Vol. 108 No. 3 September 2009

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

Editors: F. John Firriolo and Nelson I. Rhodus

Multiple sclerosis: an update for oral health care providers

Dena J. Fischer, DDS, MSD, MS,[a] Joel B. Epstein, DMD, MSD, FRCD(C), FDSRCS(Edin),[b] and Gary Klasser, DMD, cert Orofacial Pain,[a] Chicago, Illinois
UNIVERSITY OF ILLINOIS AT CHICAGO

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. The disease mostly affects young adults and is increasing in prevalence and incidence. Multiple sclerosis is characterized by periods of activity and remission which, after numerous relapses, cause permanent neurologic deficits. Diagnosis of MS is based on patient history and clinical examination supplemented by the findings of radiologic and laboratory tests. Numerous motor and sensory disturbances occur in MS and may present in the orofacial region. This medical management update highlights issues that are important to the oral health care provider, including orofacial manifestations of MS and dental considerations for patients with MS. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:318-327)**

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. The presentation and course of disease varies significantly, but it is generally marked by recurrent attacks of neurologic dysfunction which are signified by demyelinating lesions or plaques throughout the brain and spinal cord of the central nervous system (CNS). Although many aspects of the etiology and pathogenesis of this disease remain unknown, recent investigations and advances in treatment have supported the role of infection and immune system disorders in the early stages of MS.

Multiple motor and sensory disturbances occur in MS and may present as painful conditions that affect the orofacial region. The oral health care provider should be able to recognize these conditions and distinguish them from signs and symptoms of dental origin. Furthermore, with the increased prevalence of MS, the oral health care provider may participate in the management of patients with MS. In this review, we will highlight advances in the epidemiology, etiology, pathogenesis, and medical management of MS and discuss orofacial manifestations of the disease and dental considerations for patients with MS.

[a]Assistant Professor, Department of Oral Medicine and Diagnostic Sciences, UIC College of Dentistry.
[b]Professor, Department of Oral Medicine & Diagnostic Sciences, College of Dentistry; Director of the Interdisciplinary Program in Oral Cancer, UIC Cancer Center, College of Medicine.
Received for publication Dec 8, 2008; returned for revision May 24, 2009; accepted for publication May 28, 2009.
1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2009.05.047

EPIDEMIOLOGY/DEMOGRAPHICS

Clinical signs of MS usually appear during young adulthood, with a higher occurrence in women than men.[1] Most people are diagnosed between the ages of 20 and 45 years. The prevalence rate is higher among caucasians compared with individuals of other race/ethnicity groups.[2] Multiple sclerosis affects ~250,000-350,000 individuals in the United States and ~2.5 million individuals worldwide.[2] The prevalence is ~85 cases per 100,000 U.S. population[2] and ~69 cases per 100,000 world population,[3] and the overall annual incidence is ~3 cases per 100,000 world population.[3] There is an increasing prevalence and incidence of the disease in the U.S. and the world.[4] In general, the prevalence and incidence of MS increases with increasing latitude from the equator.[2,3] Although the influence of latitude gradient is decreasing,[1,5,6] indicating a migratory influence, genetic or environmental effects still remain as major risk factors.[1,7,8]

ETIOLOGY AND PATHOGENESIS

It is accepted that a complex interplay of genes and environment contribute to the etiology of MS.[4,9] The

importance of genetics has been established by studies of familial MS. Genetic linkages that may contribute to MS have been identified with alleles of the human leukocyte antigen class II region of the major histocompatibility complex (MHC). In genetic studies, highly significant linkage to the MHC has been confirmed on chromosome 6p21[10,11] and suggestive linkage on chromosomes 17q23 and 5q33.[11] However, it is likely that genetic heterogeneity exists; consequently, there may be different causative genes in different individuals. Furthermore, environmental factors, such as decreased intake or synthesis of vitamin D, decreased sun exposure, and cigarette smoking have been suggested to play a contributory role in the etiology of MS.[7,9]

Infectious agents have also been linked to MS, and current evidence supports a role for Epstein-Barr virus (EBV) infection in the pathogenesis of multiple sclerosis. A systematic review of studies comparing EBV serology in MS case and control subjects found a greater than tenfold risk of developing MS in individuals infected with EBV in early childhood compared with those who were EBV negative.[12] Furthermore, the risk of MS is 2-3 times greater in those infected with EBV later in life, inferred from a history of infectious mononucleosis, compared with individuals infected in early childhood.[8,13,14] In prospective studies, a temporal relationship between antibody responses to EBV and MS onset has also been explored. Antibody titers against the Epstein-Barr nuclear antigen (EBNA) appear to increase several years before the onset of MS. These antibodies persist at stable levels for many years, followed by a secondary increase in anti-EBNA titers which may reflect a reactivation of immune responses to EBV.[15-17] Other viruses, such as human herpes virus type 6 and human endogeneous retrovirus, have been implicated as contributing to MS, because sequences of these viruses have been isolated in plasma, serum, and cerebrospinal fluid (CSF) from patients with MS. However, further research is required before a causal relationship between the presence of these viruses and development of MS can be established.[18,19]

