Cranial Neuralgias

By Stewart J. Tepper, MD, FAHS

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: This article describes the clinical features and diagnostic criteria, pathophysiology (when known), and treatment strategies of the major cranial neuralgias.

RECENT FINDINGS: Abnormal vascular loops compressing cranial nerves are the most common known pathogenesis associated with the primary neuralgias.

SUMMARY: The most frequently encountered primary neuralgias are trigeminal neuralgia, occipital neuralgia, and, rarely, glossopharyngeal neuralgia. Nervus intermedius neuralgia is even more rare. All neuralgias merit a careful workup for secondary causes. Drug treatment generally relies on antiepileptic drugs, antidepressants, and baclofen. OnabotulinumtoxinA can be useful in treating some cranial neuralgias. Surgical and invasive treatments include ablation, gamma knife treatment, and microvascular decompression.

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Address correspondence to Dr Stewart J. Tepper, Dartmouth Headache Center, Neurology Department, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr, Lebanon, NH 03756, *Stewart.J.Tepper@Dartmouth.edu*.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Tepper discusses the unlabeled/investigational use of all listed medications for the treatment of neuralgias.

INTRODUCTION

Neuralgias of the head constitute a separate chapter in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*), which lists the major cranial neuralgias discussed in this article. The *ICHD-3* specifies the definition of neuralgia as "pain in the distribution(s) of a nerve or nerves, presumed to be due to dysfunction or injury of those neural structures. Common usage has implied a paroxysmal or lancinating quality, but the term *neuralgia* should not be reserved for paroxysmal pains."[1]

Consideration of the anatomy suggests that afferents for the major cranial nerves of the head (V, VII, IX, and X) are irritated in neuralgias. Occipital neuralgia involves the second cervical nerve root, so cervical components for the back of the head are also listed in this article. The pathology of these cranial neuralgias can be due to almost any type of lesion: compressive, metabolic, or infectious.

A problem of causation exists in naming the cranial and upper cervical neuralgias because many of the traditional neuralgias, such as trigeminal neuralgia, are no longer considered primary, since contributory compressive lesions have subsequently been defined as the most common etiology. Examples are the vascular loop compression found in what was considered primary trigeminal neuralgia and the entrapments demonstrable in occipital neuralgia, both of which are now considered secondary.

The *ICHD-3* addressed the problem as follows:

> For the trigeminal, glossopharyngeal, and intermedius neuralgias, the term classical is reserved for cases where imaging or surgery has revealed

vascular compression of the respective nerve. Strictly speaking, classical neuralgias are secondary (to the neurovascular compression), but it is beneficial to separate them from other causes on the basis of the wider therapeutic options and potentially different nerve pathophysiology.[1]

The *ICHD-3* classifies the secondary trigeminal neuropathies with the term *painful trigeminal neuropathy*, with subsets of herpetic, traumatic, demyelinating, neoplastic, and other (TABLE 10-1).[1]

The optimal approach to a patient presenting with a suspected cranial or upper cervical neuralgia is to assume a secondary cause until proven otherwise. As many as 15% of trigeminal neuralgia cases and painful trigeminal neuropathies are associated with lesions at the cerebellopontine angle, including neoplasms and demyelinating lesions. An epidermoid tumor is the most common tumor associated with trigeminal neuropathic pain, but vestibular schwannomas can present this way as well.[2] Since posterior fossa arteriovenous malformations and mass lesions can also manifest as cranial or cervical neuralgias, an MRI study with and without contrast and a magnetic resonance angiogram (MRA) are both mandatory in the workup of patients with cranial neuralgias.

TABLE 10-1 ***ICHD-3* Classification of Painful Lesions of the Cranial Nerves and Other Facial Pain**[a]

13.1 Pain Attributed to a Lesion or Disease of the Trigeminal Nerve

- **13.1.1 Trigeminal neuralgia**
  - 13.1.1.1 Classical trigeminal neuralgia
    - → 13.1.1.1.1 Classical trigeminal neuralgia, purely paroxysmal
    - → 13.1.1.1.2 Classical trigeminal neuralgia with concomitant continuous pain
- **13.1.2 Painful trigeminal neuropathy**
  - 13.1.2.1 Painful trigeminal neuropathy attributed to herpes zoster
  - 13.1.2.2 Trigeminal postherpetic neuralgia
  - 13.1.2.3 Painful posttraumatic trigeminal neuropathy
  - 13.1.2.4 Painful trigeminal neuropathy attributed to other disorder
  - 13.1.2.5 Idiopathic painful trigeminal neuropathy

13.2 Pain Attributed to a Lesion or Disease of the Glossopharyngeal Nerve

13.3 Pain Attributed to a Lesion or Disease of Nervus Intermedius

- **13.3.1 Nervus intermedius neuralgia**
  - 13.3.1.1 Classical nervus intermedius neuralgia
- **13.3.2 Painful nervus intermedius neuropathy**

13.4 Occipital Neuralgia

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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This article describes each of the major cranial and cervical neuralgias, their pathophysiology when known, and treatments, as well as some strategies in proceeding through therapies. The most frequently encountered primary or classical neuralgias are trigeminal neuralgia, occipital neuralgia, and, least common, glossopharyngeal neuralgia. Nervus intermedius neuralgia is even more rare.

As noted, all neuralgias merit a careful workup for secondary causes. Drug treatment generally relies on antiepileptic drugs (AEDs), antidepressants, and baclofen. OnabotulinumtoxinA can be useful to treat some neuralgias. Surgical and invasive treatments include ablation, gamma knife treatment, and microvascular decompression.

KEY POINT

- The *International Classification of Headache Disorders, Third Edition* uses the term classical trigeminal neuralgia for what was previously called primary trigeminal neuralgia.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is likely to be the most frequently encountered cranial neuralgia for the clinician. Because it is so severe and disabling, precision in diagnosis optimizes treatment planning.

Classification

What neurologists traditionally thought of as trigeminal neuralgia is divided into nine subtypes in the *ICHD-3*. The two divisions are classical trigeminal neuralgia and painful trigeminal neuropathies. As noted in the introduction to this article, classical trigeminal neuralgia was thought to be a primary disorder in the past. Since vascular loops are now thought to account for the majority of the cases, the term *primary* was replaced with *classical*.

The other painful trigeminal neuropathies are also secondary or symptomatic. The secondary causes include acute herpetic, postherpetic, posttraumatic, demyelinating, neoplastic, and other. These trigeminal neuropathies, conventionally thought of as secondary, are now categorized under the specific term *painful trigeminal neuropathies*.[1]

Classical Trigeminal Neuralgia

The *ICHD-3* definition of neuralgia cited at the beginning of the section on trigeminal neuralgia is a very useful place to start in the full understanding of classical trigeminal neuralgia, which is defined as the following:

> A disorder characterized by recurrent unilateral brief electric shock–like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s).[1]

CLINICAL FEATURES AND EPIDEMIOLOGY. As noted, traditionally, trigeminal neuralgia was described as consisting of lightninglike paroxysmal pains strictly in the distribution of one or more divisions of cranial nerve V. The electric shock–like pains along with wincing during the stabs were severe enough that the appellation tic douloureux was given to the disorder (CASE 10-1).

Classical trigeminal neuralgia is predominantly a geriatric cranial neuralgia. Overall, the prevalence of trigeminal neuralgia in the population is 0.7 per 100,000.[3,4] Trigeminal neuralgia is more common in women, with prevalence

ranging from 0.03% to 0.3%.[5] The *ICHD-3* diagnostic criteria for classical trigeminal neuralgia are listed in TABLE 10-2.

