

# Oral and Maxillofacial Manifestations of Multiple Sclerosis

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## A b s t r a c t

*Multiple sclerosis is a chronic demyelinating disease of the central nervous system which mostly affects young adults living in the northern hemisphere. It is a disease primarily found in temperate climates, being rare in the tropics and increasing in frequency with distance from the equator. Canada has one of the highest prevalence rates in the world. Dentists should be familiar with the clinical manifestations that affect the oral and maxillofacial areas as well as patients' general health. Three of the most frequent oro-facial symptoms include trigeminal neuralgia, trigeminal sensory neuropathy and facial palsy. Dentists should also be aware of the importance of this disease in the diagnosis, treatment and prognosis of certain oro-facial lesions or conditions. This paper reviews 2 cases of multiple sclerosis, highlights its oro-facial manifestations and discusses the dental implications of the disease.*

**MeSH Key Words:** dental care; multiple sclerosis; trigeminal neuralgia

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## Case Presentations

### Case No. 1

A 38-year-old woman with no significant medical history presented to her dentist complaining of numbness on the left side of her face for the previous 3 weeks. This problem, which appeared suddenly, was preceded by similar symptoms in her left hand. She described the numbness as superficial in character and not associated with facial pain or headaches. Upon questioning, the patient described some instability while walking and a lightness in the head when she changed position suddenly, but without marked dizziness or imbalance. A review of other systems revealed no problems. She had no muscle weakness, or auditory or visual problems. However, 2 years previously she had experienced a transitory numbness in her right hand and left leg. She was taking no medications on a regular basis. Her family history was negative.

Oral examination revealed a healthy dentition and no lesions of the oral mucosa. The patient was partially edentulous in the upper and lower arches. The oral soft tissues responded normally to sensory stimulation. The gag reflex was somewhat dampened. The tongue had a normal range of motion. Examination of the head and neck confirmed the presence of a superficial numbness of the left supra-orbital

region and a part of the area innervated by the second and third divisions of the left trigeminal nerve (Fig. 1). The other cranial nerves were normal. Certain neurological anomalies were noted: muted patellar reflexes bilaterally and some trouble with balance.

Magnetic resonance imaging (MRI) confirmed the presence of demyelinating lesions affecting the brain stem and the cerebral hemispheres (Fig. 2).

### Case No. 2

A 47-year-old woman consulted her dentist because of a severe pain on the right side of her mandible for the previous 4 days. The pain was paroxysmal, manifesting itself as repeated sharp "electric shocks" which could be triggered by chewing, tooth brushing, opening her mouth, or even lightly touching the cheek. The pain, which didn't wake the patient, was partially relieved by Lenoltec # 1 (acetaminophen 300 mg, caffeine 15 mg, codeine phosphate 8 mg). The medical history revealed that the patient had experienced parasthesia of the lower half of the right side of her face and of the right side of her tongue approximately 6 months previously (Fig. 3). This condition had resolved after 2 months following a course of prednisone. She had suffered Bell's Palsy 17 years previously and was allergic to aspirin (urticaria). The review of systems

was normal. The patient was not taking medications on a regular basis, and family history was normal.

Oral examination revealed normal mucosal tissues. The "electric shocks" could be precipitated by pulling the right cheek and by rubbing the alveolar mucosa on the buccal aspect of the fourth quadrant. The teeth were healthy, without caries or defective restorations. They were neither mobile nor tender to percussion. The periodontal tissues were normal.

Intraoral examination revealed no sensory or motor deficiencies. There was no apparent trigger zone in the right labio-mental area. The cranial nerves were normal on examination, except for bilateral nystagmus which appeared when the eyes were turned to the limit of movement. No other signs were apparent on examination of the face or the neck. Panoramic radiography revealed no pathological changes.

MRI revealed demyelination in the periventricular regions, the parietal and occipital lobes, the posterior part of the medulla and the junction of the midbrain and the middle cerebellar peduncles, which explained the trigeminal symptoms (Fig. 4). The diagnosis was of tic douloureux in conjunction with multiple sclerosis, the first manifestations of which were the parasthesias of the right side of the face and tongue.

