Trigeminal Neuralgia

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ABSTRACT

Purpose of Review: Although trigeminal neuralgia is well known to neurologists, recent developments in classification and clinical diagnosis, new MRI methods, and a debate about surgical options necessitate an update on the topic.

Recent Findings: Currently, a worldwide controversy exists regarding the classification, diagnostic process, and surgical treatment of trigeminal neuralgia. This controversy has been caused on one side by the recognition that some 50% of patients with trigeminal neuralgia, apart from characteristic paroxysmal attacks, also have continuous pain in the same territory, which results in greater diagnostic difficulties and is associated with a lower response to medical and surgical treatments. In contrast, recent developments in MRI methods allow differentiation between a mere neurovascular contact and an effective compression of the trigeminal root by an anomalous vessel, which implies more difficulties in the choice of surgical treatment, with the indication for microvascular decompression becoming more restricted.

Summary: This article proposes that the diagnosis of trigeminal neuralgia, with or without concomitant continuous pain, must rely on clinical grounds only. Diagnostic tests are necessary to distinguish three etiologic categories: idiopathic trigeminal neuralgia (nothing is found), classic trigeminal neuralgia (an anomalous vessel produces morphologic changes of the trigeminal root near its entry into the pons), and secondary trigeminal neuralgia (due to major neurologic disease, such as multiple sclerosis or tumors at the cerebellopontine angle). Carbamazepine and oxcarbazepine (ie, voltage-gated, frequency-dependent sodium channel blockers) are still the first-choice medical treatment, although many patients experience significant side effects, and those with concomitant continuous pain respond less well to treatment. The development of sodium channel blockers that are selective for the sodium channel 1.7 (Nav1.7) receptor will hopefully help. Although all the surgical interventions (percutaneous ganglion lesions, gamma knife radiosurgery, and microvascular decompression) are very efficacious, precise MRI criteria for differentiating a real neurovascular compression from an irrelevant contact will be of benefit in better selecting patients for microvascular decompression.

INTRODUCTION

Facial pain is easily misdiagnosed. When the pain is intense and recurrent and the underlying etiology is elusive, the condition is often labeled trigeminal neuralgia, although other conditions are much more likely to be the cause. The prevalence of trigeminal neuralgia in the population is 0.07%, compared to approximately 2% in patients with facial pain in general.1,2 Conversely, trigeminal neuralgia (also known as tic douloureux) is frequently mistaken for dental pain, leading to redundant diagnostic procedures such as x-rays of the jaw and, in more than a few cases, unnecessary extractions of teeth.3

Accurate diagnosis of trigeminal neuralgia depends critically on the patient’s description of its characteristic features. Clarification of the characteristics of the pain is therefore necessary to guide clinical diagnosis
and management. Successful diagnostic criteria must account for established variants of the phenotype (eg, typical versus atypical trigeminal neuralgia), incorporate symptoms or signs that correlate with different etiologies (primary trigeminal neuralgia versus trigeminal neuralgia secondary to a major neurologic disease), and identify pain features that indicate underlying pathophysiologic mechanisms (peripheral versus central), as they are relevant to direct further investigations or treatment decisions (pharmacologic therapy versus surgery). Physicians should be aware that the literature on trigeminal neuralgia has been hampered by a terminological dishomogeneity, which must be solved to the benefit of researchers, clinicians, and, ultimately, patients.

Although tic douloureux is frequently used as a synonym for trigeminal neuralgia, the term was originally introduced to describe the involuntary wincing associated with the occurrence of pain. Other diagnostic labels have been proposed to indicate differences in the etiology or clinical presentation of trigeminal neuralgia.

Variable use of seemingly interchangeable labels, such as classic and idiopathic or secondary and symptomatic, has been a major source of confusion. To differentiate idiopathic trigeminal neuralgia from manifestations of neuralgia that are secondary to an identified disease, in 1973 Strandjord established the term primary trigeminal neuralgia, which contradicts the notion of trigeminal neuralgia as a condition of neuropathic pain. MRI shows neurovascular contact in 70% to 83% of patients with typical trigeminal neuralgia. In neurosurgical case series, this frequency increases to 89%. Hence, primary trigeminal neuralgia was loosely used by many authors to describe both trigeminal neuralgia without identifiable cause and trigeminal neuralgia secondary to neurovascular contact. To solve this problem, the International Classification of Headache Disorders (ICHD) endorsed the term classic, specifying that classic trigeminal neuralgia should be diagnosed when no cause other than neurovascular contact is apparent.

The author agrees with this solution because it avoids confusion. However, the author favors additional differentiation of idiopathic trigeminal neuralgia from classic trigeminal neuralgia. Even after surgical exploration of the posterior fossa at the base of the skull for microvascular decompression, approximately 11% of patients with trigeminal neuralgia remain without diagnosis of an apparent cause. The frequency of cases without an etiology justifies their designation as idiopathic. For trigeminal neuralgia caused by a neurologic disease other than neurovascular compression, the author prefers the term secondary rather than symptomatic because it is less ambiguous. The term symptomatic may also indicate the painful side of the face or the affected trigeminal root on MRI.