A realization that not all classical trigeminal neuralgia pain is discrete and stabbing led to the subdivision of the disorder into two forms, a purely paroxysmal form, and a form with concomitant persistent interictal facial pain in a trigeminal distribution. The *ICHD-3* divides the classification between the purely paroxysmal form (numbered in the *ICHD-3* as 13.1.1.1.1) and the form with concomitant persistent interictal facial pain in a trigeminal distribution, the distinction made by what is described as persistent background facial pain (numbered as 13.1.1.1.2).[1]

The American Academy of Neurology (AAN)/European Federation of Neurological Societies (EFNS) guidelines on treatment of trigeminal neuralgia were published in 2008.[6,7] The guideline states:

> The presence of trigeminal sensory deficits, bilateral involvement, and abnormal trigeminal reflexes should be considered useful to disclose

CASE 10-1

A 75-year-old woman presented to the office for evaluation of pain. She described 3 months of terrible pain, which was the worst she had ever experienced and was worse than childbirth. The pain was not continuous, but rather paroxysmal, and she stated it was as if someone had put her cheek in an electric socket. She experienced seconds of pain on the cheek, radiating from in front of her ear to her upper lip and to just below her left nostril.

She could trigger the pain by talking, brushing her teeth, and chewing, and even a light wind on the cheek could precipitate these lightninglike pains. She reduced her eating and had lost weight. She avoided kissing her husband and grandchildren. She had volleys of the pains through the day, and she winced dramatically with each stab.

She went to her dentist, who diagnosed temporomandibular joint syndrome and prescribed a night guard, but this did not alleviate her symptoms. When she tried to put the night guard in, this elicited barrages of pains. The dentist said he would consider a left tooth extraction.

Her neurologic examination was normal. She had a normal corneal reflex on the left, both directly and consensually. Although she was reticent to allow the examination, primary sensory modalities on the left appeared normal in the V1 through V3 distributions.

COMMENT

This patient's history is consistent with classical trigeminal neuralgia, with brief lancinating pains strictly limited to a V2 distribution and no pain in between. The severity of the pain, which had caused the patient to stop eating because of the trigger, speaks to the gravity of the clinical situation, and the severity and the wincing explain the use of the term *tic douloureux*.

Workup should involve an MRI of the brain to include careful assessment of the trigeminal nerve and cerebellopontine angle with and without contrast and magnetic resonance angiogram (MRA) to look for a vascular loop, tumor, or other causes of the syndrome. Treatment should begin with oxcarbazepine.

symptomatic trigeminal neuralgia, whereas younger age of onset, involvement of the first division, unresponsiveness to treatment and abnormal trigeminal evoked potentials are not useful in distinguishing symptomatic from classic trigeminal neuralgia.[6,7]

Maarbjerg and colleagues[8] described 158 patients with trigeminal neuralgia prospectively collected at the Danish Headache Center in Copenhagen in a case series in 2014. Of patients screened for trigeminal neuralgia, 208 had classical trigeminal neuralgia, while 28 were classified as symptomatic. The average age of onset was around 53 years of age. They reported a female predominance (60%) and a slight right-sided predominance (56%) in the patients with classical trigeminal neuralgia. In this series, trigeminal neuralgia affected only V1 in just 4% of patients. Location was either V2, V3, or both in 69%. Location is thus a critical piece of information for the diagnosis. Almost all the cases were unilateral, but 3% did have bilateral pain; this is consistent with the literature, suggesting that 1% to 5% of patients experience bilateral pain, but unilateral pain almost always comes years before the pain becomes bilateral.[9] Most patients' syndrome began with paroxysmal pains (87%). The percentage who experienced concomitant persistent pain plus lancinating pain was 49%.

The overall clinical picture was periods of electriclike jabs of pain with periods of remission. The duration of each attack was 10 seconds to 2 minutes, and then a refractory period generally occurred.[8] Duration of attacks or cycles of pain was generally less than 60 minutes at a time, but 40% of patients had more than 10 cycles of paroxysmal pain per day. The number of attacks per day generally was from three to five in 22% of patients to 10 to 50 in 35% of patients,

***ICHD-3* Criteria for Trigeminal Neuralgia and Classical Trigeminal Neuralgia[a]** TABLE 10-2

Trigeminal Neuralgia

A **Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C**

B **Pain has all of the following characteristics:**

1 Lasting from a fraction of a second to 2 minutes

2 Severe intensity

3 Electric shock–like, shooting, stabbing, or sharp in quality

C **Precipitated by innocuous stimuli within the affected trigeminal distribution**

D **Not better accounted for by another *ICHD-3* diagnosis**

Classical Trigeminal Neuralgia

A **Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia**

B **Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root**

ICHD-3 = International Classification of Headache Disorders, Third Edition; MRI = magnetic resonance imaging.

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although some patients had fewer and more attacks than these bookends. Fortunately for the patients, 63% had longer times of remission, and 37% had months of no pain, while 63% had years of no pain, but the trigeminal neuralgia often returned.[8]

One of the considerations in distinguishing classical trigeminal neuralgia from secondary, painful trigeminal neuropathies is the presence of an abnormal neurologic examination, specifically sensory changes. The assumption has been that viral injury or a mass lesion would leave a footprint of sensory changes not seen with the classical form of trigeminal neuralgia. However, 29% of the Danish patients with classical trigeminal neuralgia had sensory abnormalities, usually hypoesthesia (17%), and these finding were in the painful area in 95% of patients, all on the symptomatic side. As a result, the *ICHD-3* no longer requires a normal neurologic examination for the diagnosis of classical trigeminal neuralgia.[1] An abnormal examination suggests a secondary cause, but this is not invariable.

Triggers are a common accompaniment in classical trigeminal neuralgia and occur in up to 60% of patients. Triggers are described as minimal, seemingly harmless touches to the critical areas. Among the commonly described triggers are chewing, talking, touching, cold or hot sensations, shaving, or wind, usually over the division of cranial nerve V affected. Some latency can occur between the trigger and the onset of pain.[10]

It can be difficult to distinguish classical trigeminal neuralgia from short-lasting unilateral neuralgiform headache attacks (SUNHA).[11,12] SUNHA is the term in the *ICHD-3* that includes two subsets of trigeminal autonomic cephalalgias: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). The usual ways to sort out the two disorders has been to look for the autonomic features and a V1 location for SUNHA and for the triggers in classical trigeminal neuralgia. However, in the Danish case series, 31% of patients with classical trigeminal neuralgia had autonomic features. Less surprising was that 91% of the patients with classical trigeminal neuralgia indeed had triggers, including mastication (73%), touch (69%), tooth brushing (66%), eating (59%), talking (58%), and cold wind on the face (50%).[8] Trigeminal neuralgia should be strictly localized to a trigeminal nerve distribution, while SUNHA can be out of the trigeminal distribution in 20% to 25% of cases.[13,14]

Lacrimation can accompany classical trigeminal neuralgia of any division, and rhinorrhea can occur as well.[15] Lacrimation occurs in up to 25% of patients with classical trigeminal neuralgia but is less regular than with SUNHA and is associated with severe pain.[16]

The overlap in treatment is discussed in the treatment section. Because of overlapping clinical features, some of the Danish patients could not be diagnosed definitively as having trigeminal neuralgia or SUNHA, and Benoliel and colleagues[11] speculated that some may be on a spectrum.

