Trigeminal and Glossopharyngeal Neuralgia

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KEYWORDS

- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Medical treatment
- Surgical treatment

KEY POINTS

- Trigeminal neuralgia and glossopharyngeal neuralgia are debilitating forms of paroxysmal facial pain and are diagnosed based on history.
- First-line therapy for both pathologic conditions is medication. Carbamazepine is the drug of choice; however, there are other medical options for patients unable to tolerate the side effects of carbamazepine.
- Surgical therapy with either microvascular decompression and/or an ablative procedure is often successful for medically refractory cases and can be considered early in such cases.
- Radiosurgery is emerging as a potential treatment modality for medically refractory cases and it should be considered in patients who cannot undergo more invasive treatment modalities.

INTRODUCTION

Trigeminal neuralgia (TN) is a clinical condition characterized by agonizing paroxysmal pain occurring in one or more divisions of the trigeminal nerve. The characterization of the disease process we are familiar with today, with afflicted individuals complaining of lancinating pain when chewing, speaking, or swallowing, began in the seventeenth century with the work of John Locke.1 Since that time, our understanding of the disease process has advanced significantly. Today, TN is a condition for which there are several treatment options. However, it cannot always be cured and a subset of patients remains refractory to multiple forms of treatment.

Glossopharyngeal neuralgia (GPN) is another paroxysmal pain condition that is characterized by pain in the throat, pharynx, and ears. Affected individuals can lose consciousness because of bradycardia or asystole. The treatment strategy parallels...
that for TN; however, given its rarity, less is known about its pathogenesis and the efficacy of various treatment modalities.

TRIGEMINAL NEURALGIA

Epidemiology

The only estimate on the prevalence of TN is from Penman in his 1968 contribution to the Handbook of Clinical Neurology, in which he approximated 107.5 per million men and 200.2 per million women are afflicted by this condition. The incidence, however, was more extensively studied with early studies reporting approximately 4.3 new cases per 100,000 people annually. The female to male ratio was estimated in these studies to be roughly 1.5 to 1 and there is known age dependence, with an annual incidence of 17.5 per 100,000 in individuals aged 60 to 69 years and 25.6 per 100,000 for those older than 70 years.

More recently, European studies have found significantly higher incidence rates for TN, ranging from 12.6 to 27 per 100,000. Similar to the older studies, these rates vary significantly with age, with incidences of less than 0.5 per 100,000 in subjects younger than 18 years compared with upwards of 80 per 100,000 subjects in older age groups. The female to male ratios in these newer studies are also significantly higher, at approximately 2.3 to 1.

Recent definitions of TN have separated it into two categories: classic, which is idiopathic in nature, and symptomatic, which is associated with an identifiable structural lesion excluding vascular compression. In cases of symptomatic TN, the condition can be associated with a more generalized demyelinating disease process such as multiple sclerosis. In studies evaluating subjects with multiple sclerosis, TN occurs in approximately 2% of subjects, with an increased risk of bilateral symptoms. TN has also been associated with other cranial nerve neuralgias, most notably GPN, in which approximately 11% of subjects have associated TN.

Familial cases of TN are rare but have been reported with estimates of approximately 4% to 5% in patients with unilateral TN. Bilateral TN, however, has a higher familial association of approximately 17%, suggesting a stronger hereditary component in this subpopulation. Although the data are sparse, case reports on families with a strong history of TN suggest an autosomal dominant inheritance pattern.

Pathogenesis

The cause of TN is unknown. It is suspected, however, that both central and peripheral nerve dysfunction play a role. In the case of the peripheral nerve, it is hypothesized that vascular compression of the trigeminal nerve root at the root entry zone leads to chronic focal demyelination and afferent hyperexcitability. This can lead to hyperexcitability in the trigeminal brainstem complex, which subsequently responds to both nonnoxious and noxious stimuli in the same manner leading to the symptoms seen in TN. However, in what is termed the ignition hypothesis, the injured sensory root itself can become a site of ectopic firing. This in turn leads to some neurons continuously firing, which could be the source of baseline burning pain found in some TN; however, other neurons are silent but respond to momentary stimulation for a prolonged period after discharges.

Notably, several aspects of TN suggest a central role for the central action of effective medications. In addition, gray matter in the anterior cingulated cortex, parahippocampus, and temporal lobe was diminished in correspondence with the duration of the disease in patients afflicted with TN, suggesting a mechanism by which the disease process can alter the central nervous system, which, in turn, could prolong the disease.
Diagnosis

In 2004, International Headache Society (IHS) established a set of guidelines for both classic and symptomatic TN. Diagnosis for both conditions is primarily clinical and a diagnosis of either must be based on three fundamental components:

1. Durations lasting from fractions of a second to up to 2 minutes and involving one or more regions of the trigeminal nerve.
2. Characterizations as intense, sharp, superficial, stabbing, and/or precipitated by trigger areas or trigger factors.
3. Stereotyped in the individual patient.