**CLINICAL DIAGNOSIS OF TRIGEMINAL NEURALGIA**

The International Association for the Study of Pain (IASP) defines trigeminal neuralgia as “sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.” The ICHD, Third Edition, beta version (ICHD-3 beta) describes trigeminal neuralgia in similar terms, “as a disorder characterized by recurrent unilateral brief electric shocklike pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by

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**KEY POINTS**

- Although trigeminal neuralgia is still frequently misdiagnosed, its peculiar clinical features are unmistakable.
- A neurovascular compression is acknowledged as the most frequent cause of trigeminal neuralgia (classic trigeminal neuralgia).
- Notwithstanding the most accurate and advanced investigations, no cause can be found in about 11% of patients with trigeminal neuralgia (ie, idiopathic trigeminal neuralgia).
innocuous stimuli.” According to the International Headache Society (IHS) definition, trigeminal neuralgia “may develop without apparent cause or be a result of another diagnosed disorder. There may or may not be, additionally, persistent background facial pain of moderate intensity. Classic trigeminal neuralgia develops without apparent cause other than neurovascular compression.”11 Although these descriptions are certainly correct, they do not allow for evaluating the strength of the diagnostic criteria.

The starting points for a diagnosis of trigeminal neuralgia include unilateral facial pain, pain that cannot be felt outside the trigeminal territory, and pain that is paroxysmal. Trigeminal neuralgia must be considered when episodes of orofacial pain exhibit the characteristics laid out in the definitions provided by IASP and IHS.11,12 Pain episodes in trigeminal neuralgia occur and end abruptly, are short and severe, and are felt on only one side of the face within the innervation territory of the trigeminal nerve. The sensory characteristics of the pain are usually described as stabbing or comparable to an electric shock. Bilateral trigeminal neuralgia is very rare, except for secondary trigeminal neuralgia in multiple sclerosis (MS). Occasional reports of bilateral classic trigeminal neuralgia reflect successive episodes of unilateral pain that move to the opposite side of the face rather than pain episodes that occur simultaneously on both sides.13 A recent meta-analysis of clinical studies did not find any report of truly bilateral trigeminal neuralgia in 234 patients with classic trigeminal neuralgia and found only one case of bilateral pain out of 74 patients with secondary trigeminal neuralgia.6 This meta-analysis included mixed causes of secondary trigeminal neuralgia. In their recent meta-analysis, Cruccu and colleagues14 reviewed studies of MS associated with trigeminal neuralgia and identified a total of 24 cases of bilateral trigeminal neuralgia out of 252 MS patients with trigeminal neuralgia (ie, a frequency of slightly less than 10%).

POSSIBLE TRIGEMINAL NEURALGIA

A patient’s history must fulfill two requirements for the identification of possible trigeminal neuralgia: the pain must be paroxysmal, and its distribution must be consistent with the innervation territory of the trigeminal nerve (Figure 3-1).

The paroxysmal characteristic of trigeminal neuralgia, with its abrupt onset and termination, is unmistakable, even if the verbal descriptors vary from patient to patient. Typical descriptions of temporal and sensory qualities of trigeminal neuralgia include brief, sudden, stabbing, or electric shock-like. Although the duration of trigeminal neuralgia paroxysms may last up to 2 minutes, in most patients they are only a few seconds long. The number of paroxysms per day may range from zero to more than 50.15 Refuting earlier assumptions,16 a recent study of 200 patients with classic trigeminal neuralgia did not find evidence that frequency or duration of trigeminal neuralgia paroxysms increase with duration of the disease.17 Unlike other neuropathic pains, trigeminal neuralgia may enter into periods of complete pain remission in up to 63% of patients.15 These periods may last from weeks to years, but most often last a few months.15,18

Previous definitions of trigeminal neuralgia emphasize a stereotypic character of the pain. Stereotypy, however, is not a unique feature of trigeminal neuralgia. Stereotypic pain character
FIGURE 3-1 New classification and diagnostic grading system for trigeminal neuralgia (TN).

a Trigeminal neuralgia is typically a unilateral condition. Few patients develop trigeminal neuralgia on both sides of the face over the course of a disease (eg, in multiple sclerosis), but they almost never present with simultaneous bilateral pain.

b The pain strictly follows the distribution of the trigeminal nerve branches. It does not extend to the posterior third of the scalp, the posterior part of the external ear, or the angle of the mandible (Figure 3-2).

c Paroxysmal pain is the most noted symptom, but may be accompanied by continuous pain.

d Trigger maneuvers include innocuous mechanical stimuli, facial or oral movements, or complex activities such as shaving or applying makeup. Confined trigger zones and a common combination with brisk muscle contractions (tics) help distinguish triggered trigeminal neuralgia from allodynia in other conditions of neuropathic pain. Trigger maneuvers may be tested by the examiner.

MRI readily identifies major neurologic diseases, such as tumors of the cerebellopontine angle or multiple sclerosis. Other investigations may include the neurophysiologic recording of trigeminal reflexes and trigeminal evoked potentials, which become necessary in patients who cannot undergo MRI.