PATHOPHYSIOLOGY. The cause of classical trigeminal neuralgia for most patients was described by Maarbjerg and colleagues[17] as "demyelination of primary sensory trigeminal afferents in the root entry zone." Maarbjerg and colleagues[17] explain that, "most likely, demyelination paves the way for generation of ectopic

impulses and ephaptic crosstalk. In a significant proportion of the patients, the demyelination is caused by a neurovascular conflict with morphological changes such as compression of the trigeminal root."[17]

That is, in at least 50% of patients with classical trigeminal neuralgia, an abnormal vascular loop severely compresses the symptomatic trigeminal division around the dorsal root entry zone, also called neurovascular compression. Studies suggest that these vessels cause destructive demyelination and neurolysis, although some of the described changes can also occur in asymptomatic individuals, but not to the same degree as a symptomatic side (FIGURE 10-1[18]).[19,20] A summary on the controversy of the pathogenesis of classical trigeminal neuralgia and the separation of it from SUNHA can be found in a 2016 review by Burchiel and colleagues[21] and a 2017 review by Benoliel and colleagues.[11]

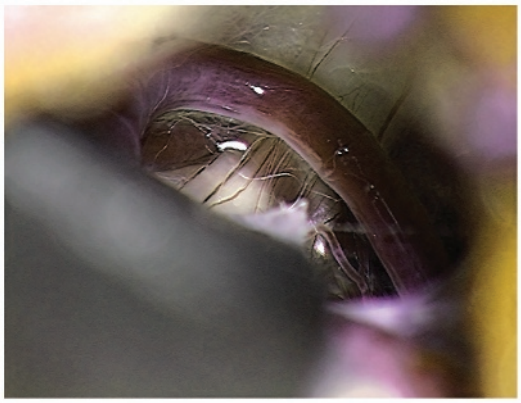

FIGURE 10-1

Aberrant vascular loop seen in classical trigeminal neuralgia.

Reprinted with permission from Rappaport ZH.[18]

Another group of patients has what appears to be classical trigeminal neuralgia but really has subclinical herpes simplex virus involvement. One piece of evidence for this is the reactivation of the virus after surgical procedures for the presumed classical trigeminal neuralgia. This observation suggests that some patients may have a different cause or two causes of symptoms or that in some patients the vascular loop may be unrelated to the presentation.[22]

TREATMENT. The AAN/EFNS trigeminal neuralgia treatment management guidelines state:

> ...carbamazepine (stronger evidence) or oxcarbazepine (better tolerability) should be offered as first-line treatment for pain control. For patients with trigeminal neuralgia refractory to medical therapy, early surgical therapy may be considered. Gasserian ganglion percutaneous techniques, gamma knife treatment, and microvascular decompression may be considered. Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain freedom.[6,7]

Pharmacologic treatment of classical trigeminal neuralgia, as noted, generally begins with an AED, usually carbamazepine or oxcarbazepine. Carbamazepine works in around 70% of patients, but tachyphylaxis can ensue. Adverse events are also an issue, with neutropenia or bone marrow suppression and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and associated hyponatremia requiring discontinuation of dosing. These problems may occur with oxcarbazepine as well but, with the exception of hyponatremia, with lower frequency than with carbamazepine. As the guidelines point out, oxcarbazepine is better tolerated.

KEY POINTS

- **Classical trigeminal neuralgia can occur in two forms: a purely paroxysmal form and a form with concomitant persistent interictal facial pain in a trigeminal distribution.**
- **Most cases of trigeminal neuralgia involve the second or third division of cranial nerve V.**
- **An abnormal examination suggests a secondary cause of trigeminal or other neuralgias, but this is not invariable.**
- **Classical trigeminal neuralgia is almost never in a V1 distribution. Consider other diagnoses and ask about accompanying autonomic features to differentiate short-lasting unilateral neuralgiform headaches, which are usually in a V1 distribution.**
- **Most cases of classical trigeminal neuralgia are thought to be secondary to an abnormal vascular loop compressing the symptomatic trigeminal division around the dorsal root entry zone, also called neurovascular compression.**

Backup medications include baclofen, gabapentin, pregabalin, topiramate, lamotrigine, and valproate, and sometimes multiple medications must be combined.[23,24] These medications work better in the purely paroxysmal classical trigeminal neuralgia with shorter attacks than in the form with concomitant persistent facial pain and longer duration attacks.[25]

SUNHA generally responds to gabapentin or lamotrigine, while classical trigeminal neuralgia responds to carbamazepine or oxcarbazepine. However, either syndrome can respond to any of the AEDs, so response to medication is only partially helpful in a difficult differential diagnosis.[11]

Unfortunately, response to oral medications for classical trigeminal neuralgia becomes less marked with time. Combining medications often becomes necessary, and this is often a harbinger of the need for more aggressive treatment, usually surgery.[26] Use of onabotulinumtoxinA is an intermediate approach between oral medications and surgical or radiologic interventions. Four randomized controlled trials as well as many case series have confirmed its effectiveness. The dose range of onabotulinumtoxinA is 25 units to 75 units, and techniques vary from prespecified injection sites to a follow-the-pain approach.[27–31]

Following oral medications and onabotulinumtoxinA, interventions become more invasive. Radiologic treatment is generally gamma knife therapy. There were more than 165 available papers on PubMed on gamma knife therapy as a treatment for trigeminal neuralgia at the time of writing of this article, and almost all are case series. A representative 2016 case series followed 117 patients for a minimum of 2 years between 1993 and 2011.[32] The authors reported complete response following gamma knife therapy in 81% of patients, excellent response with no medication in 52% of patients, and a pain-free response off medications in 85% of patients at 3 years and 81% at 5 years. About one-third had new or worse numbness on the face, but no patients developed anesthesia dolorosa. The recurrence rate was 12%.[32]

The only randomized controlled trial on gamma knife treatment prospectively compared two doses but was not randomized versus sham or a comparator.[33] With regard to gamma knife treatment, the AAN/EFNS guidelines note about a 50% recurrence rate at 3 years posttreatment and state, "facial numbness is reported in 9% to 37% of patients (although it tends to improve with time) and troublesome sensory loss and/or paresthesia are reported in 6% to 13% (whereas anesthesia dolorosa is practically absent)."[6,7]

There are peripheral nerve alternatives, as noted by the AAN/EFNS guidelines:

> …block or destruction of portions of the trigeminal nerve distal to the gasserian ganglia,…cryotherapy, neurectomies, alcohol injection, phenol injection, peripheral acupuncture, [and] radiofrequency thermocoagulation have all been reported as case series with no independent outcome assessment.[6,7]

They estimated approximately a 50% pain recurrence rate at 1 year for these techniques. Some controversy surrounds the possibility of reactivation of the herpes simplex virus with any invasive surgical procedure.[22]

More invasive techniques are "percutaneous rhizotomies [which] involve penetration of the foramen ovale with a cannula and then controlled lesion of the trigeminal ganglion or root by various means: thermal (radiofrequency thermocoagulation),… chemical (injection of glycerol), or mechanical

(compression by a balloon inflated into Meckel' s cave)."[6,7] Again, only case series exist, and no randomized controlled trials on these techniques have been completed. The AAN/EFNS guidelines note about a 50% recurrence rate by 5 years and sensory loss in at least 50% of patients.[6,7]