These 2 case presentations illustrate that the principal symptoms of multiple sclerosis in these patients presented as facial numbness and pain and that the dentist was the first health professional to be consulted.

The dentist plays an important role in the management of these conditions as part of a multidisciplinary team (general practice physicians, neurologists, psychologists, etc.) dealing with multiple sclerosis.

### **Epidemiology, Etiology and Pathogenesis**

Multiple sclerosis is a condition which affects the central nervous system and is characterized by areas of demyelination throughout the brain and spinal cord. These areas of demyelination are responsible for the various neurological signs which are pathognomonic of the condition. Multiple sclerosis usually develops slowly, in phases of progression and remission.<sup>1,2</sup> The precise cause remains unknown. Many hypotheses have been put forward, including immune deficiency and viral infection.<sup>1,3</sup> High levels of antibodies to certain viruses, including that which causes measles, have been found in cases. Environmental factors or genetic susceptibility could be important etiologic factors.<sup>1,2</sup>

Multiple sclerosis primarily affects young adults in countries in the northern hemisphere. Canada, with 55.2 to 110 cases per 100,000, is one of the countries with the highest prevalence in the world.<sup>3</sup> Two women are affected for every man. While the age of onset of the first symptoms is usually between 20 and 40, multiple sclerosis seems to be linked to the geographical area of residence for the first 15 years of life. Changing location after this time doesn't appear to modify risk.<sup>4</sup>

The condition manifests itself as plaques or islands of demyelination with destruction of oligodendrocytes accompanied by perivascular inflammation.<sup>1,4</sup> Multiple sclerosis is particularly destructive of the white matter, with a predilection

for the lateral and posterior fascicles of the cervical and dorsal regions, the optic nerves, the brain stem and the periventricular region.<sup>1,5,6</sup> Later on, the grey matter can be affected and the axons of the long tracts destroyed.

### **Clinical Manifestations and Evolution**

Multiple sclerosis is a cyclic disorder characterized by periods of activity and remission which, after a number of relapses, tend to leave permanent neurological sequelae. Some patients present with a favourable form of the condition that involves only one or 2 periods of activity throughout their life, while others suffer major complications in a rapid succession of bouts of disease progression.<sup>1,6,7</sup>

The condition is characterized by several symptoms such as parasthesias of the trunk, the face or the extremities, weakness or clumsiness in a hand or leg, visual problems (partial or complete blindness, unilateral ocular pain, diplopia), locomotor problems, muscular hypertonicity, lack of bladder control and dizziness.<sup>1,2,5</sup> Subtle emotional disturbances are apparent in several patients and behaviour can change as the disease progresses.<sup>8</sup>

Certain clinical manifestations affect the oro-facial region. Three in particular should be of interest to the dentist: trigeminal neuralgia (tic douloureux), sensory neuropathy of the trigeminal nerve (parasthesia) and facial palsy.<sup>6,9,10,11</sup> Trigeminal neuralgia usually appears after the diagnosis of multiple sclerosis has been made (as in case 2 above) and is present in about 1.9% of cases.<sup>3</sup> It is, however, the first manifestation of the disease in 0.3% of cases.<sup>12</sup>

Compared to conventional tic douloureux, which is unilateral, the trigeminal neuralgia caused by multiple sclerosis can be bilateral. The pain is paroxysmal, is described as being like an electric shock and can be provoked by touching the cheek, tooth brushing or mastication. The pain only lasts for a few seconds; however, it can return several times during the day. The pain is usually very severe.<sup>1,6,8-10</sup> It is important that the dentist can distinguish this pain from other types of facial pain, given the different approaches to treatment.<sup>13</sup>

Sensory neuropathy secondary to multiple sclerosis can be progressive, irreversible and bilateral. It preferentially affects the second and third divisions of the trigeminal nerve. Onset is sudden and is sometimes accompanied by pain.<sup>14</sup> Neuropathy of the mental nerve causes numbness of the lower lip and chin, with or without pain.<sup>15,16</sup> The differential diagnosis is complex. Parasthesia can be provoked by: local trauma, odontogenic lesions, neoplasms of the jaws or of the central nervous system, or cerebrovascular conditions. It also arises from neuropathies secondary to AIDS and other systemic conditions.<sup>17,18</sup> The differential diagnosis should include collagen disease, sarcoidosis, amyloid disease, syphilis, osteomyelitis and neuropathies caused by certain medications.<sup>17,19</sup>