Advanced MRI techniques can demonstrate neurovascular compression with morphologic changes of the trigeminal nerve root.

may be observed with other forms of neuropathic and non-neuropathic pain. In addition, it is not uncommon for trigeminal neuralgia to produce pain of variable sensory characteristics over the course of the disease. 14,16,19,20

Pain should be felt in one or more divisions of the trigeminal nerve (Figure 3-2). The examining physician should ascertain that the pain does not extend to the posterior third of the scalp, the posterior part of the external ear, or the skin overlying the angle of the mandible, as these territories are innervated by cervical nerves. The territory of the mandibular division extends up to the temple: a patient with trigeminal neuralgia in the mandibular branch of the trigeminal nerve may therefore describe pain at the temple and the lower lip (Figure 3-2). If trigeminal neuralgia involves two trigeminal divisions, they should be contiguous (most frequently a combination of the maxillary and mandibular branches of the trigeminal nerve). Trigeminal neuralgia in the ophthalmic division or the tongue has long been considered an indication of secondary trigeminal neuralgia. However, this notion has not been adequately scrutinized in clinical studies. 5,6 Of note, the affected division of the trigeminal nerve and the side of the face may change, before or after surgery. 14,16,19,20

**TRIGGERED PAIN AS A CRITERION OF CLINICALLY ESTABLISHED TRIGEMINAL NEURALGIA**

Stimulus dependence is one of the most striking features of trigeminal neuralgia. In most patients, pain is evoked by non-noxious, light mechanical stimuli.
within the trigeminal territory, including the oral cavity (Figure 3-3). Subtlety of the trigger maneuvers is unique to trigeminal neuralgia. The stimulus may simply be a touch or a whiff of air, although more complex maneuvers involving both tactile stimuli and facial movement (e.g., washing or shaving of the skin, application or removal of makeup, eating or drinking) are also common. Movement alone (e.g., smiling, talking) may suffice to provoke a pain attack. The location of the evoked pain may differ from the site of the stimulation, and the pain can be felt as radiating (similar to sciatica). These triggers are usually spontaneously reported by the patient. However, they may also be tested by the examiner, who should pay attention to the typical tic (i.e., the involuntary facial movement in reaction to the evoked pain). The term tic refers to the abruptness and short duration of the movement. The provoked movement of the face is similar to other reactions to acute nociceptive pain (e.g., after inadvertently biting one’s tongue or a tooth with pulpitis). In other diseases, this brisk movement is evoked by noxious or potentially noxious stimuli.

Although pain paroxysms may originate spontaneously, patients with a history of exclusively spontaneous attacks are very rare. It is possible that in the few patients with no apparent trigger, the pain attacks are evoked by movements that the patients are unaware of, such as eye blinking or a twitch of other facial muscles. The author searched the literature for reports of pain with “no trigger” or “without trigger” and did not find these terms in any article. The few studies that looked specifically into the presence of trigger stimuli or maneuvers in classic trigeminal neuralgia reported triggered pain in 94% of patients. Hence, the author proposes that the presence of triggered pain matching the above description confirms the diagnosis of trigeminal neuralgia and qualifies the patient as having clinically established trigeminal neuralgia (Figure 3-1). Because triggered pain paroxysms are a unique somatosensory

**FIGURE 3-3** Mechanism of pain in trigeminal neuralgia. Distribution of 31 trigger zones in 30 patients. Circles denote the typically small areas where light touch or other innocuous mechanical stimuli trigger the pain paroxysms. In some patients, the trigger zones are larger (dashed areas) or intraoral (ovals).

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Continuum (Minneap Minn) 2017;23(2):396–420

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phenomenon, it also increases the diagnostic certainty of neuropathic pain so that it should also be considered probable neuropathic pain.\(^\text{24}\) Clinically established trigeminal neuralgia represents a sufficient degree of diagnostic certainty to implement treatment or enroll patients in a clinical trial for trigeminal neuralgia.

**TRIGEMINAL NEURALGIA WITH CONCOMITANT CONTINUOUS PAIN**

Some patients with trigeminal neuralgia experience pain between attacks (Case 3-1). This pain is continuous or nearly continuous, but may vary in intensity and quality. Its sensory characteristics differ from the paroxysmal pain and are commonly described as dull, burning, or tingling. The distribution of this continuous pain coincides with that of the paroxysmal pain, and fluctuations of its intensity parallel in time those of the paroxysmal pain.\(^\text{19,25}\) A recent cross-sectional study in 158 patients with trigeminal neuralgia has well defined the characteristics of this other phenotype and has brought far more attention to it, reporting a frequency of almost 50%.\(^\text{26}\)

No generally agreed-upon term exists to describe the form of trigeminal neuralgia in which concomitant continuous pain is present. It has been known by several designations,

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**Case 3-1**

A 77-year-old woman presented to the neurology clinic for a 1-month history of facial pain. She described the pain as being on the right side only and consisting of “a burning and stabbing pain” in her cheek that sometimes lasted for hours. She also stated that when drying her face, she needed to slowly press the towel without brushing it up and down; otherwise, a lightninglike pain would go from her nose to her lip. She had already been treated with several pain killers and benzodiazepines by her primary physician with no improvement, but she had not tried voltage-gated sodium channel blockers.

The neurologic examination was normal, apart from the patient grimacing when a cotton swab was touched to the right side of her face. The patient was prescribed oxcarbazepine and titrated up to 300 mg 4 times a day.