In addition, for classic TN, there can be no clinically evident neurologic disorder and symptoms cannot be attributed to another disorder. Conversely, for symptomatic TN a causative lesion, other than vascular compression, has to be demonstrated.

According to the IHS guidelines, whereas classic TN can involve any distribution of the trigeminal nerve, most cases involve the second or third distribution. The ophthalmic division is involved in less than 5% of cases. In addition, pain never crosses midline. However, it can occur bilaterally. Although it is not part of the definition, a refractory period during which pain cannot be triggered usually follows a painful paroxysm.

The triggers areas are typically in the affected area and the nasolabial fold or chin may be particularly susceptible. The pain is commonly evoked by trivial stimuli such as brushing, shaving, smoking, or talking. However, as further stipulated by the IHS guidelines, it can occur with somatosensory stimulation outside the trigeminal area or with other strong sensory stimuli, such as bright lights or loud sounds.

Symptomatic TN typically demonstrates no refractory period, unlike the classic version. It also, by definition, requires the presence of a causative lesion, necessitating further evaluation, usually with imaging. In a recent set of management guidelines, it was estimated that routine neuroimaging with CT or MRI identifies a lesion, thus separating symptomatic from classic TN, in approximately 15% of cases.

In several studies, special three-dimensional MRI reconstruction sequences have been shown useful in identifying vascular compression, including constructive interference in steady state (CISS), fast imaging employing steady-state acquisition (FIESTA), fast inflow with steady state procession (FISP), and spoiled gradient-recalled (SPGR). However, vascular compression is also frequently seen in normal individuals and the American Academy of Neurology and the European Federation of Neurological Societies (AAN-EFNS) recommendations are inconclusive on the usefulness of using these modalities to diagnose vascular compression.

Although not discussed in the IHS diagnosis, the terms typical and atypical have been used to describe two forms of TN characterized by sporadic, burning, shock-like pain versus constant, aching, lower intensity pain, respectively. It is an often confusing classification because patients can have elements of both types. A new classification system that attempts to allay confusion was proposed in 2003. It describes two types of classic TN: (1) type I characterized by greater than 50% episodic pain, and (2) type II characterized by greater than 50% constant pain. In addition, symptomatic TN is divided into five categories depending on mechanism.

Medical Treatment

Medical therapy remains the first-line treatment of TN. Since the first successful symptom reduction with Dilantin in 1958, various degrees of success have been achieved with neuroleptic, muscle relaxant, and anticonvulsant medications, either alone or in conjunction with one another (Table 1).
Carbamazepine
Since its first implementation for TN in 1962 by Blom, carbamazepine has been the most extensively studied and validated medication for the treatment of TN. Within 10 years of Blom’s first use, four randomized placebo-controlled clinical trials were published demonstrating its effectiveness using dosages ranging from 100 mg to 2.4 g. Recently, after pooling these studies together, a Cochrane Database review further validated these results and with a number needed to treat of 1.8. However, there is evidence that this effectiveness can be reduced over time.

The overall use of carbamazepine, however, is limited by its adverse effects. These include its general side effects, such as ataxia, drowsiness, dizziness, rash, nausea, and vomiting, and its hematologic side effects, such as leukopenia and aplastic anemia. In the same Cochrane Database review, the frequency of these adverse effects was enough to give an overall number to harm of 3. In addition, it has extensive interactions with other drugs. It also has autoinduction of its own metabolism, making equilibrium levels difficult to assess before a grace period of 3 weeks.

Carbamazepine is generally started at 100 mg per day and increased slowly to avoid neurotoxicity. Typical increments are about 100 mg every 3 days until pain is relieved. Serum levels between 25 and 45 μmol/L are often used at optimal concentration ranges. Typical maintenance dosages are between 400 and 800 mg with maximum dosages of 1500 mg. No more than 400 mg should be given in one dose to avoid toxic effects. Given the propensity to drowsiness, it is optimally dosed at night and, given its potential hematologic side effects, a complete blood count is usually obtained before starting treatment and then every 2 weeks for the first few months. Liver and renal function tests should also be assessed before initiation of treatment and then at 2-month intervals. After approximately 1 month without symptoms, patients should be tapered off their medications by approximately 100 mg every week to avoid unnecessary potential side effects.

