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REVIEW

Association of Trigeminal Neuralgia with Multiple Sclerosis: A Comprehensive Review of Neuropathic Pain Treatment

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Abstract

This comprehensive review aimed to evaluate the association between trigeminal neuralgia and multiple sclerosis (MS). Neuropathic pain was analyzed, and trigeminal neuralgia and MS were compared. Pharmacological and surgical treatments for trigeminal neuralgia in patients with MS were explored in detail. The inclusion criteria were as follows: (1) studies of (2) adult participants with trigeminal neuralgia caused by MS, (3) employing pharmacological or surgical interventions and (4) evaluating outcomes related to pain reduction. Carbamazepine or oxcarbazepine is the first-line drug, and lamotrigine, baclofen, gabapentin, and pregabalin are second-line drugs. If the drug cannot control the pain, surgical options must be considered. The surgical procedures include surgical removal of peripheral lesions that are distal to the ganglion, percutaneous gasserian ganglion surgery, stereotactic radiosurgery, and microvascular decompression in the posterior fossa. Owing to the scarcity of data, medical treatment of a patient with MS-related trigeminal neuralgia is challenging. Initiating pharmacological therapy, followed by surgery, is recommended.

Keywords: Multiple sclerosis, neuropathic pain, pharmacological treatment, trigeminal neuralgia

Introduction

Multiple sclerosis (MS) is a disorder that affects the central nervous system, which is characterized by volatile elaboration and contrasting clinical instantiations. Even if pain is one of the most frequent complications of MS, the existence of trigeminal neuralgia (TN) is rare. This review aimed to evaluate the association between TN and MS. Although analogous studies have been conducted in recent times, it is precious to note new data on remedial and clinical approaches as the wisdom is fleetly evolving.

MS

MS is a degenerative disease that causes nerve fiber demyelination and axonal damage (1). The progression of damaged lesions and plaques in the brain leads to not only motor but also sensory and cognitive-communication impairments (2).

In 2013, 2.3 million people were living with MS globally, whereas in 2020, 2.8 million cases were reported (3). MS has four subtypes: relapsing-remitting (RR), secondary progressive, primary progressive, and progressive-remitting types (4). RRMS occurs in approximately 85% of cases. In addition, >50 signs are related to MS. These symptoms can vary not only in duration but also in severity (4,5). Common symptoms include numbness or weakness in one or more limbs, usually occurring on one side of the body at a time, tingling, electric shock sensation that occurs with certain neck movements, especially when the neck is bent forward (Lhermitte sign), lack of coordination, unsteady gait or inability to walk, and blurred vision. The most prominent signs of MS include intense exhaustion; unhappiness; deficits in bladder, bowel, and sexual function; insensibility and/or sensory excitement in the hands and legs; aches; dizziness; increased muscle tone; agitation; and visual, cognitive, speech, and swallowing problems (4,6,7).

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Many MS-related signs may be managed with medical remedies and multidisciplinary care from a team consisting of neurologists, psychologists, physical, occupational, and speech-language therapists (5). Interferons (IFNs) and glatiramer acetate, which are the first approved treatments, are widely used drugs that relatively reduce the frequency of MS relapses (8). Commonly used complaint-modifying curative agents for MS include ocrelizumab, natalizumab, dimethyl fumarate, teriflunomide, IFN-β, and glatiramer acetate. Mitoxantrone (9) is one of the rarely used complaint-modifying treatments for RMS in recent times, whereas alemtuzumab (10-12) and cladribine (13) are recently approved treatment options and are increasingly used.

Neuropathic Pain

According to the International Association for the Study of Pain, neuropathic pain results from a deficit in the somatosensory nervous system (14). The frequency of habitual pain ranges from 3-17. The prevalence ranges from 3.9 to 42.0/100,000 person-times in patients with post-herpetic neuralgia, from 12.6 to 28.9/100,000 person-times in patients with TN, from 15.3 to 72.3/100,000 person-times in patients with diabetic neuralgia, and from 0.2 to 0.4/100,000 person-times for patients with lingual pharyngeal neuralgia. In addition, neuropathic pain was more common in women (60.5% of cases), peaked at the age of 50-64 years, and was more constantly reported by workers and people from pastoral areas (15).