MRI of her brain with contrast was ordered to rule out major neurologic diseases. To look for a possible neurovascular compression, time-of-flight magnetic resonance angiography (MRA), three-dimensional reconstruction, and constructive interference in steady state (CISS) sequences were also ordered. A baseline complete blood count and comprehensive metabolic profile completed the investigations. After 3 weeks, the patient returned, reporting resolution of her symptoms. The patient was diagnosed with trigeminal neuralgia with concomitant continuous pain. Brain MRI showed a neurovascular compression that distorted and flattened the affected trigeminal root near its entry into the pons.

**Comment.** This patient’s symptoms were typical of trigeminal neuralgia with concomitant continuous pain, including the presence of a trigger mechanism (in this case the patient exhibited the “sign of the towel,” where she could pat a towel slowly to her face but could not brush the towel up and down because of the pain that was triggered.). Although diagnostic investigations to ascertain etiology must be performed in all patients, medical treatment can be implemented early based on clinical information only.
including atypical trigeminal neuralgia and trigeminal neuralgia type 2. The author prefers the term trigeminal neuralgia with concomitant continuous pain because it directly conveys the difference from typical paroxysmal pain. The author prefers describing the pain as continuous rather than persistent because continuous refers strictly to the temporal manifestation of the pain, whereas persistent may imply refractoriness to treatment (and can also be confused with persistent idiopathic facial pain, which is an unrelated painful condition). Several authors have favored describing the pain as constant, which is nearly synonymous with continuous but may also refer to unchanging intensity or sensory quality of the pain. Thus, continuous is the description least susceptible to confusion (Table 3-1).

The presence of continuous pain is not related to etiology and may occur in idiopathic, classic, or secondary trigeminal neuralgia. The mechanisms underlying continuous as opposed to paroxysmal pain are not fully understood. Continuous pain may develop as a result of progressive root damage after prolonged compression or reflect central mechanisms. Several authors have suggested that continuous pain is associated with poorer outcome after surgical intervention. It is unclear to what extent these reports reflect patient selection or differences in nerve pathology. However, convincing evidence exists that continuous and paroxysmal pain may improve differently after microvascular decompression, indicating that the mechanisms responsible for the two pain components may be distinct.

ETIOLOGY

MRI is the most widely used diagnostic tool to assess for secondary trigeminal neuralgia, because it is highly sensitive for detecting major neurologic diseases such as a tumor or multiple sclerosis.

**KEY POINTS**

- The presence of continuous pain is not related to etiology and may occur in idiopathic, classic, or secondary trigeminal neuralgia.
- MRI is the most widely used diagnostic tool to assess for secondary trigeminal neuralgia, because it is highly sensitive for detecting major neurologic diseases such as a tumor or multiple sclerosis.

### TABLE 3-1 Definition and Classification of Trigeminal Neuralgia

<table>
<thead>
<tr>
<th>Definition</th>
<th>Trigeminal neuralgia is orofacial pain restricted to one or more divisions of the trigeminal nerve. Except for trigeminal neuralgia caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously, but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they do report additional continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are considered to have trigeminal neuralgia with concomitant continuous pain.</th>
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<tbody>
<tr>
<td>Classification</td>
<td>Trigeminal neuralgia is classified in three etiologic categories. Idiopathic trigeminal neuralgia occurs without apparent cause. Classic trigeminal neuralgia is caused by vascular compression of the trigeminal nerve root. Secondary trigeminal neuralgia is the consequence of a major neurologic disease (e.g., a tumor of the cerebellopontine angle or multiple sclerosis). Either phenotype (purely paroxysmal pain or with additional continuous pain) may occur with any of the three categories.</td>
</tr>
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KEY POINT

- MRI may reveal neurovascular contact of the trigeminal nerve root, but the frequency of mere contact between root and blood vessels in trigeminal nerves in asymptomatic patients cautions against its use as a diagnostic criterion.

Diseases such as a tumor or MS. MRI may reveal neurovascular contact of the trigeminal nerve root, but the frequency of mere contact between root and blood vessels in trigeminal nerves in asymptomatic patients cautions against its use as a diagnostic criterion. Supported by negative findings at operation, recent studies have emphasized the importance of differentiating the type of contact and its physical impact on the nerve, to the point that Cruccu and colleagues became convinced that the reintroduction of the term idiopathic trigeminal neuralgia was needed. The degree of morphologic trigeminal root changes is therapeutically relevant. The long-term outcome after surgical correction of simple neurovascular contacts is poorer compared to the decompression of dislocated, distorted, or flattened nerve roots (Figure 3-4). Advanced MRI techniques now allow radiologic verification of morphologic changes of the compressed trigeminal root. These changes of symptomatic nerve roots are highly suggestive of physical alteration and have a high predictive value for pain relief after decompression.

In a recent meta-analysis of nine high-quality blinded and controlled studies, mere neurovascular contact was found in 471 out of 531 symptomatic nerves and in 244 out of 681 asymptomatic nerves, indicating high sensitivity but low specificity. Nerve dislocation or signs of atrophy increased the specificity to 97%. These results are corroborated by two prospective studies. Location of the neurovascular contact appears to be relevant. Compression of the trigeminal nerve at its entry into the brainstem increased the specificity to 100%. It is important to acknowledge that all the studies cited here rely on a clinical diagnosis of trigeminal neuralgia.