The pathogenesis of MS appears to involve both inflammatory and neurodegenerative phases, and it is theorized that MS is a primary degenerative or infectious process with secondary inflammation.[20] The inflammatory phase involves the stimulation of T cells and macrophages which selectively attack oligodendrocytes or the myelin sheath, promoting demyelination.[20,21] B-cell activation and antibody responses also appear to contribute to demyelination, because studies of MS lesions have found activation of lymphocytes and an increase in the synthesis of antimyelin IgG in the CSF.[20,22] In the neurodegenerative phase, axonal damage occurs secondary to conduction block by depolarization of the axonal plasma membrane. The resulting lesions (plaques) consist of varying amounts of perivenular cell inflammation, demylenation, loss of oligodendrocytes, and astrocyte proliferation which cause gliosis (scarring).[22-24] Plaques can occur within the CNS wherever there are myelinated nerve fibers and are typically disseminated in time and location with sizes ranging from 1 or 2 mm to several centimeters.

GENERAL CLINICAL PRESENTATION/PHYSICAL FINDINGS

Multiple sclerosis is a progressive disease that may have an insidious or sudden onset. The clinical course may vary, but it is generally characterized into four clinical types: 1) relapsing/remitting: episodic acute attacks of worsening condition; 2) primary progressive: gradual progressive deterioration of neurologic function; 3) secondary progressive: relapsing/remitting disease followed by change in clinical course to progressive deterioration; and 4) progressive/relapsing: steady deterioration of neurologic function exacerbated by episodic acute attacks. Manifestations of MS vary from a benign illness to a progressive and incapacitating disease.[25]

Initial symptoms are often fluctuating and transient, disappearing after a few days or weeks. Common presenting symptoms include monocular visual impairment with pain (optic neuritis), weakness and/or paresthesias in one or more extremities, heat sensitivity, and Lhermitte sign (electrical sensation down the spine on neck flexion). Other symptoms include unsteadiness of a leg or hand, fatigue, and pain and bladder urgency or retention, and accompanying signs include impaired coordination, ataxia (uncoordinated movements), spasticity, tremor, and decreased strength.[26,27]

Acute relapses or "attacks" occur throughout the course of disease and vary in type, frequency, and severity. Presenting signs and symptoms may gradually resolve with relapsing/remitting disease or may accumulate with a progressive condition. With repeated relapses or progressive disease, permanent neurologic deficits tend to develop. Classic features of moderate to advanced disease include pain, vertigo, spasticity, ataxia, loss of sight, paraperesis, impairment of superficial and deep sensation, Charcot triad (intention tremor, scanning speech [slurring, monotonous speech] and nystagmus [rapid oscillating eyeball movements]), cognitive deficits, and bladder dysfunction. Pain is common in patients with MS, both at disease onset and during disease progression. It affects quality of life physically and emotionally and is an important factor requiring medical management of the disease. Signs and symptoms of MS may contribute to an inability to manage activities of daily living (ADL), ambulation, and/or mobility.[28] These com-

plications may lead to permanent impairment and/or disability. Approximately one-half of patients with MS remain ambulatory and independent in ADL, whereas one-third develop clinically significant paraparesis, paraplegia, or tetraplegia.[29]

DIAGNOSIS

Diagnosis of MS is based on history of exacerbations/remissions as well as clinical signs, symptoms, and examination(s) supplemented by the findings of radiologic and laboratory tests. Although diagnostic criteria have been proposed,[27,30] there is no single clinical feature or diagnostic procedure that is specific for MS. Diagnosis should include a complete physical examination performed by an experienced neurologist to evaluate for clinical signs of neurologic dysfunction. This evaluation may be accompanied by the use of various tests and procedures to evaluate for the existence of CNS lesions that have not produced clinical signs.[30] The cornerstone of diagnosis involves dissemination of plaques in time and space, indicating evidence of multiple lesions of the CNS and the occurrence of distinct symptomatic episodes at least 30 days apart. This results in transitory neurologic dysfunction that contributes to the clinical presentation. Initially, symptoms often resolve spontaneously, so a diagnosis of MS may be overlooked.[26]

Among the diagnostic tests, magnetic resonance imaging is highly sensitive for detecting plaques in the CNS and, therefore, is the most useful test for confirming the diagnosis of MS.[30] Typical MS lesions are ovoid and periventricular and may appear anywhere in the white matter. Sensory evoked potential testing assesses function in CNS sensory pathways. This test may be beneficial in demonstrating the presence of subclinical lesions along these pathways or in providing objective evidence of lesions suspected on the basis of subjective complaints. In general, visual evoked responses provide the most useful information.[30] CSF analysis may show an IgG concentration that is elevated relative to other CSF proteins in ~90% of the cases.[26] CSF analysis may be most useful in ruling out infections or neoplastic conditions that may mimic MS. Finally, serologic testing may help rule out other conditions.

MEDICAL MANAGEMENT AND TREATMENT

Treatment of acute attacks

Symptomatic relief of acute attacks or relapses is typically accomplished with brief courses (<1 month) of corticosteroids (i.e., prednisone, methylprednisolone), which may shorten the duration and accelerate recovery of acute relapses. In rare circumstances, immunosuppressants may be used on a short-term basis. Adjunctive treatment, such as physical therapy, occupational therapy, and counseling, may also be needed.

