]. Theoretically, a role for EBV in MS pathogenesis is plausible, since the EBV affects the immune function; it remains latent within the memory B lymphocytes and it can have an epigenetic effect on the DNA and the transcription of the genes involved [Fernández-Fernández *et al.* 2011].

Higher anti-EBV nuclear antigen (EBNA) levels and HLA-DRB1*15 positivity appear to be independent risk factors for MS, although their cooccurrence results in a marked increase in MS risk (e.g. 10 fold) compared with just having one [De Jager *et al.* 2008]. Infectious mononucleosis and ultraviolet B radiation exposure can explain an important proportion of the heterogeneity of MS [Ramagopalan *et al.* 2011].

Smoking

Smoking has been suggested to increase the risk of MS. One study showed that the cumulative exposure to smoking was associated with an increased incidence of MS [Hernán *et al.* 2001], and a meta-analysis gave a pooled OR for developing MS of 1.51 for smokers compared with nonsmokers [Hawkes, 2007]. Active smokers are at a higher risk than passive smokers, and the passive smokers have a higher risk than nonsmokers [Ascherio and Munger, 2007b]. Nevertheless, the strength of association is moderate. The explanation of the implication of smoking in MS could be due to a direct toxic effect of the nicotine on immunity or an increase in the level of toxicity through nitric oxide production caused by the free radicals in tobacco smoke [Fusby *et al.* 2010].

Other environmental factors

There is an association of month of birth and the risk of developing MS in some countries (e.g. Scotland) but not in others (e.g. Sardinia). People born in spring seem to have a higher risk of developing MS than those born in autumn because of the ultraviolet radiation effect [Willer *et al.* 2005].

A transient worsening of neurological symptoms caused by an increase in body temperature is known as Uhthoff's phenomenon; factors include exposure to high ambient temperatures, exercise, fever, infection, perimenstrual period or psychological stress [Frohman *et al.* 2013; Sá, 2012]. The physiopathological basis for Uhthoff's phenomenon has been attributed to changes in the electrical properties of demyelinated axons upon raised body temperature [Sá, 2012]. Patients are therefore usually advised to avoid situations that might increase the body temperature [Sá, 2012].

There is sufficient evidence that parasite infections are correlated with reduced disease activity in MS, including a reduction of relapses, less accumulation of disability and fewer new enhancing lesions in MRI associated with infection. The parasitic infection produces an immunological response with increases in the levels of T helper 2 anti-inflammatory and regulatory T and B cells, which could benefit the course of MS [Correale and Farez, 2007, 2011]. For these reasons, two pilot trials focusing on the ingestion of helminth eggs have already begun. A new hypothesis proposes that alterations in certain populations of bacteria in the gut can trigger a proinflammatory response or protect against inflammation in experimental autoimmune encephalomyelitis [Ochoa-Repáraz *et al.* 2011] and these responses could be modified by antibiotics or diet.

Improving our understanding of the environmental factors involved in the development and progression of MS will lead to new and more effective approaches for the prevention of this disease [Ascherio *et al.* 2012]. Some of these environmental risk factors are modifiable and changing them could improve the course of the disease or avoid it.

Vitamin D supplementation in people with vitamin D deficiency or insufficiency due to reduced sun exposure or inadequate vitamin D intake could have a great effect on the prevention of MS. Not smoking or smoking cessation may influence the risk of MS and disease progression. Inhibiting EBV infection would seem to be a potential option for preventing MS. The possibility of an EBV vaccination should be carefully investigated.

Surgery

The majority of patients with MS are young adults with no other concomitant diseases, whose risks during elective surgical procedures are about the same as in the general population. MS is generally not a reason to avoid having surgery. There is no evidence to suggest that the stress of surgery will bring on a relapse of MS [National Multiple Sclerosis Society, 2013b]. As a precaution, surgery should be performed during stable disease phases or after the initiation of an appropriate therapy [Kompetenznetz: Multiple Sklerose, 2013].