**FIGURE 3-4** Morphologic changes of the trigeminal root showing examples of classic right trigeminal neuralgia. Two schematic drawings show axial sections at the level of the trigeminal roots where gray indicates nervous tissue, red indicates arteries, and black indicates bone. Atrophy of the right trigeminal root caused by a crossing artery (A) and a downward loop of the superior cerebellar artery that provokes distortion of the right trigeminal root at its entry into the pons (B) can be seen.
prior to MRI. Consequently, MRI findings alone cannot be used as biomarkers to diagnose trigeminal neuralgia unless the investigation is preceded by an evaluation of clinical symptoms and signs that indicate the presence of trigeminal neuralgia. However, a combination of clinical signs and morphologic changes caused by a vascular compression involving the symptomatic trigeminal nerve provides strong enough evidence to confirm the etiology of classic trigeminal neuralgia (Figure 3-1).

Detection of neurovascular compression requires the use of specific imaging paradigms with three-dimensional reconstruction MRI techniques. An increasing number of imaging options are available to depict the nerve and any blood vessels in proximity to the posterior fossa. Typical imaging paradigms include sequences for three-dimensional T2-weighted MRI (eg, constructive interference in steady state [CISS]) for a detailed examination of the cisternal and cavernous segments of the nerve and three-dimensional time-of-flight magnetic resonance angiography (MRA) for visualization of arteries. The necessary but sufficient scope of the MRI evaluation to identify dislocation, distortion, flattening, or atrophy of the trigeminal root (ie, the morphologic changes considered essential to distinguish between a mere contact and a real compression) must still gain wide consensus.

Several studies suggest that compression-induced microstructural changes may be estimated using diffusion-tensor imaging (DTI) and tractography to measure focal demyelination and edema. A recent report suggests that effective treatment for trigeminal neuralgia reverses several DTI abnormalities at the trigeminal root entry zone. Although many believe that in the future DTI will reliably demonstrate microstructural damage in the trigeminal root and thus become the ultimate investigation, so far the available evidence is still insufficient.

Trigeminal reflex testing is an established neurophysiologic assessment of nerve function (Figure 3-5). Trigeminal reflex testing requires only standard nerve conduction study equipment; for stimulation, it uses surface electrodes placed over the emergence of the supraorbital, infraorbital, and mental nerves and for recording uses surface electrodes placed over the orbicularis oculi and masseter muscles. Allowing a between-side quantitative assessment of the ophthalmic, maxillary, and mandibular divisions, trigeminal reflex testing is a reliable method to detect secondary forms of trigeminal neuralgia and has been recommended in guidelines for the evaluation of neuropathic pain involving the trigeminal nerve. In a meta-analysis of 629 patients with trigeminal neuralgia, trigeminal reflex testing achieved a sensitivity of 94% and a specificity of 87% in identifying patients with secondary trigeminal neuralgia, comparable to the diagnostic accuracy of MRI. Trigeminal reflex testing is particularly helpful if a patient cannot undergo MRI or if trigeminal neuralgia secondary to trigeminal neuropathy is suspected in spite of a normal MRI result (refer to the following section on secondary trigeminal neuralgia).

Various evoked potentials after electric or thermal stimuli have been studied in trigeminal neuralgia. In contrast to trigeminal reflex testing, which is normal in idiopathic or classic trigeminal neuralgia, evoked potentials may be altered, but their mean specificity of 64% is low. Evoked potentials are adjuvant measures...
to demonstrate functional abnormalities in trigeminal neuralgia. It is worth emphasizing that all electric stimulations within the trigeminal territory are bound to elicit reflex responses that unavoidably contaminate the scalp signals. Only electric stimulation via two fine needle electrodes inserted into the infraorbital foramen provides a safe scalp recording of subcortical far-field potentials whose generation site has been located near the trigeminal ganglion, root, or pons. In a clinical setting, this method of stimulation detailed by Leandri and Gottlieb is useful during radiofrequency thermocoagulation of the ganglion because it allows the identification of the affected trigeminal division under general anesthesia.