Oxcarbazepine
Oxcarbazepine is a derivative of carbamazepine, with similar mechanisms of actions, but with less complex pharmacokinetics and a better side-effect profile. Oxcarbazepine has shown to have a similar efficacy to carbamazepine. It was also shown to be efficacious in patients in whom carbamazepine was ineffective, usually within the first month of treatment, but has decreased efficacy over time. Practically,
oxcarbazepine is started at 150 mg per day and increased by 150 mg per day every 3 days until pain relief is achieved. Maintenance doses range from 400 to 1200 mg per day.

**Lamotrigine**

Lamotrigine, a sodium channel modulator, was shown to be efficacious as treatment modality in case studies for both classic and symptomatic TN secondary to multiple sclerosis. Practically, lamotrigine is started at approximately 25 mg per day and increased by 25 mg per day every 3 days until pain relief is achieved. Typical maintenance doses range from 150 to 400 mg per day. Although lamotrigine has a favorable adverse-outcome profile in general, it has been known to lead to Stevens-Johnson syndrome, characterized by a severe rash that appears early in treatment, in which case it should be immediately discontinued.

**Baclofen**

Baclofen, a γ-aminobutyric acid (GABA) derivative, has also been shown effective as both monotherapy and in combination with other medications. Baclofen is generally started at 15 mg per day; typically divided into 5 mg three times a day. The dosage is increased by 5 mg every other day until pain relief is achieved, which is typically at maintenance dosages of around 50 mg per day. If used as an adjuvant medication, the primary medication can be reduced and pain still controlled. Once pain relief is achieved, the dosage of baclofen should be tapered to reduce side effects. This is typically done in increments of 5 mg per week. Tapering can too quickly lead to withdrawal symptoms, including seizures and anxiety. The most common side effects of baclofen itself are gastrointestinal distress and drowsiness.

**Phenytoin**

Phenytoin, which works by stabilizing sodium channels, was the first widespread medication used in the treatment of TN. Now, because of newer medications, it is rarely used alone for chronic management. When used, it is typically started at dosages of 100 mg per day and increased to approximately 100 to 200 mg three times a day. Complications include gingival hyperplasia, hirsutism, and depression. It is also known to interact with several medications, including carbamazepine, which decreases the half-life and thereby increases the concentration. However, in some reports, intravenous phenytoin was shown to be effective at doses of 650 mg and rates of 25 mg per minute in managing acute exacerbations of otherwise medically refractory TN attacks. This effect has also been appreciated in fosphenytoin, which has a better parenteral tolerance than phenytoin. Treatment with intravenous fosphenytoin resulted in symptomatic improvement in 2 days, making it an ideal medication for acute treatments.

**Gabapentin**

Gabapentin, a GABA analogue, was shown effective in patients with both classic and symptomatic TN. Its primary advantage over other medications is its safer adverse-effects profile; the most common side effects are dizziness, fatigue, and weight gain. It is typically started at dosages of 100 mg three times a day and increased up to 2400 mg per day. Mean effective doses are typically around 900 mg.

**Pregabalin**

Pregabalin, another GABA analogue, was also shown to be successful in the treatment of TN. Like gabapentin, it has a relatively benign side-effect profile; most commonly dizziness, drowsiness, dry mouth, and weight gain. It is typically started at dosages of 75 mg twice a day and increased to 150 mg twice a day if no
improvement is seen in 1 week and to 300 mg twice a day if no improvement is seen in 2 weeks. A mean dosage required for improvement is approximately 270 mg per day.55

**Topiramate**

Topiramate, an antiseizure medication, was shown effective in treating classic TN in dosages ranging from 50 mg to 100 mg per day.57 It has also been effective in symptomatic TN secondary to multiple sclerosis58 or postinjury.59 In a meta-analysis of six randomized controlled trials out of China, topiramate was actually found to be more effective than carbamazepine after 2 months of treatment.60 There was, however, no significant difference in adverse effects at 2 months.

**Sumatriptan**

Sumatriptan has also recently been shown to be effective in treating refractory TN when taken orally at dosages of 50 mg twice a day,61 intranasally as an adjuvant,62 or subcutaneously.53 Subcutaneous delivery of 3 mg was shown to significantly improve symptoms within 15 minutes of delivery with effects lasting for approximately 8 hours, making it an ideal potential treatment of acute attacks. This can be combined with oral sumatriptan for both prompt and prolonged control.64

**Surgical Treatment**

Although medical therapy remains the first-line treatment of TN, patients who are refractory to medical therapy or cannot tolerate the side effects can be candidates for interventional therapies.65 These procedures can be divided into two categories: (1) destructive, which includes percutaneous ablative techniques and radiosurgery, and (2) nondestructive or microvascular decompression (MVD) (Table 2).