Finally, most invasive, but possibly most effective, is microvascular decompression. Although this procedure can be done with endoscopic techniques, most neurosurgeons still perform an open craniotomy. The vascular loop compressing one or more trigeminal nerve roots or divisions is separated from the nerve, with, generally, a gelatin sponge pledget inserted between the vessel and the nerve. The AAN/EFNS guidelines state the following:

> Ninety percent of patients obtain pain relief. Over 80% will still be pain free at 1 year, 75% at 3 years, and 73% at 5 years. The average mortality associated with the operation is 0.2%, although it may raise to 0.5% in some reports. Postoperative morbidity is lowest in high-volume units. Up to 4% of patients incur major problems such as CSF leaks, infarcts, or hematomas. Aseptic meningitis is the [most common] complication (11%). Diplopia due to fourth or sixth nerve damage is often transient… Sensory loss occurs in 7% of patients. The major long-term complication is ipsilateral hearing loss, which can be as high as 10%.[6,7]

Recurrence is up to 50% at 5 years posttreatment, making the effectiveness of microvascular decompression about the same as percutaneous rhizotomies and lower than gamma knife treatment.[6,7] Benoliel and colleagues[10] rated the effectiveness, recurrence, side effects, and complications of trigeminal neuralgia surgery (FIGURE 10-2 and FIGURE 10-3).

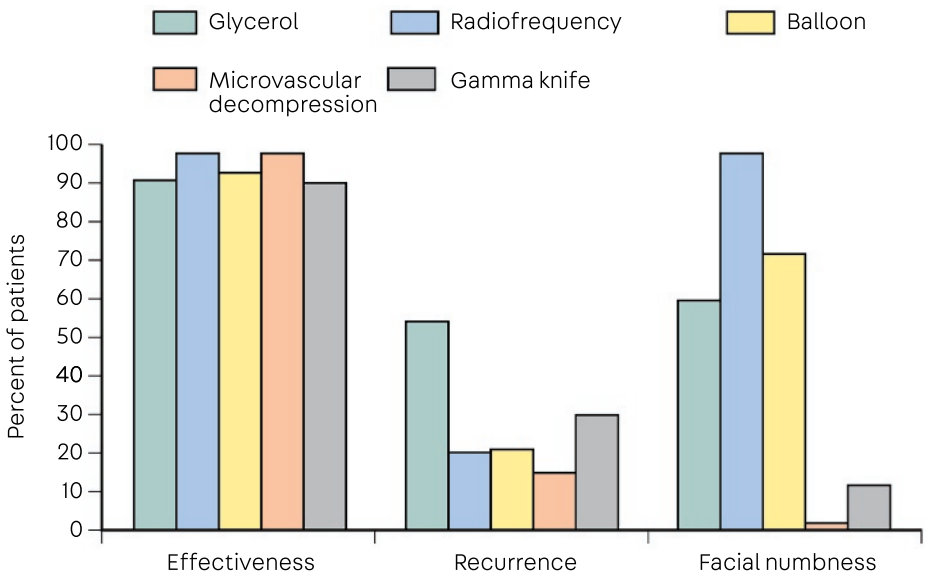

FIGURE 10-2

Effectiveness, recurrence, and side effects of surgical and radiofrequency interventions for trigeminal neuralgia.

Reprinted with permission from Benoliel R, et al.[10] © 2015 Quintessence Publishing Co, Inc.

KEY POINTS

- **Although most cases of classical trigeminal neuralgia respond initially to carbamazepine or oxcarbazepine, short-lasting unilateral neuralgiform headache attacks can also respond to these antiepileptic drugs, so that therapeutic response does not always yield a clear diagnosis.**
- **Numerous peripheral and central surgical and nonsurgical approaches can be tried for classical trigeminal neuralgias, including block or destruction of portions of the trigeminal nerve distal to the gasserian ganglia, percutaneous rhizotomies, gamma knife treatment, and microvascular**
- **The most common painful trigeminal neuropathy is herpetic.**
- **Pain related to any of the painful trigeminal neuropathies is best treated with antiepileptic drugs or tricyclic antidepressants. Early addition of gabapentin to the antiviral regimen in acute shingles may help prevent postherpetic trigeminal neuropathy.**

TREATMENT TRENDS. Because tachyphylaxis appears to occur frequently with the medications used to treat classical trigeminal neuralgia, and combining medications becomes the rule rather than the exception with time, use of gamma knife treatment or microvascular decompression is increasing. The time to consider these procedures has moved to earlier in the disease course, as well.

Painful Trigeminal Neuropathies

The painful trigeminal neuropathies listed by the *ICHD-3* include those due to acute herpes zoster infection, postherpetic, posttraumatic, multiple sclerosis (MS) plaque, and neoplasm. The terminology remains controversial, with some specialists lobbying for a return to the term *symptomatic trigeminal neuralgia*, which did not get adopted in the *ICHD-3* and is therefore archaic.

PAINFUL TRIGEMINAL NEUROPATHY ATTRIBUTED TO ACUTE HERPES ZOSTER. Diagnosis of acute herpetic trigeminal infection (shingles) is made by a confluence of a previous history of chicken pox and an anatomy of dermatologic lesions that respects a division of the trigeminal nerve. It is most common in V1, unlike classical trigeminal neuralgia, which is more common in V2 and V3 (FIGURE 10-4[34]). In the absence of rash or when clinically necessary, a positive assay for varicella-zoster antigen direct immunofluorescence or varicella-zoster viral polymerase chain reaction (PCR) will confirm the diagnosis. There is a female predominance. Acute herpetic infection should always raise the question of immunocompromise either by infection, such as human immunodeficiency virus (HIV), or by cancer.[1,34] Other illnesses or associations with the onset of shingles include trauma, malnutrition, diabetes mellitus, steroid use or dependence, chemotherapeutic or cytotoxic medications, stress, and the presence of chronic obstructive pulmonary disease.[35]

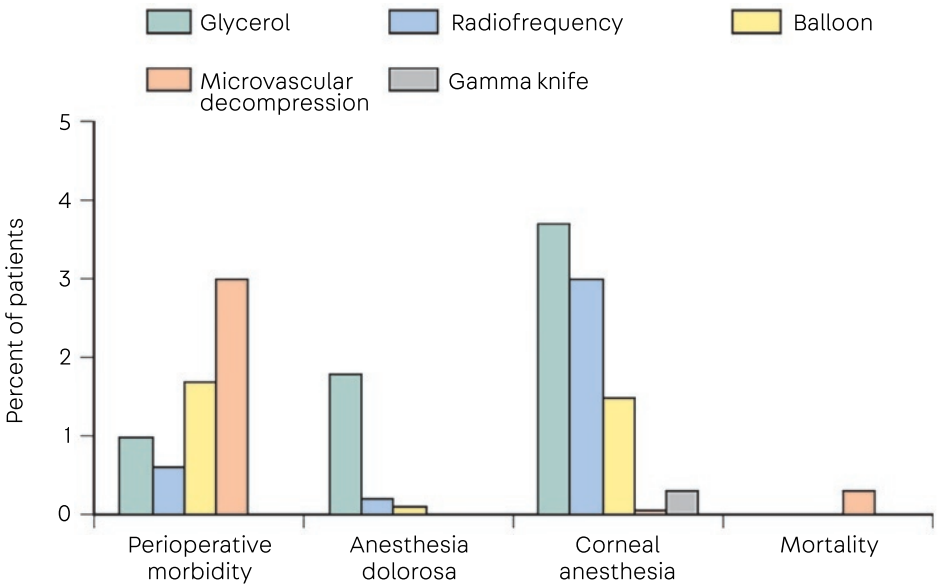

FIGURE 10-3

Complications and side effects of surgical and radiofrequency interventions for trigeminal neuralgia.