SECONDARY TRIGEMINAL NEURALGIA
Trigeminal neuralgia caused by a major neurologic disease is readily identified by MRI or other appropriate investigations. In 15% of patients with typical pain attacks, trigeminal neuralgia is caused by benign tumors at the cerebellopontine angle or MS (Figure 3-6). Tumors causing trigeminal neuralgia are mostly benign and compress the root near its entry into the pons. They include meningiomas, epidermoid cysts, acoustic neuromas, and cholesteatomas. Local compression induces focal demyelination and may trigger paroxysmal ectopic discharges, whereas infiltrative tumors lead to axonal degeneration. The different pathology of nerve damage by malignant tumors is commonly associated with hypesthesia and continuous pain rather than trigeminal neuralgia. Evidence of tumors as a cause of secondary trigeminal neuralgia comes from four main studies that reported a total of 20 (8%) out of 243 patients with trigeminal neuralgia. On the other hand, about 20% of...
Cerebellopontine angle tumors produce trigeminal neuralgia. All symptomatic tumors compress the trigeminal nerve root. Trigeminal neuromas almost never produce trigeminal neuralgia. Patients with MS have a 20-fold increased risk of trigeminal neuralgia. The prevalence of trigeminal neuralgia in MS is 2% to 5%. The cause of trigeminal neuralgia has conventionally been attributed to demyelinating plaques in the pons. It has been clearly shown, however, that the onset age of the population with trigeminal neuralgia and MS is lower than that of classic trigeminal neuralgia but significantly higher than that of MS. Although trigeminal neuralgia in MS may be one of several other common MS disturbances, some patients have trigeminal neuralgia as their sole clinical manifestation for all their life, thus being classified as having clinically isolated syndrome. These patients typically have multiple demyelinated areas on MRI and strongly delayed responses on neurophysiologic tests (trigeminal reflexes and evoked potentials), which are characteristic of MS. It has been hypothesized that the pontine plaque and a neurovascular compression exert a dual, additive mechanism, in which inflammatory demyelination (the intraaxial plaque) and mechanical demyelination (the extraaxial neurovascular compression) create a double crush syndrome on the same primary afferents near the root entry zone. Very recently, this theory has found sound evidence.

FIGURE 3-6 Common causes of symptomatic trigeminal neuralgia. A, Benign tumors along the extraaxial course of the trigeminal root (arrows). B, Demyelinating plaques along the intraaxial course of the trigeminal afferents (arrows).

Because patients with MS-related trigeminal neuralgia usually respond insufficiently to pharmacologic treatment or must stay on high dosages that worsen their fatigue or may become toxic for the liver, microvascular decompression or another surgical procedure for trigeminal neuralgia becomes necessary sooner or later. In these patients, however, the benefit yielded by any type of surgical treatment is shorter in duration than in classic trigeminal neuralgia.53,54

A smaller group of patients may present with trigeminal neuralgia secondary to a trigeminal neuropathy. These neuropathies may be divided into three subgroups in descending order of frequency: posttraumatic, associated with connective tissue diseases, and idiopathic/genetic. Facial trauma, dental procedures, or maxillofacial or neurosurgical procedures may damage branches of the trigeminal nerve. Although the primary symptom in trigeminal neuropathy is sensory loss, sometimes these focal neuropathies present with episodes of paroxysmal pain. The pain attacks are usually longer than those associated with trigeminal neuralgia, and most patients also describe continuous pain.55 The trauma or the intervention should not escape medical history. Painful trigeminal neuropathy caused by a connective tissue disease or genetic disorder is usually bilateral but may begin asymmetrically and occasionally present with paroxysmal pain similar to trigeminal neuralgia.25,29,56,57 Indeed a paroxysmal pain similar to that of trigeminal neuralgia may be the first symptom of an underlying connective tissue disease.58 The patients will eventually develop bilateral sensory deficits and continuous pain, which clarifies the diagnosis. MRI is normal, but trigeminal reflexes are invariably delayed or absent.56

**KEY POINT**

- Both in classic and secondary trigeminal neuralgia, the primary mechanism is focal demyelination of primary afferents near the entry (extraaxial or intraaxial) of the trigeminal root into the pons.

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**PATHOPHYSIOLOGY OF TRIGEMINAL NEURALGIA**

One aspect of pathophysiology is supported by established neurophysiologic, neuroimaging, and histologic evidence. Both in classic and secondary trigeminal neuralgia, the primary mechanism is focal demyelination of primary afferents near the entry (extraaxial or intraaxial) of the trigeminal root into the pons. Some investigators believe this area represents a locus minoris resistentiae (a site of lower resistance or higher susceptibility to damage) because it is the site where Schwann cells are substituted by oligodendroglia in providing the myelin sheath.

A second pathophysiologic theory, admittedly more debatable, is that the damaged primary afferents in the area of focal demyelination become a source of ectopic generation of impulses. The author proposes that, because mitochondria and the energetic apparatus necessary to pump sodium off are physiologically concentrated at the level of the nodes of Ranvier, when the demyelinating process allows the passage of ions in and out of the axon, then the axons do not have enough energy to promptly reestablish the resting potential. Hence, the axons tend toward a depolarization level, which makes them hyperexcitable. Spontaneously, or because of a local direct mechanical stimulus such as the artery pulsation, ectopic activity is generated. More supported by evidence in animal models of focal demyelination of the trigeminal root is the concept of ephaptic transmission (cross talk) from close, healthy nerve fibers and the generation of high-frequency discharges.59–61

A third potential pathophysiologic theory, with almost no sound evidence at all at this time, is that the
hyperactivity of primary afferents secondarily induces central sensitization of wide dynamic range neurons in the spinal trigeminal nucleus or even more central changes.\textsuperscript{28,62}

**MEDICAL TREATMENT OF TRIGEMINAL NEURALGIA**

The guidelines on trigeminal neuralgia management that were agreed upon and jointly published by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) are very clear as to medical treatment (Supplemental Digital Content 3-1, links.lww.com/CONT/A215).\textsuperscript{6} Based on evidence, the treatment should begin either with carbamazepine 400 mg/d to 1200 mg/d or with oxcarbazepine 900 mg/d to 1800 mg/d. The author’s first-line choice is oxcarbazepine because of its better tolerability.\textsuperscript{17,63} If the patient reaches the dosages adequate for most patients (1200 mg/d to 1500 mg/d) without achieving the desired pain relief (ie, she or he is one of the rare cases of a real nonresponder), no other drug will be enough. Hence surgery, being extremely efficacious in trigeminal neuralgia, should be proposed.\textsuperscript{5,6}