According to Finnerup en al. (16), the vast majority of patients diagnosed with neuropathic pain complain of continuous or sporadic impulsive pain. Neuropathic pain is often characterized as flaming, shooting, stabbing, pressing, or freezing pain (17,18). Neuropathic pain is typically categorized according to its causative condition. The latest ICD 11th edition classified neuropathic pain into peripheral and central neuropathic pain according to the state of damage or condition, which may be located in the peripheral or central somatosensory nervous system (19).

Tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (duloxetine, and venlafaxine) are the first-line medications. Capsaicin patches, lidocaine patches, and subcutaneous botulinum toxin type A injections are recommended only for peripheral neuropathic pain with mild severity (20). Tramadol and opioids are quite tolerable drugs; however, in general, they are not prescribed to patients with chronic pain (21,22). Most medical treatments often have side effects. Thus, many cases do not progress in the pain scale when receiving these medicines at tolerated doses (20). When monotherapy is partially effective, physicians proceed to combination treatment.

TN

The trigeminal nerve is the fifth cranial nerve. Its main function is to innervate sensory and motor sensations in the face. TN is described as a one-sided, abrupt, shock-like pain in one or more parts of areas innervated by the trigeminal nerve are touched.

TN is divided into classic TN and secondary TN (23). The incidence of TN ranges from 0.03 to 0.3 (24-27). In addition, 2-4% of patients with MS (pwMS) may present with trigeminal symptoms and may be the main feature of the disease in 1-5% of patients. By contrast, 2-14% of patients with TN are also diagnosed with MS (23,24,28-36).

The origin of pain is the trigeminal nerve or the region around it. In 80-90% of cases, the pain is caused by vessels that compress the nerve root in the posterior fossa (37-39). Other conditions may also cause pain, for example, MS causes pain in the root entry zone (REZ) of the trigeminal nerve (40). Initial treatment of TN includes drug treatment with anticonvulsants [carbamazepine (CBZ), oxcarbazepine (OXC), phenytoin, fosphenytoin, baclofen, lamotrigine, pimozide, levetiracetam, gabapentin, pregabalin, clonazepam, valproate, and misoprostol]. If drug treatment fails, the pain persists, or the side effects are unacceptable, the physician needs to consider percutaneous radiation therapy or open surgery (Figure 1). In essence, percutaneous, radiosurgical, and open incisional treatments are more effective in patients with TN type 1. Compared with patients with type 1 TN, those with TN type 2 are more likely to have pain recurrence and a shorter pain-free interval. Patients with secondary AI (e.g., tumors) should be treated for underlying pathology (e.g., resection and tumor decompression) to be relieved from pain. In patients who are not candidates for surgery, drug treatment of secondary TN may be offered for symptom control (41).

MS, TN, and Neuropathic Pain

According to the International Classification of Headache Disorders (42) and the TN classification as presented by the Special Interest Group on Neuropathic Pain, classic TN, caused by vascular contraction leading to morphological acclimation in the trigeminal root, is distinguished by secondary TN, due to an identifiable underpinning neurological complaint and idiopathic TN (43).

Over 15% of cases with TN are classified as secondary TN (44-46) and are analyzed in the presence of anatomical abnormalities stirring the trigeminal nerve in addition to vascular compression, in conjunction with plaques caused by MS, tumors, and cranial base abnormalities. The most commonly comprehensible anomalies are plaques caused by MS. PwMS are 20 times more likely to develop TN (32). This neuropathic pain status is observed in 1.9-4.9% of pwMS (47-51), regardless of the MS type. By contrast, only 2-14% of patients with TN are also diagnosed with MS (49).

Secondary TN caused by MS, like classic and idiopathic traumatic brain injury, presents with abrupt, usually one-sided, sharp, or electric shock-like recurrent pain, which is distributed in one or more branches of the trigeminal nerve. The rough attacks,