Facial paralysis appears later in the course of the disease. It may be difficult to distinguish between the paralysis caused by multiple sclerosis and that due to Bell's Palsy, despite the sophistication of diagnostic tools.<sup>12</sup> Up to 24.3% of multiple sclerosis sufferers may experience facial paralysis.<sup>20</sup>



**Figure 1:** Numbness in left supra-orbital region and area innervated by the second and third divisions of the left trigeminal nerve (affected zones outlined by dots).



**Figure 3:** Numbness of the lower half of the right side of the face (affected zone outlined by dots).

### Investigation and Diagnosis

Diagnosis usually follows detailed clinical examinations and special tests and is usually confirmed by specific diagnostic imaging techniques such as MRI.<sup>6,7,11</sup> Analysis of the cerebrospinal fluid (CSF) is often used to confirm the diagnosis. CSF is abnormal in 55% of cases.<sup>6,7</sup> The level of immunoglobulin G (IgG) is greater than 13%, while the level of lymphocytes and proteins is slightly elevated. These changes are not, however, pathognomonic of multiple sclerosis. MRI is the most sensitive and effective means of detecting areas of demyelination in the central nervous system.<sup>11</sup>

### Treatment

It is essential to manage the symptoms of the condition to improve the quality of life of the patient. The treatment objectives are: prevention of relapse, slowing the progression of the condition, reduction of the severity and intensity of disease progression.<sup>21</sup> The chief treatment modalities focus on the control of symptoms and on the disease itself. Treatment requires the use of steroids, ACTH (adrenocorticotropic hormone), interferon and immunosuppressors (**Table 1**).<sup>21</sup> One of the principal steroids used is prednisone, which coun-



**Figure 2:** Magnetic resonance image confirming the presence of demyelinating lesions in the cerebral hemispheres (dense white areas).



**Figure 4:** Magnetic resonance image confirming the presence of lesions in the brain stem and the median cerebellar peduncles.

ters the progression of multiple sclerosis and has anti-inflammatory properties. This medication, taken orally, has numerous side effects.<sup>22,23</sup> In severe cases, steroids may be administered intravenously for a short period and subsequently taken orally. Dentists should be careful when treating patients on steroid therapy, as such patients may suffer from adrenal atrophy which can lead to adrenal crisis (shock, nausea, vomiting, abdominal pain, diarrhea and further complications including death). Because these patients are more prone to bacterial infections, a dentist performing a surgical intervention should place such a patient on a course of prophylactic antibiotics.<sup>24</sup> Furthermore, it is important to avoid prescribing aspirin and NSAIDs (nonsteroidal anti-inflammatories) for these patients as they greatly raise the risk of gastric and duodenal ulcers.<sup>22,23</sup>

The interferons used to combat multiple sclerosis are powerful medications with numerous side effects. Those most commonly used, Beta 1-a interferon (Rebif) and Beta 1-b interferon (Betaseron), have anti-viral properties and modify the immune response. Their action against multiple sclerosis isn't fully understood.<sup>23</sup> We do know, however, that their effectiveness diminishes after prolonged use.<sup>21</sup> Interferon reduces the frequency of active periods of the disease. It is