Disease-modifying therapies

Disease-modifying therapies are immunomodulating agents targeted against the inflammatory component of the disease process to prevent or reduce the biologic activity of MS. Evidence suggests that these emerging therapies prevent new lesion formation and progression, particularly when initiated early in the course of the disease.[31-34] Currently, six DMT agents are FDA approved in the U.S. for use in relapsing/remitting MS: three interferon-β (IFNβ) drugs, glatiramer acetate, a monoclonal antibody (natalizumab), and a chemotherapeutic agent (mitoxantrone).[35] The IFNβs have immunomodulating effects and down-regulate inflammatory activity by targeting T lymphocytes. These drugs have demonstrated a beneficial effect on reducing relapse rates and progression by approximately 30% compared with placebo in patients with relapsing/remitting disease.[35,36] Glatiramer acetate was designed to mimic and compete with myelin basic protein. It has a mechanism of action that is distinct from that of the IFNβs but also targets T lymphocytes, resulting in antiinflammatory activity. Glatiramer acetate has been shown to slow annual attack rates and accumulation of disability[37,38] and is recommended for individuals who cannot tolerate IFNβ therapy.[37] Mitoxantrone is an antineoplastic agent that has been shown to decrease progression of MS.[39] It is recommended for use in patients with worsening forms of MS or as an induction therapy. The cumulative dose of this medication must be limited, owing to severe side effects, including cumulative cardiotoxicity.[40] Natalizumab is a monoclonal antibody directed against an adhesion molecule called very-late-antigen 4 which interferes with the binding of T lymphocytes to inflamed vessels in the CNS.[41] This therapy has been shown to reduce active lesions and to decrease MS relapses in clinical trials[42,43] and is indicated for patients with very active or breakthrough relapsing MS.[41]

Symptomatic therapy

Other management strategies are symptomatic therapies aimed at reducing symptoms of MS. Mild spasticity may be managed with stretching and exercise, and γ-aminobutyric acid agonists (i.e., baclofen), α-agonists (i.e., tizanidine), or benzodiazepines may be effective when spasms or clonus interferes with function. Dystonic spasms and paroxysmal pain syndromes may be treated with anticonvulsants (i.e., gabapentin, carbamazepine) or tricyclic antidepressants (i.e., amitriptyline). Pain associated with these symptoms is common and may require analgesics. Medical management of the

neurogenic bladder may involve smooth muscle relaxants and anticholinergic drugs for failure to store urine or α_1-adrenergic receptor agonists for failure to empty urine. Depression occurs in ~20% of patients with MS, and fatigue affects almost 50%.[28,44,45] These conditions may be managed with supportive measures or conventional medications targeting these symptoms.

PROGNOSIS

At 15 years after disease onset, approximately 80% of patients have functional limitation. Thirty to fifty percent of these individuals will have progressed to secondary progressive multiple sclerosis (SPMS) and will require assistance with ambulation.[29,46] After 25 years of disease, almost all patients with functional limitation will develop ambulatory impairment or disability. The remaining 20% have a benign variant of MS and experience minimal or no disability. Multiple sclerosis has minimal effect on life span, although it is estimated that the 25-year survival is 85% of the expected life span, usually with death occurring as a complication in the debilitated patient.[46]

For relapsing-remitting disease, the mean relapse frequency is about once every 2 years.[25] Although it is difficult to establish the clinical course, certain factors may be associated with a more favorable prognosis, such as female gender, younger age at onset, <2 relapses in the first year of illness, and optic neuritis or sensory symptoms as presenting symptoms.[47,48]

OROFACIAL MANIFESTATIONS OF MS

Initial signs and symptoms of neurologic disturbances associated with exacerbations of MS may occur in the orofacial region. These attacks typically last for at least 24 hours with an average frequency of 3 times per year. The most common presenting symptoms include intermittent unilateral facial numbness or pain (neuropathic or neuralgic pain), facial palsy or spasm, mild dysarthria (impaired ability to articulate words), Lhermitte sign, and monocular visual disturbances, such as partial loss of vision with pain or diplopia. Heat or exercise may temporarily exacerbate symptoms and signs, known as the Uhthoff phenomenon. The oral health care provider should consider referral to a neurologist for a thorough evaluation of MS in patients presenting with these early symptoms.

Numerous sensory and motor disturbances resulting from disease progression of MS may occur in the orofacial region. These conditions are often painful, although paresthesias, facial palsy, hemifacial spasm, Charcot triad (see General Clinical Presentation, above) and tremor have also been reported.[49,50]

Paroxysmal pain syndromes

Paroxysmal pain syndromes may develop as central or peripheral disturbances and may involve the orofacial region. These conditions are characterized by brief duration, electric or shock-like severe lancinating pain, and high frequency (5-40 episodes per day). Trigeminal neuralgia (TN) is not common in patients with MS, although it may develop as a presenting symptom or a complication of the disease. TN is diagnosed in 1%-5% of patients with MS,[51,52] which is approximately 20 times the prevalence in the general population. MS patients with TN are typically <50 years old, and the neuralgia is more frequently bilateral compared with the general TN population.[53-55] No differences in duration or quality of pain, branches of the trigeminal nerve involved, presence or absence of trigger(s), or refractive periods have been described.[53] Evidence has demonstrated that TN in MS patients is caused by demyelinating lesions of the trigeminal sensory fibers located in the nerve root or, less frequently, the nerve entry zone in the brainstem.[55-57]