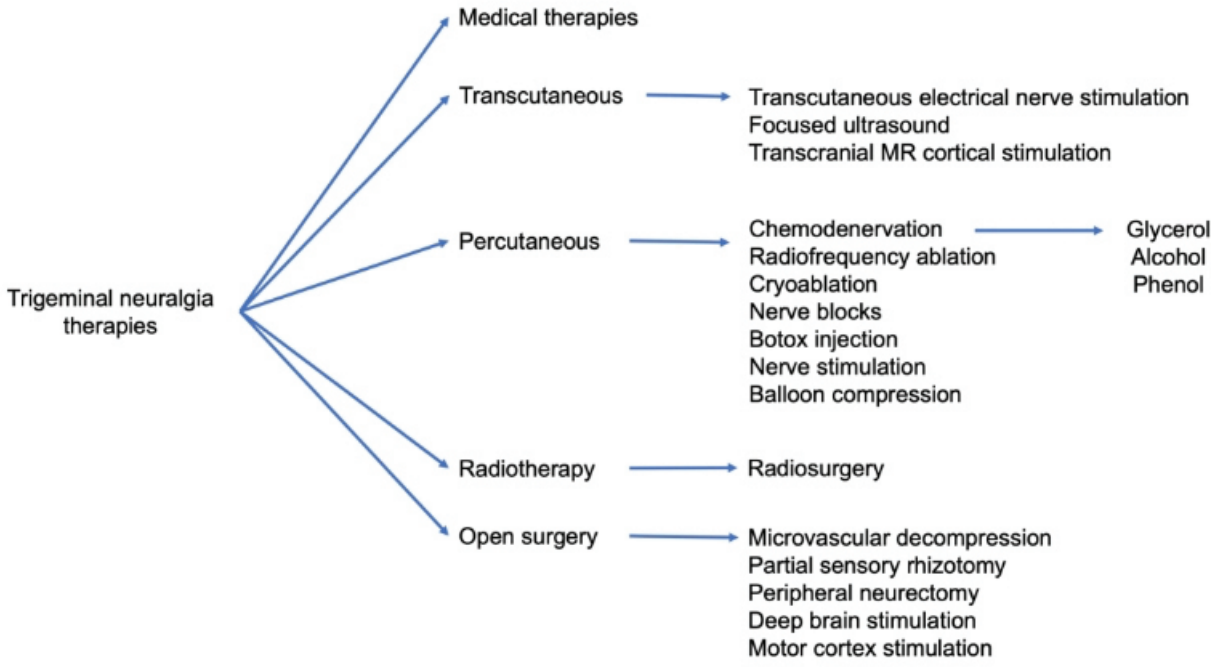

Figure 1. Chart of treatment options for trigeminal neuralgia

which may last from a fraction of a second to 2 min, are usually caused by stimulation of cutaneous or mucosal areas of the trigeminal ganglion called fire chambers.

MS-related TN mostly affects women more than men and mostly on the right side than on the left side (36,52). Still, MS-related TN occurs at a young age in pwMS, with the age of onset between 40 and 50 years (36,52). In MS-related TN, only the first branch may be affected, although the alternate and/or third branch may be affected in approximately 90% of patients (45,46,52). Although signs of MS-related TN resemble those of classic TN, pwMS more often experience bilateral pain. In particular, 18% of pwMS exhibit bilateral TN (36,52). Clinical preferences in sensitive places, which are clear locations of secondary TN, were observed in 37 patients with secondary TN (45,47). Although a younger age and trigeminal sensitivity are related to a high risk of secondary TN and should be regarded as helpful in differentiating secondary TN from classic TN, the lack of these clinical signs does not count TN secondary to MS (53,47). Secondary TN in MS is considered associated with murine demyelinating plaque.

Methods

This review addressed the question of whether pharmacological or surgical treatment is more beneficial in pwMS and TN. Fifty-seven studies were included (17 focused on pharmacological treatment and 40 on surgical treatment). Literature studies were searched in PubMed, Springer Link, Neurology.org, JAMA Neurology, and Journal of Neurosurgery databases. Data recorded between 1966 and 2022 were collected, and the following keywords were also used in the search: neuropathic pain, MS, medications for TN, and surgeries for TN.

So far, no placebo-controlled trials have been conducted. Current studies include small, open-label trials focused on therapies with gabapentin, topiramate, CBZ, misoprostol, lamotrigine, or their combination (23,24,30,32,54-66). These reported cases imply the efficacy of lamotrigine as monotherapy or in combination with gabapentin or CBZ, topiramate, and gabapentin (32). Initial treatment, as in classical and idiopathic TN, is grounded on the use of sodium-channel blockers, namely, CBZ and OXC (67,68).