**Table 1 Primary treatment of multiple sclerosis<sup>21-24</sup>**

Medication	Role	Secondary effects	Precautions
Steroids	<ul style="list-style-type: none"> <li>Prevent and control acute attacks</li> </ul>	<ul style="list-style-type: none"> <li>Adrenal atrophy</li> <li>Heightened risk of infection</li> <li>Gastro-intestinal problems</li> <li>Candidiasis</li> </ul>	<ul style="list-style-type: none"> <li>Prophylactic antibiotics where indicated</li> <li>Possible adjustment of corticotherapy</li> </ul>
ACTH	<ul style="list-style-type: none"> <li>Prevent and control acute attacks</li> </ul>	<ul style="list-style-type: none"> <li>Same as steroids</li> <li>Limited to the treatment period, usually a few days</li> </ul>	<ul style="list-style-type: none"> <li>Same as steroids</li> </ul>
Interferons	<ul style="list-style-type: none"> <li>Prevent and control acute attacks</li> </ul>	<ul style="list-style-type: none"> <li>Cheilitis</li> <li>Glossitis</li> <li>Gingivitis</li> <li>Stomatitis</li> <li>Candidiasis</li> <li>Xerostomia</li> <li>Dysgeusia</li> <li>Neutropenia</li> <li>Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>Anti-hemorrhagic formula before invasive treatment</li> <li>Prophylactic antibiotics when necessary</li> </ul>
Immunosuppressors	<ul style="list-style-type: none"> <li>Prevent and control acute attacks</li> </ul>	<ul style="list-style-type: none"> <li>Stomatitis</li> <li>Ulcers</li> <li>Gingivitis</li> <li>Candidiasis</li> <li>Thrombocytopenia</li> <li>Neutropenia</li> <li>Anemia</li> <li>Cancer</li> <li>Opportunistic infection</li> </ul>	<ul style="list-style-type: none"> <li>Same as interferons</li> </ul>

self-administered by means of subcutaneous injections which can provoke local reactions of inflammation, pain and necrosis at the injection site.

Flu-like symptoms (fever, shivering, fatigue, headaches, myalgia) can also appear at the beginning of treatment with interferon.<sup>21</sup> These symptoms can be relieved by acetaminophen.<sup>23</sup> Psychiatric problems ranging from depression to suicide can also arise. Finally, interferon can modify certain hematological parameters, notably: hematocrit, hemoglobin, and platelet and white cell counts.<sup>22,23</sup>

The dentist may notice certain oral side effects of the medications such as: cheilitis, gingivitis, stomatitis, xerostomia and candidiasis, dysgeusia or certain changes secondary to neutropenia and thrombocytopenia.<sup>23</sup> Some cases of salivary gland hyperplasia have also been noted.<sup>23</sup>

ACTH, or corticotrophin, is used during acute crises<sup>21</sup> because it stimulates the production of steroids produced by the adrenal gland. We should be cautious about prescribing NSAIDs in combination with ACTH because of the elevated risk of gastro-intestinal ulceration.<sup>22-24</sup>

Among the immunosuppressants prescribed, azathioprine and methotrexate work to inhibit T lymphocyte production. The secondary effects of these medications (anemia, neutropenia and thrombocytopenia) have important implications for dentists.<sup>25</sup> Patients taking these medications have a predisposition to hemorrhage and are particularly susceptible to infection. The principal side effects in the oral cavity are: stomatitis, ulcers, gingivitis, candidiasis and certain other opportunistic infections (e.g. herpes simplex). Finally the long-term use

of immunosuppressors can raise the risk of developing malignant neoplasias.<sup>23</sup>

Other medications can be prescribed to treat or reduce the symptoms of multiple sclerosis. Examples are muscle relaxants, anticonvulsants, antidepressants, anticholinergics and amantadine (Table 2).<sup>21</sup>

The principal muscle relaxants prescribed are baclofen (Lioresal) and diazepam (Valium) which relieve muscle spasms by blocking gamma amino butyric acid (GABA) and by inhibiting mono- and polysynaptic reflexes in the spinal cord.<sup>21</sup> The most common secondary effects of these drugs are: fatigue, somnolence, blackouts, dizziness, hypotension and ataxia.<sup>23</sup>

The anticonvulsants are administered to control the pain of tic douloureux. The most commonly prescribed are carbamazepine (Tegretol), phenytoin (Dilantin) and gabapentine (Neorontin).<sup>21,26</sup> The main oral side effect of Dilantin is gingival hyperplasia. Tegretol can provoke bone marrow suppression, leading to anemia, neutropenia and thrombocytopenia.<sup>23</sup> This must be taken into account when planning dental treatment for these patients.