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Once a diagnosis of acute herpes zoster in a trigeminal root is established, the first step for treatment is antiviral medication; treatment can consist of acyclovir, famciclovir, valacyclovir, and, where available, brivudine. Doses are listed in TABLE 10-3.[36]

Neuralgic pain from any of the painful trigeminal neuropathies, including acute herpetic infection, is best treated with AEDs, specifically gabapentin and pregabalin or tricyclic antidepressants (TCAs), eg, amitriptyline and nortriptyline.[36,37] The pain of acute trigeminal herpes zoster infection may actually play a role in precipitating postherpetic neuropathy, and some case series suggest that the addition of gabapentin to the antiviral regimen from the beginning may reduce the rate of onset of the delayed syndrome.[38]

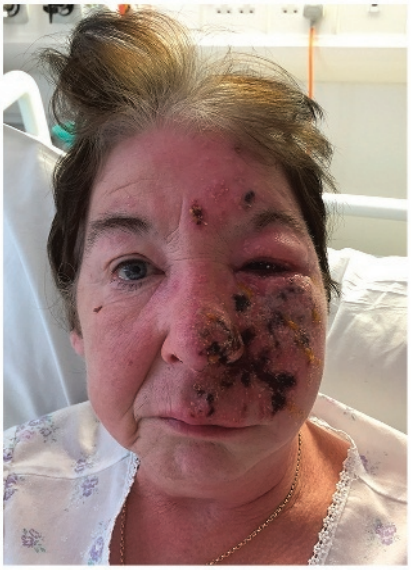

FIGURE 10-4
Painful trigeminal neuropathy attributed to acute herpes zoster.
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POSTHERPETIC TRIGEMINAL NEUROPATHY. When the pain within a trigeminal division from a herpes infection persists beyond 3 months, the diagnosis of postherpetic neuropathy, also called postherpetic neuralgia, can be made. This problem is more frequent in older patients. Again, the usual location is V1 in at least 22% of patients. Most patients have continuous pain, generally described as burning, sometimes with paroxysms of pain superimposed.[10] The prevalence of postherpetic neuropathy has been reported to be as low as 0.09 and as high as 0.7 per 100,000.[3,4,39]

The cause of postherpetic neuropathy is localized trigeminal demyelination where the acute infection occurred. (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of postherpetic neuropathy.[1]) A wide range of estimates for the likelihood of developing the delayed syndrome have been promulgated, from 9% to 73%, but a predictor is

Antiviral Therapy for Acute Trigeminal Herpes Zoster Infection[a] TABLE 10-3

Medication	Dose
Acyclovir	800 mg orally 5 times daily for 7–10 days
Famciclovir	500 mg orally every 8 hours for 7 days
Valacyclovir	1 g orally every 8 hours for 7 days
Brivudine	125 mg/d orally for 7 days (not available in the United States)

[a] Data from Klasser GD, Ahmed AS, J Can Dent Assoc.[36]

when pain is present after the dermatologic eruption clears.[35,38] As noted, the addition of gabapentin during the acute phase may help prevent the later symptom development.[38]

Proven pain-reducing medications for postherpetic trigeminal neuropathy begin with the AEDs, the most effective of which are gabapentin, pregabalin, carbamazepine, and phenytoin. If these fail or are contraindicated, TCAs and serotonin norepinephrine reuptake inhibitors (SNRIs) can be useful, as can topical capsaicin (8%) and lidocaine. Again, when all else fails, there have been a handful of case reports on the use of onabotulinumtoxinA in treatment of the syndrome.[35] Finally, reports of performance of dorsal root entry zone lesioning procedures have described benefit in more than half of patients.[18]

PAINFUL POSTTRAUMATIC TRIGEMINAL NEUROPATHY. Painful posttraumatic trigeminal neuropathies come from a wide variety and severities of injuries, from dental surgery to fractures. One form of this disorder was previously called anesthesia dolorosa, now subsumed into this group of disorders when trigeminal in location. Benoliel and colleagues[37] summarized the pathophysiology:

> Following traumatic tissue damage, an inflammatory response is initiated, crucial to the onset of neuropathic pain… If as a consequence of trauma, neuronal tissue is severely injured (eg, transection), cell death may ensue. However, if the proximal stump survives, healing involves disorganized sprouting of nerve fibers that form a neuroma. Neuroma formation is often dependent on the degree of nerve damage and always occurs when the perineurium is cut. Milder injuries, such as nerve constriction or compression, may also cause regions of neuroma formation and focal demyelination. These regions are characterized by ectopic discharge… also seen in the cell bodies of injured nerves in the dorsal root or trigeminal ganglia. These phenomena partly explain spontaneous neuropathic pain.[37]

Medical, not surgical, management is recommended for painful posttraumatic trigeminal neuropathies; the standby medications remain AEDs and TCAs. Gabapentin and pregabalin work in both postherpetic and posttraumatic trigeminal painful neuropathies. SNRIs also work in posttraumatic painful trigeminal neuropathies.

Benoliel and colleagues[37] list the following algorithm:

> The choice between TCAs or SNRIs and the use of gabapentin or pregabalin is based on the medical profile and other patient-based variables (profession, comorbidities). TCAs are more effective than gabapentin/pregabalin but have significantly more side effects. SNRIs have not been as extensively tested as TCAs but seem less effective for neuropathic pain.[37]

PAINFUL TRIGEMINAL NEUROPATHY ATTRIBUTED TO MULTIPLE SCLEROSIS PLAQUE. MS lesions at the dorsal root entry zone can trigger neuropathic pain in a trigeminal division, and at times can be difficult to distinguish from classical trigeminal neuralgia. Cruccu and colleagues[40] studied 130 patients with MS who had trigeminal neuralgia or trigeminal disturbances; the patients were

imaged and usually demonstrated pontine demyelinating lesions (FIGURE 10-5[41]). Tenser and colleagues[42] described patients with MS with both a plaque and a vascular loop, so there may be a dual mechanism in some cases.

Prevalence of painful trigeminal neuropathy attributed to an MS plaque ranges from 1.5% to 7.9% of patients with MS, with onset of the syndrome occurring at a mean of 12 years into established MS. The pain of MS trigeminal neuralgia can be bilateral.[43,44]

Once a diagnosis of MS is established, treatment is empiric. No randomized controlled trials exist for MS plaque-induced trigeminal pain, and the level of evidence is quite low. The pain may be more refractory in MS than in classical trigeminal neuralgia.

Small case series and reports suggest possible benefit of AEDs including gabapentin, carbamazepine, topiramate, and lamotrigine. Two case series describe the effectiveness of misoprostol.[6]

Both percutaneous retrogasserian balloon compression and gamma knife treatment have been suggested for refractory MS trigeminal neuralgia pain. Again, prospective randomized controlled trials are lacking.

KEY POINTS

- Proven pain-reducing medications for postherpetic trigeminal neuropathy begin with antiepileptic drugs. If these fail or are contraindicated, tricyclic antidepressants or serotonin norepinephrine reuptake inhibitors can be useful, as can topical capsaicin and lidocaine.
- Medical, not surgical, management is recommended for treatment of painful trigeminal neuropathies.
- Prevalence of painful trigeminal neuropathy attributed to a multiple sclerosis plaque ranges from 1.5% to 7.9% of patients with multiple sclerosis.