For pwMS in whom pharmacologic therapy failed, percutaneous, surgical, and radiosurgical options are available. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous techniques at the gasserian ganglion, stereotactic radiosurgery (SRS), and microvascular decompression (MVD) in the posterior fossa (69-71). The main surgical methods include surgical removal of peripheral lesions of the terminal trigeminal nerves at their exit from the facial bones: neurectomy, alcohol injection, radiofrequency thermocoagulation (RFT), or cryosurgery. Transcutaneous ganglion lesions include RFT, chemical lesions by injection of highly concentrated glycerol, and mechanical compression by balloon inflation. Several studies with more than 1 year of follow-up have examined the role of surgical procedures in repairing damage to the gasserian ganglion. The procedures were performed chemically with glycerol injections (72-75), mechanically with balloon compression (76-79), or thermally

with RFT (70,80-82). Although most of the patients reported complete acute pain relief after the lesion procedures, the recurrence rate during follow-up and the incidence of adverse events varied widely.

In the case series by Mohammad-Mohammadi et al. (83), 96 patients underwent 277 procedures to treat TN secondary to MS, including percutaneous glycerin infusion, balloon compression, SRS, RFT, and MVD. Symptoms recurred in 66% of the patients, and 181 procedures were performed for symptom recurrence. Balloon compression was the first procedure to have the highest initial pain-free rate and the longest median pain-free interval, followed by glycerin infusion (83).

Other studies with more than 1 year of follow-up examined the role of SRS in patients with TN of secondary MS (71,84-87). The likelihood of remaining pain-free without resorting to medication after 5 years and the incidence of adverse events are still unclear (32).

In a case series of patients with TN and MS who underwent SRS, only 38% of the patients were still pain-free without medication after 5 years. The incidence of complications, consisting of sensory disturbances of the trigeminal nerve, ranged from 5% to 57% (88). A recent retrospective review of long-term outcomes in 42 patients showed that the incidence rates of cases with pain relief after SRS were 62%, 29%, 22%, and 13% after 1, 3, 5, and 7 years, respectively (89). Retrospective studies have compared the efficacy of SRS with gasserian ganglion surgery (74-90). These studies have shown that patients who underwent gasserian ganglion surgery experience immediate pain relief and no longer need to resort to AI therapies than patients treated with SRS.

In a recent study of a small sample of cases, RFT and SRS originally provided pain relief in 71 cases. Over time, further interventions were needed to achieve satisfactory pain relief in 60 and 29 of the cases with RFT and SRS, respectively (91). MS has long been considered a contraindication of MVD because it affects demyelinating pillars in the central trigeminal pathways (92) or in the REZ of the trigeminal pathway (93).

In the literature, only a few pwMS had undergone MVD for TN, and the results are inconsistent (94,95).

In one series, 5 of 10 patients fared well at a follow-up of 12-39 months. Although the small series and short follow-up time do not allow definitive conclusions, the results suggest that it may be worthwhile not to withhold potential treatment from pwMS (69).

Truini et al. (36) screened 1628 pwMS and found that the incidence of neurovascular compression and its association with demyelinating pontine plaques were higher on the affected side than on the unaffected side (54% vs 0%, p=0.0001). The authors suggested that neurovascular compression with murine demyelinating plaques in combination may represent a dual mechanism underlying the pathophysiology of TN in pwMS.

Some studies support vascular contraction in MS (69,96,97). Neurovascular contraction may act as an attendant medium leading to focal demyelination of primary afferents near the entrance of the trigeminal root into the pons. This thesis is supported by the finding that severe neurovascular contraction in the trigeminal REZ is noted in most cases during surgery (50-100 of cases with TN secondary to MS) (98-100).

MVD in patients with classic TN results in immediate pain relief in most patients. However, this technique is generally described as less effective in patients with MS-related TN than in patients with classic TN. After 5 years, <50% of patients in the case series described by Broggi et al. (69) and 15% in the case series described by Aria et al. (99) were still pain-free compared with approximately 80% of patients who were pain-free after surgery for classic TN. The rate of adverse events during MVD is very low. In the above two case series, only one patient suffered long-term morbidity (facial nerve palsy). Two studies (100,69) reported issues after MVD and one after partial sensory rhizotomy (PSR) (101) in an aggregate of 77 pwTNMS. After MVD, 73% of cases reported pain relief, whereas in one PSR study, 87% reported pain relief, and the rush rates were 39% after MVD and 21.7% after PSR. Impassiveness occurred in 22/23 cases after PSR, including one with dolorosa anesthesia, and this also occurred in 2/105 cases in the MVD group. Hearing impairment was observed in two cases after MVD.