Aside from responders and non-responders, however, a third type of patient exists who requires some consideration. Some patients cannot take either of the two choice drugs because of specific contraindications (most frequently cardiac conduction problems or severe arrhythmias). Some other patients encounter serious side effects and allergic dermatitis, which, unfortunately, tend to be cross-reactive (ie, the patients who had the allergic reaction to one of the two drugs cannot be switched to the other) or, in the case of carbamazepine, a fall in blood elements (white cells, red cells, or platelets) rarely reaching aplastic anemia. Indeed, patients on carbamazepine must undergo a complete blood count every 3 to 4 months. Both drugs may cause sodium depletion (Case 3-2). Both drugs, being antiepileptic drugs, induce central nervous system (CNS) depression, presenting as somnolence, confusion, or imbalance. These central side effects, which are more frequent with carbamazepine than oxcarbazepine (Figure 3-7),\textsuperscript{17} may prevent patients from maintaining adequate doses. Hence, in this third group of patients, who are neither responders nor nonresponders, other drugs can be tried. In this case, the AAN/EFNS guidelines suggest trying other pharmacologic options as monotherapy or add-on medications. In particular, analysis of the evidence-based trials led to the following suggestions: lamotrigine, baclofen, and pimozide.\textsuperscript{6} Lamotrigine is supported by evidence if used as an add-on to carbamazepine.\textsuperscript{64} Unfortunately, the comparatively high risk of dermatitis imposes a very slow titration,\textsuperscript{63,65} and, naturally, this drug is not devoid of side effects on the CNS, which would add to those of carbamazepine or oxcarbazepine. Baclofen, an agonist of the \(\gamma\)-aminobutyric acid B (GABA-B) receptor, was believed to be very promising because it was well supported by animal experiments.\textsuperscript{66} Now it is known that unless baclofen is administered intrathecally, the side effects restrict the oral dosage to a level lower than the one necessary to reach antinociceptive effects. Although pimozide was found more efficacious than carbamazepine in a small head-to-head clinical trial, it was never tried again.\textsuperscript{67} Some reports about the efficacy of gabapentinoids and antidepressants exist, but there have been no adequate trials in trigeminal neuralgia. Both gabapentinoids and antidepressants, however, are expectedly more

**KEY POINTS**

- Medical treatment of trigeminal neuralgia is based on frequency-dependent sodium channel blockers, namely oxcarbazepine and carbamazepine.
- The adverse events caused by both oxcarbazepine and carbamazepine may often require discontinuation of these agents.
Case 3-2

A 67-year-old woman with a history of hypertension presented with a 6-month history of right-sided facial pain. The pain was paroxysmal (she described it as similar to an electric shock), and it was evoked by typical trigger maneuvers for trigeminal neuralgia: light touch on the forehead and eyebrow, eyelid movement when looking upward, and combing her hair. She had previously been prescribed carbamazepine 600 mg/d, and her pain had disappeared. Her problems were twofold: first, the carbamazepine induced central nervous system side effects (eg, somnolence, dizziness, imbalance), which she found unbearable, and second, no investigation had yet occurred to ascertain the etiology.

Neurologic examination was normal. She was switched to oxcarbazepine, with increasing doses up to 1200 mg/d. In addition, trigeminal reflex testing, a standard brain MRI, and a dedicated three-dimensional MRI and magnetic resonance angiography (MRA) study were ordered to check for a neurovascular compression.

The patient returned for follow-up 3 weeks later, and she still had central nervous system depression, although to a far lower degree, which she felt was tolerable. The trigeminal reflex testing was normal, and the standard MRI showed some small ischemic lesions in the cerebral white matter; however, the dedicated MRI study for possible neurovascular compression showed a very rare compression by a wide-collar berry aneurysm of the superior cerebellar artery. The artery looped downward, and the aneurysm distorted the trigeminal root. The possibility of an endovascular intervention was discussed, but its efficacy was considered uncertain.

One week later, the patient suddenly developed severe weakness and confusion and was seen in a local emergency department, where she was diagnosed with severe hyponatremia (120 mEq/L) and was begun on saline infusions. She was also seen by another neurologist, who quickly tapered and stopped oxcarbazepine, as well as an interventional neuroradiologist who, as soon as the electrolyte abnormality resolved, proceeded with endovascular intervention first with a coil in the aneurysm and then with a stent in the artery. Within 24 hours after the intervention, she had complete disappearance of the neuralgic pain attacks and continued to have no further symptoms when seen in follow-up 6 months later.

Comment. With oxcarbazepine, sodium depletion occurs in 6% to 8% of patients. Regarding medication side effects, although oxcarbazepine by no means requires the three to four checks per year of blood elements that are mandatory for the duration of therapy for patients on carbamazepine, monitoring of serum sodium is necessary at least once. In this case, in retrospect, this patient’s cardiologist had recently introduced a diuretic to her antihypertensive regimen that probably added to oxcarbazepine in depleting sodium.