Generally, in the absence of complications, patients with MS who undergo surgery do not find that it impacts their neurological status. Infection or fever, however, may tend to aggravate symptoms of MS. Patients who have severe muscle weakness and who have been confined to bed for more than several days may find it harder to recover from surgery; physical therapy could be useful in these instances [National Multiple Sclerosis Society, 2013b].

The risks of anaesthesia are generally not greater in patients with MS; standard anaesthesia can be tolerated without undue risk [NCC-CC and NICE, 2003]. All forms of anaesthesia are considered safe for pregnant women with MS during labour and delivery. There are very few studies on the effects of anaesthesia and surgery; however, the few completed showed that there is no association between anaesthesia and the deterioration of MS [Bader *et al.* 1988; Kyttä and Rosenberg, 1984; Bamford *et al.* 1978]. There are no specific interactions between the drugs used for anaesthesia and MS [Schneider, 2005]. Patients should be informed that there is no increase in the risk of relapse [NCC-CC and NICE, 2003].

Overall, patients with severe, advanced MS who are seriously weakened by the disease could experience anaesthetic complications. Patients with bulbar and respiratory involvement are at risk of airway compromise, hypoventilation and

atelectasis [Dorotta and Schubert, 2002]. Perioperative infections and fever can exacerbate symptoms, so the anaesthetic plan should include body temperature and respiratory monitoring and other measures to prevent hyperthermia and infections [Dorotta and Schubert, 2002]. Patients with MS should be carefully monitored postoperatively. Elevated body temperature should be anticipated and treated aggressively [Dorotta and Schubert, 2002].

Osteoporosis

Patients with MS have a higher risk of fractures, lower bone mineral density (BMD) and osteoporosis than their age-matched and gender-matched peers. Osteoporosis is a major cause of morbidity and mortality, and is more common in patients with MS than the general population [Dobson *et al.* 2012]. The causes could be the limited mobility, low vitamin D levels and smoking [Goldman *et al.* 2006]. Mutations in the gene CYP27B1, when loss of function causes vitamin D dependent rickets, have been associated with the risk of MS. High-dose pulse steroids seem not to increase the loss of bone mass in patients with MS [Zorzon *et al.* 2005].

In summary, patients with MS should have BMD measurements taken within a couple of years of diagnosis, which would mean that those with reduced BMD are identified early to allow appropriate management. Smoking cessation and correction of low serum levels of vitamin D should be recommended in all patients with MS, irrespective of BMD.

Conclusion

This review aims to increase awareness of the specific aspects of MS relating to lifestyle choices, challenges and changes that might be faced in the context of managing this chronic, degenerative disease. Diagnosis is often confirmed during early adulthood and individuals need ways to meet the requirements of modern daily living without exacerbating their illness.

Family planning and pregnancy-related issues are of considerable relevance. While the beneficial effect of pregnancy on MS relapses is well known, the long-term impact of pregnancy on MS is less clear. Overall, the outcome of pregnancies of patients with MS is good. However, the impact of DMTs on outcomes is not well understood, and discontinuation of treatment prior to pregnancy or during breastfeeding is recommended.

The need to protect from communicable disease, without increasing the risk of relapse or gaining inadequate protection due to immunosuppressive medication, is also an issue that needs to be managed with care. Vaccinations in general are not a risk factor for the onset or relapse of MS. For individuals receiving DMTs, the measurement of antibody titres may be relevant to ensure full protection is gained following vaccination.

The environmental risk factors of MS are vitamin D deficiency and low exposure to sunlight, cigarette smoking and EBV infection. More prospective studies are necessary to determine whether vitamin D supplementation is beneficial. Smoking cessation should be considered to avoid the risk of MS. The levels of vitamin D in patients with MS should be assessed in order to aid the maintenance of normal accepted values.

The risks of surgery are generally not greater in patients with MS than the general population. Patients with MS should be carefully monitored postoperatively. Patients with MS have a high risk of low BMD and osteoporosis, and should have their BMD analyzed shortly after diagnosis to identify those with reduced BMD early.

Awareness and careful planning, with the support of a dedicated medical team, can minimize the risks faced by patients with MS and enable them to live their lives as fully as possible.

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