Anticholinergic agents are used to treat the bladder problems experienced by many patients. Amantadine (Symmetrel) seems to be effective in reducing the fatigue caused by multiple sclerosis.<sup>21</sup>

## Planning Dental Treatment

Patients suffering from multiple sclerosis are taking medications, either short- or long-term, that can have important implications for the planning of dental treatment. The dentist should be particularly prudent in providing treatment to patients taking interferon, steroids or immunosuppressors.

**Table 2 Medications taken to treat the complications of multiple sclerosis<sup>2,14-16</sup>**

Medication	Role	Secondary effects	Precautions
Baclofen	• Muscle relaxant	• Fatigue • Dizziness • Hypotension • Ataxia	• Watch for depression of central nervous system
Diazepam	• Same as Baclofen	• Same as Baclofen	• Same as Baclofen
Carbamazepine	• Treatment of tic douloureux	• Possible bone marrow suppression	• If necessary, check hematological values
Phenytoin	• Treatment of tic douloureux	• Gingival hyperplasia	• Ensure good oral hygiene
Amantadine	• Relief of chronic fatigue	• Xerostomia	
Anticholinergics	• Control of bladder function	• Xerostomia	

In particular, because interferon and immunosuppressors cause anemia and neutropenia, the dentist should prescribe a course of prophylactic antibiotics before performing surgery.<sup>24</sup>

These drugs also may give rise to thrombocytopenia, which may greatly elevate the risk of post-operative hemorrhage.<sup>24</sup> A complete blood count must be instituted before embarking on invasive treatment for patients taking immunosuppressors or interferon.

Patients taking steroids will have adrenal hypofunction and have heightened susceptibility to infection. Antibiotic prophylaxis and adjustment of steroid dosage should be contemplated prior to certain surgical interventions.<sup>24</sup> The dentist should keep in mind that the cardinal signs of inflammation are masked in patients taking steroids or immunosuppressors and that aspirin and NSAIDs significantly increase the risk of ulcers of the digestive tract in patients taking steroid therapy.<sup>23,24</sup>

A certain number of drugs currently prescribed by dentists may interact with medications prescribed for multiple sclerosis. This is the case with aspirin, NSAIDs, acetaminophen, narcotic analgesics and erythromycin. Aspirin and NSAIDs should be used very prudently with patients taking methotrexate. Through various mechanisms (inhibition of tubular secretion, modifying albumin fixation sites, etc.), these drugs have the effect of increasing the amount of free methotrexate, thereby amplifying its cytotoxicity.<sup>21,25</sup>

It is better to avoid the long-term use of acetaminophen in patients taking Dilantin and Tegretol because these medications, which induce the production of microsomal enzymes, can lead to the accumulation of certain hepatotoxic derivatives of acetaminophen.<sup>21,24,25</sup> Narcotic analgesics have a tendency to amplify the central nervous system depression caused by Tegretol and tricyclic antidepressants, and thus should be used with prudence with multiple sclerosis patients taking these drugs. Finally, erythromycin diminishes the clearance of Dilantin and Tegretol (inhibition of cytochrome P-450), thereby amplifying the toxic effects of these drugs.<sup>23,24</sup>

Several types of oral lesions can be observed in patients with multiple sclerosis such as stomatitis, oral ulcers, glossitis, cheilitis, gingivitis, gingival hyperplasia (Dilantin), xerostomia, candidiasis, herpes, opportunistic infections, hemorrhagic changes and even certain forms of cancer (lymphoma, squa-

mous cell carcinoma) in some patients who have been on long-term immunosuppressant treatment.<sup>23,24</sup>

## Conclusion

The cause of multiple sclerosis remains unknown. Both the disease itself, and the many medications taken to manage it, influence the oral health and oral health care of sufferers. The dentist must never forget that these patients tire easily and therefore appointments should be of relatively short duration, preferably early in the morning.<sup>24</sup> ♦

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MEDLINE searches on multiple sclerosis can be requested by CDA members by contacting the Resource Centre at tel.: **1-800-267-6354** or **(613) 523-1770**, ext. 2223; fax: **(613) 523-6574**; e-mail: **info@cda-adc.ca**. Results of searches can be sent by regular mail or e-mail.