**Microvascular decompression**

In 1967, Jannetta66 described arterial compression of the trigeminal nerve at the pons as the source of TN, a theory that was postulated by Dandy around 30 years earlier.1 Most neurosurgeons and neurologists now believe that microvascular compression is the source for most idiopathic TN. Largely, this stems from numerous studies demonstrating the effectiveness of MVD in which the contact between the compressing vascular structure and underlying trigeminal nerve is removed. In one of the largest series, Barker and colleagues67 reviewed more than 1100 subjects who had undergone MVD over a 20-year period. At the 10-year evaluation, 70% were pain free.

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<th>Surgical treatments for trigeminal neuralgia</th>
<th>Time to Relief</th>
<th>Success Rates</th>
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and another 4% were controlled with medications. Approximately 30% had recurrence and 11% underwent a second operation. The overall adverse-effect rate was low, with 1% having hearing loss, 1% having facial numbness, 0.2% dying within the postoperative period, and 0.1% having brain stem infarcts. Other studies have demonstrated similar findings of approximately a 70% long-term pain-free rate. This rate of long-term pain relief was seen in other studies, though initial success rates are higher.\textsuperscript{68,69}

Most recurrence after MVD happens within the first 2 years. Although some factors, such as female gender and long pain duration, generally show a positive correlation with recurrence, other factors, such as age at surgery and character of TN, have been unequivocal.\textsuperscript{68–70} Options for recurrence include repeat exploration; however, the potential for adverse effects is higher in these cases.\textsuperscript{71}

**Ablative techniques**

Three percutaneous ablative techniques are commonly used to treat medically refractory TN: radiofrequency rhizotomy (RFL), percutaneous retrogasserian glycerol rhizotomy (PRGR), and balloon microcompression (BMC). Typically, only BMC requires general anesthesia. All three techniques rely on accurate cannulation of the trigeminal cistern through the medial portion of the foramen ovale. This uses three anatomic landmarks, originally described in 1912 by Hartel\textsuperscript{72}, in addition to C-arm fluoroscopic guidance. Using anterior or posterior radiographic views, the foramen oval can also be visualized just posterior to lateral pterygoid wing. A 20-gauge to 22-gauge spinal needle is passed from the entry point toward the foramen. Once the foramen is penetrated, the patient may experience a brief episode of pain and there is often jaw jerk elicited due to penetration of V3 and the semilunar ganglion. Once the cannula is inside the arachnoid of the trigeminal cistern, there is a spontaneous return of cerebrospinal fluid. In general, using lateral radiographs, the cannula should not extend past the clival control to avoid damage to critical neurovascular structures.

**Radiofrequency rhizotomy**

RFL involves inserting an electrode through the foramen ovale into the retrogasserian rootlets and thermally ablating conducting fibers. Stimulation before thermally ablation helps ensure that the desired distributions of the trigeminal nerve are targeted and that no side effects, such as extraocular movement involvement, are elicited. Results with RFL are effective, with almost 100% pain-free rates reported in multiple large series.\textsuperscript{73,74} Recurrence rates in these trials range between 25% and 45% after a single session, but drop to almost zero after multiple sessions. Complications include depressed corneal reflex, which is reported in up to 20% of cases, and, less frequently, masseter weakness or dysesthesias. Patients with symptomatic TN from multiple sclerosis have good results with overall pain-free rates of approximately 70% after 5 years.\textsuperscript{75} Some practitioners argue that the success of RFL shows that it should be used as a first-line surgical treatment except in individuals who specifically want to preserve sensation or have V1 and/or all three distribution involvements.\textsuperscript{76} However, this has been controversial with some studies showing a significantly higher rate of recurrence after RFL versus MVD.\textsuperscript{77}

**Percutaneous retrogasserian glycerol rhizotomy (PRGR)**

The technique of PRGR was first described by Hakanson\textsuperscript{78} in 1982. It uses glycerol injection to destroy the retrogasserian fibers. Like RFL, it was shown effective for both symptomatic TN and classic TN, with initial pain resolution rates of approximately 90% in the first 2 months, which drops to 60% at 1 year, 50% at 3 years, and 40% at
5 to 6 years. Complications are similar to those for RFL and occur in approximately 11% of cases.

**Balloon microcompression**

BMC involves compression of the retrogasserian rootlets using an inflatable balloon. This procedure requires a larger cannula. Compression of the trigeminal ganglion can trigger bradycardia. It is commonly done under general anesthesia. Similar to other percutaneous methods, it has also proven effective. Immediate pain relief is seen in 85% to 99% of patients with recurrence rates ranging from 20% to 40% across multiple series. Complication rates in these studies are also low and range from 4% to 8%.