Isolated case reports of other orofacial pain conditions, such as glossopharyngeal neuralgia (severe lancinating pain in the posterior pharynx, tonsillar fossa, and base of tongue),[58] paroxysmal "cluster-like pain" (headache disorder characterized by attacks of severe periorbital pain associated with autonomic symptoms),[59,60] and trigeminal autonomic cephalgia (headache disorder associated with ipsilateral cranial autonomic dysfunction),[61] have been reported in the literature. The common etiology of these paroxysmal pain conditions may be root entry zone demyelinating lesions of the affected trigeminal and/or glossopharyngeal nerves in MS patients.[58-61] Orofacial paroxysmal pain syndromes are not common. When a patient presents with such symptoms, oral health care providers should suspect them as the presenting symptoms of MS and should consider referral to a neurologist for further evaluation, particularly when symptoms present bilaterally and/or in individuals <50 years old.

Musculoskeletal conditions

Demyelination affecting motor neurons may result in musculoskeletal conditions causing muscle weakness, tremor, hemifacial spasms, and involuntary facial muscle contractions (myokymia).[62-64] These conditions are most often reported in the extremities and can cause significant disability and musculoskeletal pain.[65] In the orofacial region, myofascial and neck pain has been observed[63] and may contribute to a high prevalence of temporomandibular disorders symptomatology in MS patients.[66]

Table I. Common medications used in the management of MS and potential side effects[93-95]

	Drug class and medication	*Potential side effects*
Treatment of acute attacks	Corticosteroids: Prednisone Methylprednisolone	• Immunosuppression/increased risk of infection (e.g. oral fungal (candidal) infections, postoperative wound infection) • Delayed wound healing • Adrenocortical unresponsiveness/insufficiency • Exacerbation of congestive heart failure and hypertension (secondary to sodium retention and fluid retention) • Osteoporosis • Increased risk of peptic ulcer (with possible perforation and hemorrhage) • Psychiatric disturbances (depression, euphoria, insomnia, mood swings, and personality changes)
	Immunosuppressants: Methotrexate Azathioprine Mycophenolate Cyclophosphamide	• Increased risk of severe dermatologic reactions • Bone marrow suppression (leukopenia, thrombocytopenia) • Increased risk of secondary lymphomas • Increased risk of peptic ulcer (with possible perforation and hemorrhage) • Hepatotoxicity • Increased risk of acute renal failure • Neurotoxicity • Increased risk of systemic and/or oral opportunistic infection (e.g., fungal (candidal), bacterial, and viral infections) • Mucositis, ulcerative stomatitis
Disease-modifying therapies	Interferon-β drugs: IFNβ-1a (Avonex) IFNβ-1a (Rebif) IFNβ-1b (Betaseron)	• Bone marrow suppression (leukopenia) • Hepatic impairment • Fatigue • Myalgia • Headache • Mucositis, ulcerative stomatitis • Glossitis • Dysgeusia • Increased risk of oral infection (e.g., fungal [candidal] infections) • Xerostomia
	Glatiramer acetate (Copaxone)	• Cardiovascular effects (e.g., vasodilation, palpitation) • Arthralgia • Weakness • Mucositis, ulcerative stomatitis • Salivary gland enlargement • Increased risk of infection (e.g., oral fungal [candidal], bacterial, and viral infections)
	Monoclonal antibody: Natalizumab (Tysabri)	• Increased risk of progressive multifocal leukoencephalopathy (viral opportunistic infection) • Hepatotoxicity • Allergic reaction • Arthralgia • Headache • Depression • Increased risk of systemic and/or oral opportunistic infection (e.g., fungal [candidal], bacterial, and viral infections) • Mucositis, ulcerative stomatitis
	Immunosuppressant: mitoxantrone (Novantrone)	• Potential for myocardial toxicity and heart failure (risk increases with cumulative dosing) • Bone marrow suppression (leukopenia, thrombocytopenia) • Increased risk of secondary malignancy • Hepatic impairment • Renal impairment • Increased risk of gastrointestinal bleeding • Fatigue • Mucositis, ulcerative stomatitis • Increased risk of infection (e.g. oral fungal [candidal], bacterial, and viral infections)

Table I. Continued

	Drug class and medication	*Potential side effects*
Symptomatic therapy	Muscle relaxants: Baclofen (Lioresol) Tizanidine (Zanaflex)	• CNS depression (including sedation, fatigue, dizziness, ataxia) • Hypotension • Potential for hepatotoxicity • Visual hallucinations • Xerostomia
	Tricyclic antidepressants: Amitriptyline (Elavil)	• Increased risk of suicidal ideation/behavior • Psychiatric disturbances (depression, euphoria, insomnia, mood swings, and personality changes) • Anticholinergic effects (e.g., constipation, blurred vision, urinary retention, xerostomia) • Cardiovascular effects (tachycardia, arrhythmia, palpitation, orthostatic hypotension) • CNS depression (including sedation, fatigue, dizzinesss, ataxia)
	Anticonvulsants: Gabapentin (Neurontin) Carbamazepine (Tegretol)	• Bone marrow suppression (leukopenia) • Hepatic impairment • CNS depression (including fatigue, dizzinesss, ataxia) • Gingival hyperplasia • Xerostomia
	Anticholinergics: Oxybutinin (Ditropan) Tolterodine (Detrol)	• Secondary anticholinergic effects (e.g. agitation, confusion, hallucinations, constipation, xerostomia) • CNS depression (including sedation, fatigue, dizzinesss, ataxia)

CNS, Central nervous system.