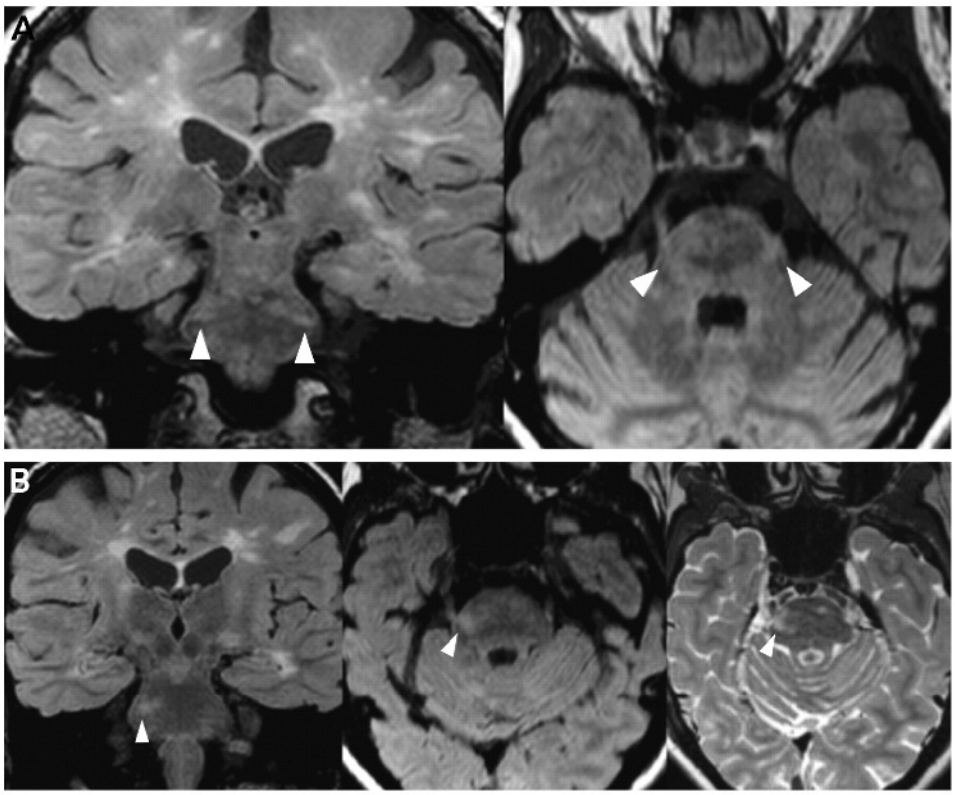

FIGURE 10-5

Multiple sclerosis demyelinating lesions causing painful trigeminal neuropathy. *A*, Coronal fluid-attenuated inversion recovery (FLAIR) (*left*) and axial reconstruction (*right*) showing bilateral hyperintense lesions in the trigeminal root entry zones and tracts (*arrowheads*), with increased signal in the transcisternal parts of the nerves. *B*, Coronal FLAIR (*left*), axial reconstruction (*middle*), and the corresponding axial T2 turbo spin echo axial reconstruction (*right*) showing a hyperintense lesion in the trigeminal root entry zone (*arrowheads*), with high signal seen in the transcisternal part of the trigeminal nerve.

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In 2014, Tuleasca and colleagues[45] described an uncontrolled but prospectively collected series of 43 patients with MS who had trigeminal neuralgia who were treated with gamma knife treatment and were followed for a mean of 53.8 months. More than 90% of patients experienced immediate pain relief, and the study showed a 12.8% relapse rate at 1 year, a 29.2% relapse rate at 3 years, and a 66.9% relapse rate at 5 years. Hypoesthesia occurred in 11.5% of patients for up to 2 years. This case series was suggestive of a very fast onset and long duration of effect.[45]

A large retrospective comparison of case series was reported in 2017. A quick response for pain relief was reported in 87% of patients treated with balloon compression and in 23% of patients treated with gamma knife, which often requires a longer period of time to show clinical effect. The 50% recurrence rate was at 1 year for the patients treated with balloon compression and at 18 months for the patients treated with gamma knife. The adverse events were higher with balloon compression at 21% versus only 3% for gamma knife.[46] This may confirm a number of features of gamma knife treatment observed in classical trigeminal neuralgia in that it is perhaps slower to show onset, perhaps has a lower ceiling of effect, and has a potential for longer effect duration.

GLOSSOPHARYNGEAL NEURALGIA

The *ICHD-3* description on glossopharyngeal neuralgia is very helpful in setting the stage for the clinician and is defined as the following:

> A disorder characterized by unilateral brief stabbing pain, abrupt in onset and termination, in the distributions not only of the glossopharyngeal nerve but also of the auricular and pharyngeal branches of the vagus nerve. Pain is experienced in the ear, base of the tongue, tonsillar fossa, and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking, or coughing and may remit and relapse in the fashion of trigeminal neuralgia.[1]

Anatomy

Recognition of the anatomy of the glossopharyngeal nerve is necessary for understanding the variety of presentations of glossopharyngeal neuralgia. The nerve has both efferent and afferent functions, including motor, parasympathetic, and sensory. The nerve connects with the sympathetic nervous system, the facial nerve, and the vagus nerve.

The afferent part of the nerve has two major branches: the auricular branch, also called the tympanic, and the pharyngeal branch. The auricular branch carries sensation from the auricle and external auditory meatus of the ear and from the mastoid. The pharyngeal branch conducts sensation from the mucosa of the pharynx. The connections between the vagal sensory nerves and the pharyngeal branches allow for sensory transmission from the posterior throat, soft palate, the tongue base, and the tonsils.

These afferents synapse in the trigeminal nucleus caudalis and spinal nucleus of V. Because there is a combination of nerves from the somatic, visceral, and autonomic pathways peripherally and centrally, the admixture activation can result in syncope and other vagal manifestations, described below.

Clinical Features and Epidemiology

The onset of glossopharyngeal neuralgia is often subacute, as patients begin to have unpleasant sensations in one side of the jaw, inside the mouth, and in the ear for weeks to months. The actual distribution of pain not only includes the glossopharyngeal nerve, but, by virtue of the anatomy described above, can extend into the pharyngeal and auricular vagal branches.

The location of pain can be in the ear, throat, tongue, larynx, and jaw or inferior to the angle of the jaw. The pain often radiates, most commonly from the mouth and pharynx to the ear. Patients can trigger attacks by chewing, swallowing cold liquids, talking, coughing, sneezing, touching the inside of the mouth, or yawning.

The pain is usually paroxysmal, from 2 seconds to 2 minutes (average duration is 8 to 50 seconds); however, many patients have lingering, burning, deep interictal pain. Sometimes patients experience globus or a foreign body sensation in the throat. The quality of the pain is lightninglike but can be described as clicking or scratching. The attacks can awaken patients at night, and stabbing pains can occur 30 to 40 times up to 200 times per day.[47] Diagnosis can be confirmed with administration of a local anesthetic to the pharynx and tonsils, which can stop the paroxysms transiently.