**Stereotactic radio surgery**

Over the past 10 years, stereotactic radio surgery (SRS) has emerged as another treatment of refractory TN. Two SRS modalities have been investigated: Gamma Knife (Elekta, Atlanta GA), in which multiple beams of simultaneous radiation are used to create an isolated treatment area, and CyberKnife (Accuray, Sunnyvale CA), in which a single radiation beam is maneuvered in three-dimensional space to create a targeted treatment area.

Multiple retrospective series have been published analyzing the effectiveness of treatment with Gamma Knife. For all studies, typical isocenter areas are 4 mm and doses range from 70 to 90 Gy with doses higher than 90 Gy correlating with dysthesias. Similar to other methods of treatment, immediate improvements are relatively high with values of 80% to 90% of patients being pain-free within the first year. However, this value progressively declines to approximately 55% being pain-free at 3 years. The percent of patients with significant pain reductions, characterized by pain adequately controlled with medication, also drop from approximately 60% to 80% at 1 year to 22% to 30% at 7 to 10 years. Similar findings have been found in patients with symptomatic TN. Comparison studies between Gamma Knife and MVD have found MVD to be significantly better in maintaining pain-free status, but MVD is also associated with higher rates of cerebrospinal fluid leak, hearing loss, and persistent diplopia; both modalities have equal rates of facial dysthesias.

CyberKnife has also been shown efficacious in treating TN. Optimal treatment parameters were found to be a maximal median dose of 78 Gy and a median length of treated nerve of 6 mm. Excellent pain relief was found in approximately 70% to 88% of patients with a median time to relief of 7 to 14 days but, similar to other treatment modalities, this value drops progressively to roughly 50% at 2 years. Approximately 50% of patients have posttreatment numbness and approximately 18% have some form of complications.

**GLOSSOPHARYNGEAL NEURALGIA (GPN)**

GPN is an uncommon facial pain syndrome typified by paroxysmal episodes of pain along the auricular and pharyngeal branches of the glossopharyngeal and vagus nerves. Patients typically complain of stabbing pain along one side of the throat, near the tonsillar area, with occasional radiation to the ear. When the parasympathetic functions of the vagus nerve are involved, patients also can have bradycardia, asystole, syncopal episodes, and convulsions. It is often misdiagnosed as TN and can easily be confused with nervus intermedius neuralgia and/or superior laryngeal neuralgia.

**Incidence**

Much less frequent than TN, the incidence of GPN is estimated to be approximately 0.2 to 0.7 per 100,000 patients. Approximately a quarter of these will have
bilateral presentations, which is appreciably higher than in TN, with most patients presenting older than 50 years of age. Also unlike TN, the female to male ratio is approximately equal.7,8

**Diagnosis**

Using the IHS diagnosis guidelines, GPN is also divided into classic and symptomatic GPN, in which the latter requires a causative lesion to be demonstrated by surgery and/or special investigation.23,24 Both types require paroxysmal attacks of facial pain lasting from fractions of a second to up to 2 minutes that are stereotyped in the individual patient. The attacks must be (1) characterized as sharp, stabbing, and severe; (2) precipitated by swallowing, chewing, talking, coughing, or yawning; and (3) within the posterior part of the tongue, tonsillar fossa, pharynx, or beneath the angle of the lower jaw and/or in the ear. Symptomatic GPN may also have an aching pain that persists between paroxysms and can be associated with sensory impairment within the distribution of the glossopharyngeal nerve.

**Treatment**

Similar to TN, the first-line treatment of GPN is pharmacologic with many of the same agents and dosages described above, including carbamazepine or oxcarbazepine, gabapentin, pregabalin, and phenytoin.97 Surgical options, including MVD and rhizotomy, are also available and were shown to be very effective. MVD, in particular, has shown in several studies to have long-term pain-free outcomes in upwards of 80% and usually greater than 90% of subjects treated14,98–101 with a low rate of complications such dysphagia or hoarseness. Other treatment options for TN (described above) have also been performed in GPN in several case series and reports with good results, including radiofrequency ablation102,103 and Gamma Knife ablation.104–108

**SUMMARY**

TN and GPN are painful conditions that, though rare, are often debilitating to those affected. Accurate diagnosis and treatment are crucial for improving patient outcomes. Medical therapy remains the first-line treatment of both, but surgical and radiosurgical modalities are often effective options for patients who remain refractory to medical treatment.

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