Headache

The link between MS and primary headache is poorly understood. The frequency of headache among MS patients ranges from 54% to 58% in recent studies, suggesting that headaches are more common in patients with MS than in the general population.[67-69] Among MS patients with headache, a high prevalence of migraine (25%-35%) and tension-type headache (32%-48%) has been reported.[67-69] It is hypothesized that headache, and migraine in particular, is believed to be a result of a reduction of T8 lymphocytes and a shared immune mechanism[70,71] or repeated demyelination of brainstem structures.[72,73] Several studies have suggested that IFNβ treatment may induce de novo headache and exacerbation of preexisting headache,[74-76] particularly in subjects receiving high-frequency IFNβ treatment.[76]

Other oral considerations

Sensory neuropathy secondary to MS may present as a bilateral, progressive, and often irreversible condition. The paresthesia preferentially affects the second and third divisions of the trigeminal nerve and may be accompanied by extraoral or intraoral numbness, tingling, and/or pain.[49] This peripheral neuropathy may or may not be associated with a concurrent central pain condition.[51] Facial paralysis may also occur in MS, typically later in the course of disease, in up to one-quarter of patients and is often associated with brainstem lesions.[77]

Medications for therapy of MS and pain may cause xerostomia, increasing the risk for dental disease. Furthermore, orofacial pain, whether acute or chronic, may have significant clinical implications that may affect quality of life and the ability to perform daily activities, including effective oral hygiene. Oral health care providers must be aware of prevention and treatment strategies for xerostomia and oral health.

DENTAL MANAGEMENT OF MS PATIENTS

From a historical perspective, the controversy that the mercury present in amalgam may precipitate or exacerbate MS symptoms erupted in the middle 1980s. This argument was proposed based on anecdotal observations of "miracle cures" coincident with the replacement of amalgam with nonmercury-containing restorative materials.[78] However, scientific evidence has strongly refuted the contention that the placement of or exposure to mercury in amalgam restorations can cause neurologic symptoms[79] or disorders,[80-83] such as MS or Alzheimer disease. It seems likely that the "miracle cures" were more likely associated with an incidental resolution of the underlying pathology or a placebo effect.[84] Therefore, the removal and replacement of amalgam restorations with other less "toxic" materials is not justified.

Table II. Dental considerations for patients with multiple sclerosis

	Dental consideration	*Rationale*
Before dental treatment	Enable dental facilities to accommodate wheelchairs	Elimination of barriers of access to care
	Consultation with physician; obtain results of laboratory tests if indicated	Management of complications/adverse effects due to medical condition and/or medications
	Consider performing dental procedures under IV or general anesthesia	Outpatient dental treatment may not be suitable secondary to neurologic symptoms and/or anxiety
During treatment	Appropriate appointment times and lengths to suit the individual	Owing to physical limitations, neurologic symptoms and/or anxiety, patients may not be able to tolerate lengthy appointments.
	Use of mouth props during lengthy treatment	Prevention of muscle fatigue or spasm
	Avoid supine position	Risk of pulmonary aspiration secondary to dysphagia[50]
	Maintain the dental environment at a comfortable temperature	Patient comfort[85]
Home/self-care	Use of custom fabricated toothbrush handle[96] and/or electric toothbrush[50]	Improve hand grip in response to loss of manual dexterity or muscle coordination
	Tailor oral hygiene instruction and recommendations to patient's capabilities	Physical or neurologic deficits may impair ability to perform effective oral hygiene
	Preventive regimens to include frequent recalls, dietary advice, reinforcement of effective oral hygiene, chlorhexidine mouth rinses (short-term)	Oral health maintenance
	Systemic sialogogues or saliva substitutes	Warranted if patient is experiencing xerostomia, possibly secondary to medications
	Fluoride supplementation, often applied with custom-fabricated carriers or with mouth rinses and varnishes	Warranted if patient is at high risk for caries

Another controversial issue is whether or not there is a greater prevalence of dental caries and periodontal disease in MS patients compared with the general population. Although there is conflicting evidence regarding this matter,[66,84,85] studies that attempted to address this issue used small numbers of subjects and were not generalizable to the larger population. Nevertheless, oral health may be affected by access to care issues or difficulty in performing oral hygiene procedures owing to motor disturbances produced by MS. In a study by Griffiths and Trimlett[86] ~25% of 73 MS subjects reported an inability to clean their own teeth or dentures, and >30% had difficulties in performing oral hygiene procedures. Interestingly, ~30% of the subjects had changed their dominant hand as a result of their MS disability. Furthermore, Baird et al.[87] found that when individuals with MS were compared with the general population, a higher number of people with MS were registered with a dentist (88% vs. 49%, respectively) and displayed more frequent dental visits (81% vs. 71%, respectively) in the past year. However, patients with MS reported difficulties in visiting a dentist and maintaining oral health, which were exacerbated by deterioration in general health. Problems relating to reduced personal mobility had the greatest effect on dental visits. Therefore, the presence of dental disease in this population may be related to complications of the MS disease process rather than to specific changes in oral biology.