About 25% of glossopharyngeal neuralgia presents bilaterally. There is a geriatric predominance, with mean age of onset at 64 years of age.[48] Although prevalence numbers are lacking, the incidence of glossopharyngeal neuralgia in population-based studies has been reported from 0.2 to 0.8 per 100,000.[4] (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of glossopharyngeal neuralgia.[1])

The distribution of pain is glossopharyngeal but also vagal in the auricular and pharyngeal branches. When these vagal branches are more involved, vagal consequences can be seen clinically, which can include voice abnormalities such as hoarseness and cough, as well as neurocardiogenic bradycardia, sick sinus syndrome, asystole, and syncope.[49] When both the vagus and the glossopharyngeal cranial nerves are involved, some prefer the term vagoglossopharyngeal neuralgia, a term which is not included in the *ICHD-3*.

As with any neuralgia, the neuralgia can be primary or classical or secondary or symptomatic. The primary pathogenesis again is attributed to neurovascular compression (**FIGURE 10-6**[50]). The secondary causes, requiring a careful imaging workup, include tumor, trauma, infection, carotid aneurysm, demyelinating lesions, Chiari malformation, or elongation of the stylohyoid ligament or process lateral to the glossopharyngeal nerve (**CASE 10-2**).

As noted for diagnosis, topical anesthesia of the trigger areas stops both the trigger and the pain of glossopharyngeal neuralgia transiently. Further treatment for classical glossopharyngeal neuralgia starts with the same medications used for trigeminal neuralgia: carbamazepine, oxcarbazepine, baclofen, gabapentin, pregabalin, lamotrigine, or phenytoin. Invasive procedures suggested if medications fail include radiofrequency ablation, gamma knife treatment, glossopharyngeal and vagal rhizotomy, or microvascular decompression; the latter treatment is suggested if a vascular loop is identified on imaging. Recurrence rates may be lower with surgical

KEY POINTS

- **The pain of glossopharyngeal neuralgia not only includes the distribution of the glossopharyngeal nerve but can extend into the pharyngeal and auricular vagal branches.**

- **Glossopharyngeal neuralgia is generally felt in the posterior tongue, pharynx, tonsillar fossa, or below the lower jaw angle and the ear. Clinical manifestations such as hoarseness, cough, neurocardiogenic bradycardia, sick sinus syndrome, asystole, seizures, and syncope suggest vagal involvement.**

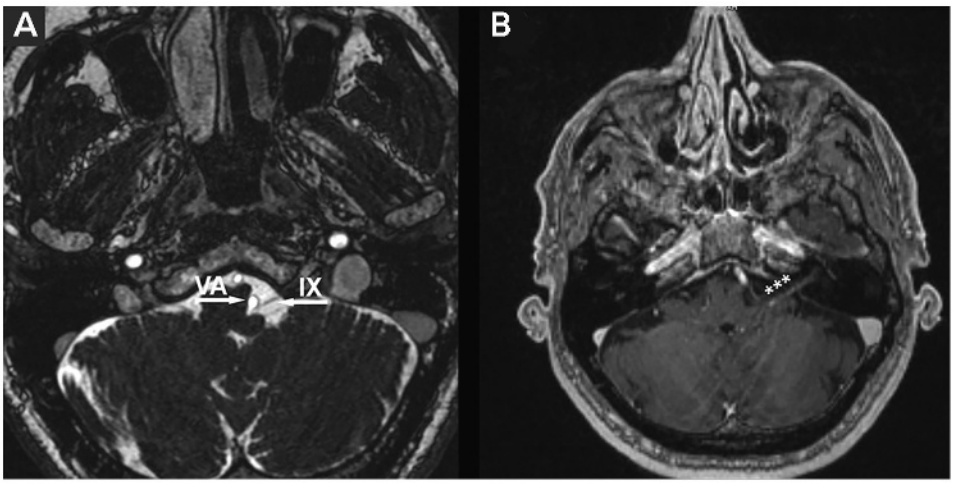

FIGURE 10-6

MRI findings in a patient with recent-onset glossopharyngeal neuralgia. Axial T2-weighted image (*A*) shows the neurovascular conflict between the left glossopharyngeal nerve (IX) and the vertebral artery (VA). The VA, lying on the medulla, compresses the proximal portion of the glossopharyngeal nerve. On postcontrast T1-weighted image (*B*), the nerve shows homogeneous enhancement (*asterisks*) after gadolinium.

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CASE 10-2

A 65-year-old woman was referred for a 6-month history of paroxysms of severe, shooting pains in the back left side of her mouth at the tongue base, radiating up to the angle of the jaw and bottom of the ear. Each stab lasted about 10 seconds, and she experienced about six shocks of pain per hour. She could trigger the pains by swallowing or yawning.

The pains were terrible, but even worse was that she had been fainting with some of the attacks, losing consciousness for 10 to 30 seconds. She did not experience tongue biting, incontinence, or postevent confusion. Sometimes she experienced severe coughing jags.

She had a normal brain MRI with and without contrast and a normal EEG. She underwent cardiac monitoring during a syncopal pain spell and had severe bradycardia and premature atrial contractions. A magnetic resonance angiogram (MRA) showed an abnormal loop of the posterior inferior cerebellar artery near the left cranial nerves IX and X.

COMMENT

This patient meets *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for glossopharyngeal neuralgia, but the syncope and bradycardia point to vagal involvement as well, also suggested by the MRA findings. Her diagnosis would have been vagoglossopharyngeal neuralgia by the old *ICHD-3 beta* terminology, now just a subset of *ICHD-3* glossopharyngeal neuralgia. The cardiac manifestations are severe and potentially life-threatening. Surgical intervention, most likely with microvascular decompression, should be considered urgently rather than waiting to see if medications will suppress her vagal signs and symptoms.

glossopharyngeal neuralgia procedures than for classical trigeminal neuralgia, but, in the past, operative mortality has been reported as high as 5%. Adverse events from surgery include dysphagia and hoarseness.[51]

Treatment Trends

The presence of syncope, suggestive of vagal involvement, makes an imaging search for a surgically remediable vascular loop more urgent. Also, glossopharyngeal neuralgia with or without vagal involvement is so rare that a secondary cause should always be thought of and searched for first.

When glossopharyngeal neuralgia is poorly responsive to medication, a more invasive procedure, such as microvascular decompression or gamma knife treatment, is clearly indicated. Current thought is to consider proceeding to these interventions without first stepping through medications, as the consequences of untreated vagal discharge can be fatal.

NERVUS INTERMEDIUS (FACIAL NERVE) NEURALGIA

The nervus intermedius is a sensory branch of the facial nerve. It serves sensation around the ear, including the external auditory meatus and the skin behind the ear, as well as over the mastoid. The nerve travels centrally with the perikaryons in the geniculate ganglion. A former term for this neuralgia was geniculate neuralgia. In 1907, Hunt[52] originally described this neuralgia, which he called "prosopalgia," as involving both ear pain and a poorly characterized and deep facial pain.

Nervus intermedius neuralgia can present as either a set of brief, severe, stabbing, shooting, piercing, or sharp pains, or pains of longer duration, from 2 seconds to minutes in length. Continuous persistent pain is also described in this condition.

The location of pain is recognizable, as it is deep within the internal auditory canal. The patients usually have a trigger that occurs with touching the posterior wall of the external auditory canal or a zone around the ear.

Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of nervus intermedius neuralgia.[1] Nervus intermedius neuralgia is rare enough that a very careful workup for secondary causes is required. Herpes zoster is the most frequently described attributable etiology.