In six studies (74,83,86-88,102), an aggregate of 180 pwTNMS had undergone SRS. The mean age of 60 years was significantly advanced when compared with that of patients with MVD/PSR (52 years). Pain was relieved in 83.6% of cases after the procedure; however, 51.1% experienced recurrence during the follow-up period. Facial numbness, loss of sensation, and paresthesias were reported in 11.7% of the patients.

Eight studies have reported the use of percutaneous glycerol rhizotomy in 299 pwTNMS whose mean age was 51 years (73,76,83,103-105). The standard follow-up time was 42 months, 77.3% of the patients had good pain relief after the treatment, and 53.4% experienced recurrence during the follow-up period. In these patients, the median time to recurrence was 20.3 months, which was significantly shorter than that in patients who underwent SRS (30.4 months).

A total of 74 pwTNMS had undergone balloon microcompression (BC) (78,79,83,106), and 58 had undergone RFT (70,81,92,107), with 86.4% of those who underwent BC and 97.8% of those who underwent RFT reporting good pain relief. However, those who underwent BC reported the highest recurrence rate of 67.0%, whereas those who underwent RFT reported the lowest recurrence rate of 27.5%. For all procedures, recurrence

was reported in 50% of pwTNMS after 2.5 years, and studies providing comparative data with non-pwTNMS showed better outcomes for the latter. The only non-destructive procedure was MVD, an important neurosurgical procedure for which studies are limited. Destructive (ablative) procedures were frequently reported either in the REZ or at the gasserian ganglion.

Deep-brain stimulation of the posterior hypothalamus can be appraised as an ancillary procedure for resistant first-division TN (108), principally in MS (109). TN after failed MVD, significant medical multimorbidity, and MS are generally recommended to undergo gamma knife radiosurgery (110).

Results

Owing to the lack of data, the medical treatment of a patient with pwTNMS is burdensome. It is widely recommended to start with pharmacological therapy and then proceed to surgery. Pharmacological treatment of MS-related TN is demanding because of indigent drug tolerance and lack of evidence-based information (96). CBZ or OXC is the first-line drug, and second-line drugs include lamotrigine, baclofen, gabapentin, and pregabalin (111,112).

If medications cannot control the pain, the physician should consider surgical options. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous gasserian ganglion surgery, SRS, and MVD in the posterior fossa (69-71). These procedures are usually well tolerated; however, none of these methods have ever been supported by studies adequately (113).

Studies of surgical procedures in patients with MS-related TN did not describe in detail short-term and long-term outcomes. In general, both percutaneous and surgical interventions are less effective in terms of postoperative pain enhancement and sustained pain relief rates (23,24,32,83,36).

Discussion

MS is one of the most common chronic neurological conditions; however, its cause is unknown, and its course is unpredictable (114).

TN is characterized by unilateral, touch-induced, brief, ferocious shock-like pain in one or more parts of the trigeminal nerve. Secondary TN in MS is characterized, like classical and idiopathic TN, by unforeseen, generally unilateral, brief, knife- or electric shock-induced, recurrent pain with a distribution consistent with one or more parts of the fifth cranial nerve (43). Established knowledge assumes that MS-related TN is associated with demyelinating pontine plaques.

Initiating pharmacological therapy, followed by surgery, is widely recommended. CBZ or OXC is the first-line drug, and second-line drugs include lamotrigine, baclofen, gabapentin, and pregabalin (111,112). The drugs should be administered slowly, the dosage should be increased gradually, and the patient should be monitored for side effects and possible worsening of existing MS symptoms (115). If medications cannot control the pain, the physician should consider surgical options. Surgical procedures include surgical removal of peripheral lesions distal to the ganglion, percutaneous gasserian ganglion surgery, SRS, and MVD in the posterior fossa (69-71). These procedures are usually well tolerated; however, none of these methods have ever been supported by adequate studies (113).

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: C.P., A.D., Design: C.P., A.D., M.A.B., K.P., Data Collection or Processing: C.P., M.A.B., K.P., Analysis or Interpretation: C.P., Literature Search: C.P., Writing: C.P.

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