There is no cure for MS; therefore, the focus of treatment is on prevention and/or reduction of disability and maintenance of quality of life. Consequently, symptomatic treatments are used to minimize and control specific symptoms due to MS itself as well as complications related to the disease. Medications are a mainstay in this process. It is important for the dental practitioner to be aware of the potential interactions of these medications with commonly used medications in dentistry. Some of these concerns involve the use of analgesics, such as acetaminophen and narcotics, and nonsteroidal antiinflammatory drugs, such as aspirin. Interactions among these medications may result in cytotoxicity and hepatoxicity and/or amplify depression and alter the metabolism of certain drugs.[49] The dental practitioner must also be aware of the potential side effects from medications used in MS (Table I). It is important to minimize or manage these side effects from both a systemic and oral health perspective.[88-91] The most common oral side effects of medications used to manage MS include xerostomia, gingival hyperplasia, mucositis/ulcerative stomatitis, dysgeusia and overgrowth of opportunistic infections resulting in candidiasis, angular cheilitis, and reactivation of herpes viruses.[49] This, in combination with the other issues previously discussed, may pose a challenge for the treating dental practitioner.

Dental management of MS patients should be modified and tailored to their special needs (Table II). The

optimal time for treating MS patients is during periods of remission, when neurologic symptoms may be minimal.[92] In the event the disease is progressive, there are no contraindications to dental treatment other than those related to medical management of MS. It is reported that there is a high level of dental anxiety present in MS patients, with a surprisingly high proportion of these individuals receiving dental treatment with intravenous sedation or general anesthesia.[86] It is unclear whether the use of these sedative techniques is a result of patient choice or considered to be clinically necessary to manage anxiety or some other symptoms of MS. In any event, the dental practitioner must be aware of this and should consider scheduling appointments for a shorter duration and at a time when the individual is more relaxed.[85] If dental procedures under IV sedation or general anesthesia are warranted, the patient may benefit from treatment in a hospital outpatient dental clinic or operating room setting. The entire dental team must play an active role in providing advice, skills, motivation, and support throughout the lifetime of a patient with MS to provide and maintain good oral health, thereby contributing to the overall well-being of the individual. Orofacial pain may be complex in MS patients; dental origin of the pain must be ruled out, and referral to experts in orofacial pain diagnosis and management should be considered.

CONCLUSION

Multiple sclerosis is a complex disease that varies considerably in presentation and progression. Management of this condition requires a multidisciplinary team approach to include health care providers and allied health professionals. Because the prevalence and incidence of MS is increasing, it is likely that oral health care providers will participate in the dental management of patients with this disease. Furthermore, oral health care providers may identify initial signs and symptoms in undiagnosed patients and may be involved in the management of orofacial manifestations of MS.

REFERENCES

1. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology 2008;71:129-35.
2. Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. Neurology 2002;58:136-8.
3. Zivadinov R, Iona L, Monti-Bragadin L, Bosco A, Jurjevic A, Taus C, et al. The use of standardized incidence and prevalence rates in epidemiological studies on multiple sclerosis. A meta-analysis study. Neuroepidemiology 2003;22:65-74.
4. Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurol Sci 2001;22:117-39.
5. Hernan MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. Neurology 1999;53:1711-8.
6. Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. Ann Neurol 2004;55:65-71.
7. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 2007;61:504-13.
8. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: The role of infection. Ann Neurol 2007;61:288-99.
9. Giovannoni G, Ebers G. Multiple sclerosis: the environment and causation. Curr Opin Neurol 2007;20:261-8.
10. Lincoln MR, Montpetit A, Cader MZ, Saarela J, Dyment DA, Tiislar M, et al. A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. Nat Genet 2005;37:1108-12.
11. Sawcer S, Ban M, Maranian M, Yeo TW, Compston A, Kirby A, et al. A high-density screen for linkage in multiple sclerosis. Am J Hum Genet 2005;77:454-67.
12. Ascherio A, Munch M. Epstein-Barr virus and multiple sclerosis. Epidemiology (Cambridge, Mass) 2000;11:220-4.
13. Nielsen TR, Rostgaard K, Nielsen NM, Koch-Henriksen N, Haahr S, Sorensen PS, et al. Multiple sclerosis after infectious mononucleosis. Archf Neurol 2007;64:72-5.
14. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann Neurol 2006;59:499-503.
15. Ascherio A, Munger KL, Lennette ET, Spiegelman D, Hernan MA, Olek MJ, et al. Epstein-Barr virus antibodies and risk of multiple sclerosis: a prospective study. JAMA 2001;286:3083-8.
16. DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A. Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. Arch Neurol 2006;63:839-44.
17. Levin LI, Munger KL, Rubertone MV, Peck CA, Lennette ET, Spiegelman D, et al. Temporal relationship between elevation of epstein-barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA 2005;293:2496-500.
18. Alvarez-Lafuente R, Garcia-Montojo M, De Las Heras V, Dominguez-Mozo MI, Bartolome M, Benito-Martin MS, et al. Herpesviruses and human endogenous retroviral sequences in the cerebrospinal fluid of multiple sclerosis patients. Mult Scler 2008;14:595-601.
19. Christensen T. Association of human endogenous retroviruses with multiple sclerosis and possible interactions with herpes viruses. Rev Med Virol 2005;15:179-211.
20. Holmoy T, Hestvik AL. Multiple sclerosis: immunopathogenesis and controversies in defining the cause. Curr Opin Infect Dis 2008;21:271-8.
21. Kornek B, Lassmann H. Neuropathology of multiple sclerosis-new concepts. Brain Res Bull 2003;61:321-6.
22. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Phil Trans R Soc Lond B Biol Sci 1999;354(1390):1649-73.
23. Bitsch A, Kuhlmann T, Da Costa C, Bunkowski S, Polak T, Bruck W. Tumour necrosis factor alpha mRNA expression in early multiple sclerosis lesions: correlation with demyelinating activity and oligodendrocyte pathology. Glia 2000;29:366-75.
24. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47:707-17.
25. Lublin FD, Reingold SC, National Multiple Sclerosis Society

(USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996;46: 907-11.
26. Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician 2004;70:1935-44.
27. Poser CM, Brinar VV. Diagnostic criteria for multiple sclerosis. Clin Neurol Neurosurg 2001;103:1-11.
28. Stolp-Smith KA, Carter JL, Rohe DE, Knowland DP 3rd. Management of impairment, disability, and handicap due to multiple sclerosis. Mayo Clin Proc 1997;72:1184-96.
29. Rodriguez M, Siva A, Ward J, Stolp-Smith K, O'Brien P, Kurland L. Impairment, disability, and handicap in multiple sclerosis: a population-based study in Olmsted County, Minnesota. Neurology 1994;44:28-33.
30. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
31. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001; 357(9268):1576-82.
32. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. The N Engl J Med 2000;343:898-904.
33. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;67:1242-9.
34. Kinkel RP, Kollman C, O'Connor P, Murray TJ, Simon J, Arnold D, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;66: 678-84.
35. DeAngelis T, Lublin F. Multiple sclerosis: new treatment trials and emerging therapeutic targets. Curr Opin Neurol 2008;21: 261-71.
36. Clerico M, Faggiano F, Palace J, Rice G, Tintore M, Durelli L. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. Cochrane Database of Syst Rev 2008(2):CD005278.
37. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al., Copolymer 1 Multiple Sclerosis Study Group. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology 1998;50:701-8.
38. Johnson KP, Brooks BR, Ford CC, Goodman A, Guarnaccia J, Lisak RP, et al., Copolymer 1 Multiple Sclerosis Study Group Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Mult Scler 2000;6:255-66.
39. Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 2002;360(9350):2018-25.
40. Ghalie RG, Edan G, Laurent M, Mauch E, Eisenman S, Hartung HP, et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. Neurology 2002;59:909-13.
41. Lutterotti A, Martin R. Getting specific: monoclonal antibodies in multiple sclerosis. Lancet Neurol 2008;7:538-47.
42. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.
43. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006;354:911-23.
44. Feinstein A, Feinstein K. Depression associated with multiple sclerosis. Looking beyond diagnosis to symptom expression. J Affect Disord 2001;66):193-8.
45. Krupp LB, Rizvi SA. Symptomatic therapy for underrecognized manifestations of multiple sclerosis. Neurology 2002;58(8 Suppl 4):S32-9.
46. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993;116(Pt 1):117-34.
47. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002;346:158-64.
48. Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008;131(Pt 3):808-17.
49. Chemaly D, Lefrancois A, Perusse R. Oral and maxillofacial manifestations of multiple sclerosis. J Can Dent Assoc 2000;66:600-5.
50. Fiske J, Griffiths J, Thompson S. Multiple sclerosis and oral care. Dent Update 2002;29:273-83.
51. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis—prevalence and clinical characteristics. Eur J Pain 2005;9:531-42.
52. Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. Acta Neurol Scand 1991;84:197-200.
53. De Simone R, Marano E, Brescia Morra V, Ranieri A, Ripa P, Esposito M, et al. A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. Neurol Sci 2005;26(Suppl 2):s150-1.
54. Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. Neurology 1995;45:1294-6.
55. Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. Acta Neurol Scand 1982;65:182-9.
56. Gass A, Kitchen N, MacManus DG, Moseley IF, Hennerici MG, Miller DH. Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with magnetic resonance imaging. Neurology 1997;49:1142-4.
57. Love S, Gradidge T, Coakham HB. Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. Neuropathol Appl Neurobiol 2001;27:238-44.
58. Minagar A, Sheremata WA. Glossopharyngeal neuralgia and MS. Neurology 2000;54:1368-70.
59. Gentile S, Ferrero M, Vaula G, Rainero I, Pinessi L. Cluster headache attacks and multiple sclerosis. J Headache Pain 2007;8:245-7.
60. Leandri M, Cruccu G, Gottlieb A. Cluster headache-like pain in multiple sclerosis. Cephalalgia 1999;19:732-4.
61. Davey R, Al-Din A. Secondary trigeminal autonomic cephalgia associated with multiple sclerosis. Cephalalgia 2004;24:605-7.
62. Sedano MJ, Trejo JM, Macarron JL, Polo JM, Berciano J, Calleja J. Continuous facial myokymia in multiple sclerosis: treatment with botulinum toxin. Eur Neurol 2000;43:137-40.
63. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage 2004;28:140-75.
64. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler 2004;10:589-95.

65. Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7:1-111.
66. Kovac Z, Uhac I, Bukovic D, Cabov T, Kovacevic D, Grzic R. Oral health status and temporomandibular disorders in multiple sclerosis patients. Coll Antropol 2005;29:441-4.
67. D'Amico D, La Mantia L, Rigamonti A, Usai S, Mascoli N, Milanese C, et al. Prevalence of primary headaches in people with multiple sclerosis. Cephalalgia 2004;24:980-4.
68. Nicoletti A, Patti F, Lo Fermo S, Liberto A, Castiglione A, Laisa P, et al. Headache and multiple sclerosis: a population-based case-control study in Catania, Sicily. Cephalalgia 2008;28: 1163-9.
69. Rolak LA, Brown S. Headaches and multiple sclerosis: a clinical study and review of the literature. J Neurol 1990;237:300-2.
70. Leone M, Biffi M, Leoni F, Bussone G. Leukocyte subsets and cortisol serum levels in patients with migraine without aura and chronic tension-type headache. Cephalalgia 1994;14:139-42.
71. Reder AT, Antel JP, Oger JJ, McFarland TA, Rosenkoetter M, Arnason BG. Low T8 antigen density on lymphocytes in active multiple sclerosis. Ann Neurol 1984;16:242-9.
72. Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. Headache 1993;33:452-5.
73. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 2001;41:629-37.
74. La Mantia L, D'Amico D, Rigamonti A, Mascoli N, Bussone G, Milanese C. Interferon treatment may trigger primary headaches in multiple sclerosis patients. Mult Scler 2006;12:476-80.
75. Pollmann W, Erasmus LP, Feneberg W, Then Bergh F, Straube A. Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. Neurology 2002;59:636-9.
76. Villani V, Prosperini L, Ciuffoli A, Pizzolato R, Salvetti M, Pozzilli C, et al. Primary headache and multiple sclerosis: preliminary results of a prospective study. Neurol Sci 2008;29 Suppl 1:S146-8.
77. Fukazawa T, Moriwaka F, Hamada K, Hamada T, Tashiro K. Facial palsy in multiple sclerosis. Journal of neurology 1997;244:631-3.
78. Miller AE. Cessation of stuttering with progressive multiple sclerosis. Neurology 1985;35:1341-3.
79. Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luis H, Amaral H, et al. Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial. J Am Dent Assoc 2008;139:138-45.
80. Saxe SR, Wekstein MW, Kryscio RJ, Henry RG, Cornett CR, Snowdon DA, et al. Alzheimer's disease, dental amalgam and mercury. J Am Dent Assoc 1999;130:191-9.
81. Bates MN. Mercury amalgam dental fillings: an epidemiologic assessment. Int J Hyg Environ Health 2006;209:309-16.
82. Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T. Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol 2004;33:894-902.
83. Eley BM, Cox SW. "Mercury poisoning" from dental amalgam—an evaluation of the evidence. J Dent 1988;16:90-5.
84. McGrother CW, Dugmore C, Phillips MJ, Raymond NT, Garrick P, Baird WO. Multiple sclerosis, dental caries and fillings: a case-control study. Br Dent J 1999;187:261-4.
85. Symons AL, Bortolanza M, Godden S, Seymour G. A preliminary study into the dental health status of multiple sclerosis patients. Spec Care Dentist 1993;13:96-101.
86. Griffiths JE, Trimlett HJ. Dental status and barriers to care for adults with multiple sclerosis. Int Dent J 1996;46(Suppl 2):445.
87. Baird WO, McGrother C, Abrams KR, Dugmore C, Jackson RJ. Verifiable CPD paper: factors that influence the dental attendance pattern and maintenance of oral health for people with multiple sclerosis. Br Dent J 2007;202:E4; discussion 40-1.
88. Baid SK, Nieman LK. Therapeutic doses of glucocorticoids: implications for oral medicine. Oral Dis 2006;12:436-42.
89. Chainani-Wu N, Wu TC. Immunosuppressants. J Calif Dent Assoc 2008;36:775-9.
90. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 2: Coagulopathies from drugs. Br Dent J 2003;195:495-501.
91. McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 2008;20:131-7.
92. Little JW, Falace DA, Miller CS, Rhodus NL. Neurologic disorders. Dental management of the medically compromised patient. 7th ed. St. Louis: Mosby; 2008. p. 483-4.
93. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. Columbus, OH: McGraw-Hill; 2006.
94. Merck Manual Online Medical Library. 18th ed. Porter RS, Kaplan JL, Homeier BP, editors. Whitehouse Station, NJ: Merck Research Laboratories; 2007.
95. Drug Information Handbook for Dentistry. 14th ed. Wynn RL, Meiller TF, Crossley HL, editors. Hudson, OH: Lexi-Comp; 2009.
96. Dickinson C, Millwood J. Toothbrush handle adaptation using silicone impression putty. Dent Update 1999;26:288-9.

Reprint requests:

Dena J. Fischer, DDS, MSD, MS
Assistant Professor
Department of Oral Medicine and Diagnostic Sciences
University of Illinois College of Dentistry
Chicago, IL 60612-7213
fischerd@uic.edu