Treatment recommendations are empiric, and the medications used are similar to those used with other neuralgias. A small noncontrolled series of refractory patients have successfully undergone surgical removal of the geniculate ganglion and the nervus intermedius.[53]

OCCIPITAL NEURALGIA

Occipital neuralgia is a neuralgia that is often overdiagnosed when patients with migraine have posterior pain and tenderness over the greater occipital notch or where the greater occipital nerve exits. The *ICHD-3* criteria for diagnosis of occipital neuralgia require that paroxysms of pain occur, variously described as brief (seconds to minutes) or sharp or stabbing strictly localized to one or more of the three occipital nerves, greater, lesser, or third, and either unilateral or bilateral.[1] Thus, persistent chronic, aching pain is not consistent with this diagnosis.

Furthermore, the criteria require tenderness, dysesthesia, or allodynia over the emerging symptomatic nerve or a trigger point there. A positive Tinel sign

KEY POINTS

- **Nervus intermedius neuralgia can present as either a set of brief, severe, stabbing, shooting, piercing, or sharp pains, or pains of longer duration, from 2 seconds to minutes in duration deep within the internal auditory canal. The patients usually have a trigger that occurs with touching the posterior wall of the external auditory canal or a zone around the ear.**
- **Occipital neuralgia is paroxysmal and generally occurs in the distribution of the greater occipital nerve. A different location or a continuous pain, especially with other associated symptoms, should call for a reconsideration of the diagnosis.**
- **Treatment of occipital neuralgia begins with a peripheral nerve block.**

can occur over the nerve. Finally, elimination of the pain with a nerve block over the affected nerve is mandatory for diagnosis. Location can be radiating up the posterior part of the head to the vertex. The affected nerve is the greater occipital nerve 90% of the time.[54]

Occasionally, the pain may reach to frontal and periorbital locations as trigeminocervical interneurons overlap in the spinal nucleus of V,[55] but generally the pain should respect the dermatome of the affected nerve from a diagnostic standpoint. Complicating the diagnosis are connections with cervical sympathetic pathways and cranial nerves VIII, IX, and X, which can result in descriptions by patients of alteration of vision, eye pain, nausea, dizziness, tinnitus, and nasal congestion.

The greater occipital nerve derives from the C2 dorsal ramus, travels below the inferior oblique, then pierces the semispinalis capitis, splenius capitis, and trapezius. The usual cause of greater occipital neuralgia is entrapment along the path from C2 to the trapezius aponeurosis (**FIGURE 10-7**).[54]

Again, differential diagnosis requires elimination of secondary causes, including neoplasm, infection, vascular malformations, giant cell arteritis, or Chiari malformations. Structural causes can include abnormalities in the atlantoaxial, atlantooccipital, or zygapophysial joints or cervical facet arthritis. No studies exist on the prevalence of occipital neuralgia in the general population (**CASE 10-3**). Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of occipital neuralgia.[1]

Treatment begins with the nerve block. This is generally done over the occipital notch, but ultrasound can give greater accuracy.[56]

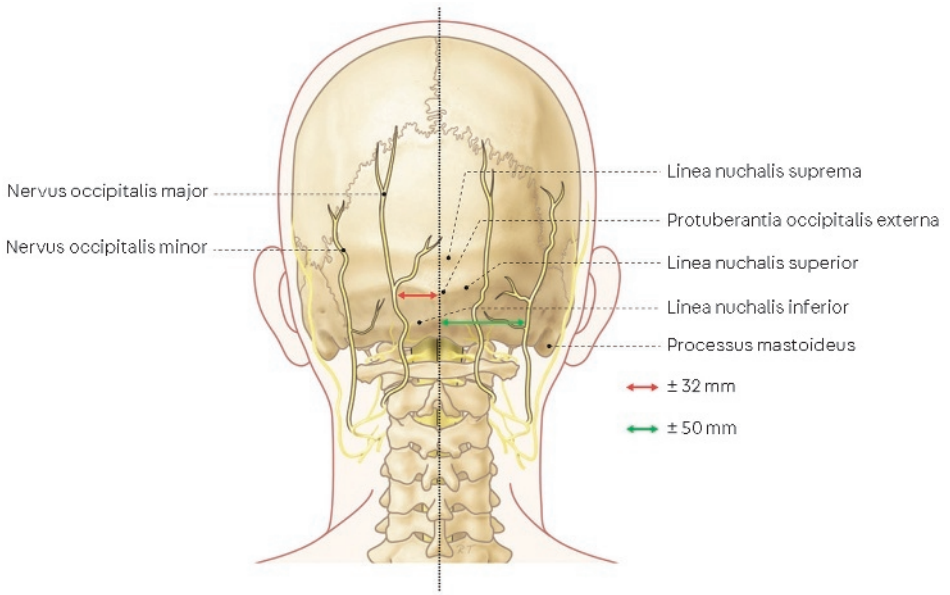

FIGURE 10-7
Anatomy of the occipital nerves.
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Controversy exists about whether this should be done simply with anesthetic or whether steroids should be included. The block should work rapidly, but if repeated blocks prove necessary, radiofrequency ablation can be considered.[54]

CONCLUSION

This article covered classical trigeminal neuralgia, painful trigeminal neuropathies, glossopharyngeal neuralgia, nervus intermedius neuralgia, and occipital neuralgia. These neuralgias are, for the most part, brief, lancinating pains in the distribution of the nerve in question but sometimes also have an achy or severe persistent interictal pain, depending on the nerve involved.

The *ICHD-3* is the referral document to standardize diagnosis so that concern for secondary causes can be weighed. However, classical trigeminal neuralgia and glossopharyngeal neuralgias are generally secondary to an anomalous vascular loop pathologically compressing the nerve, and so the terminology has moved on from primary and symptomatic to the current hierarchy.

Treatment for most of the neuralgias includes AEDs, baclofen, TCAs, and SNRIs. Following medication or combination medication failures, invasive

CASE 10-3

An 83-year-old woman presented to the emergency department for evaluation of new-onset severe pain exclusively in the right suboccipital region. She said that the pain occurred in stabs or bursts, lasted only a few seconds, and radiated up the back of her head to the right vertex. She had no pain between the paroxysms.

Palpation over the right greater occipital notch reproduced her pain and triggered attacks. No autonomic features were seen during the witnessed pain, which lasted about 2 seconds and spontaneously remitted.

The trigger zone was infiltrated with 2% lidocaine and a steroid, and the patient called the next day to say that the attacks had stopped.

COMMENT

This is a classic presentation of occipital neuralgia, and the response to injection is so definitive that further workup is probably not necessary. The paroxysmal presentation and its location and treatment response in this age group confirm the diagnosis.

Note that migraine pain is often posterior, in the occiput and neck, throbbing, bilateral in at least 40% of patients, occurs in attacks lasting 4 to 72 hours, is worse with activity, and is associated with nausea, photophobia, and phonophobia. Although both conditions can be associated with notch tenderness, the other features of migraine easily help to differentiate the two conditions. A migraine attack can be responsive to greater occipital nerve injections, but the treatment response does not diagnose occipital neuralgia by itself. Occipital neuralgia is paroxysmal and lancinating (and focal, as in this case) and is not generally associated with other migrainous features.

procedures can be considered, up to and including gamma knife treatment and microvascular decompression. Exceptions to this approach include glossopharyngeal neuralgia with neurocardiac events, when surgical approaches may be necessary early, and occipital neuralgia, which often remits with anesthetic and steroid injection over the nerve affected.

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