Regarding the etiologic classification of this patient, although secondary trigeminal neuralgia is usually attributed to tumors or multiple sclerosis, other major neurologic diseases (eg, the rare trigeminal isolated sensory neuropathy or aneurysms) should be kept in mind when something in the history or symptoms suggests a secondary origin. In this case, the only unusual clinical factor was the location of her pain, which exclusively involved the opthalmic division (this was long considered a

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sign of probable secondary trigeminal neuralgia, although this association was not confirmed by the American Academy of Neurology [AAN] and the European Federation of Neurological Societies [EFNS] 2008 guidelines).

Regarding pathophysiology, it is well known that microvascular decompression relieves neuralgic pain far before a remyelinating process might take place. This case suggests the need for a pulsating stimulus on the demyelinated nerve fibers to induce the ectopic generation of high-frequency discharges. In microvascular decompression, the neurosurgeon leaves a tiny sponge to keep the artery and the nerve root separate. In this case, the artery pulsation was eliminated by the stent.

efficacious in continuous than paroxysmal pain and are often tried as an add-on to oxcarbazepine or carbamazepine in patients with the atypical form of trigeminal neuralgia with concomitant continuous pain. A dedicated clinical trial has never been reported in trigeminal neuralgia with concomitant continuous pain, nor has the safety of these combinations been verified.

Often, this third group of patients is eventually referred for surgery. Many patients, however, may not accept surgery that easily. The author believes that in those patients who do not want to undergo any kind of surgical intervention, botulinum toxin injections of the trigger areas should be tried. The amount of published evidence is growing day by day, and the safety profile is very high. Reportedly, the pain relief lasts several months, and the main side effect is a transient weakness of the facial muscles in the

FIGURE 3-7
Trigeminal neuralgia (TN) treatment algorithm.
MRI = magnetic resonance imaging.
Several surgical procedures for trigeminal neuralgia exist that are very efficacious.

injected area. Naturally, botulinum toxin injections should be performed by neurologists experienced in botulinum toxin injections for other established indications. This treatment, so efficacious in other conditions, has not yet achieved US Food and Drug Administration (FDA) indication for trigeminal neuralgia.

Finally, BIIB074, a new voltage- and frequency-dependent sodium channel blocker that has selectivity for the sodium channel 1.7 (Na\textsubscript{v}1.7) subtype, has been discovered. Na\textsubscript{v}1.7 is a major sodium receptor in the nociceptive system, but no Na\textsubscript{v}1.7 receptors exist in the brain. This absence of brain Na\textsubscript{v}1.7 receptors promises to prevent any side effects associated with depression of CNS excitability. Na\textsubscript{v}1.7 has been validated as a key pain target by human genetic linkage, as gain of function mutations are linked to a severe chronic pain syndrome, whereas loss of function mutations lead to the inability to feel pain. Furthermore, its efficacy and extreme tolerability has already been proved in patients in a phase 2 trial. Zakrzewska and colleagues have now demonstrated that BIIB074 can inhibit the firing of trigeminal neurons, adding further mechanistic support to the potential of this new molecule.

SURGICAL TREATMENT OF TRIGEMINAL NEURALGIA

A first, difficult question is whether some patients, according to their inclination, should be offered the early choice between medical and surgical treatment. A study in patients who had undergone surgery for trigeminal neuralgia found that many, after experiencing the long-lasting benefit, would have opted for surgery from the very beginning.

Although trigeminal neuralgia is perhaps the neuropathic pain condition where surgery is most effective, each surgical method entails its own potential problems, thus the author believes that the first treatment should be oxcarbazepine or carbamazepine. If the standard dosages are not enough or the side effects are too severe, then surgery should at least be proposed and discussed with the patient.

Surgical methods for treating trigeminal neuralgia can be divided in four groups: lesions distal to the ganglion, lesions at the ganglion level, lesion of the root by gamma knife radiosurgery, and posterior fossa intervention of microvascular decompression.

The first group of surgical methods includes all sorts of peripheral lesions of the trigeminal terminal nerves at their emergence from the facial bones: neurectomy, alcohol injections, radiofrequency lesions, or cryolesions. None of these methods has ever been supported by adequate trials. In fact, these lesions were often the source of anesthesia dolorosa (pain in area of sensory loss).

The second group of surgical methods involve percutaneous gasserian (ie, trigeminal) ganglion lesions. In all cases, a long cannula or electrode is inserted first through the cheek, then between the mandibular arch and the maxillary bone, to reach the infratemporal fossa, and aimed at the foramen ovale, through which it penetrates the skull base reaching the Meckel cave, where the gasserian ganglion lies. All these procedures need fluoroscopic guidance. When on target, three types of lesions can be done: thermocoagulation by radiofrequency, chemical lesion by injection of high-concentration glycerol, or mechanical compression by balloon inflation. Radiofrequency thermocoagulation was conceived to preferentially damage the small pain fibers. Balloon compression and glycerol
injection preferentially damage the large myelinated fibers; thus, the rationale is that of blocking the triggering impulses. Whereas balloon compression and glycerol injection can be performed under continuous general anesthesia, radiofrequency thermocoagulation requires anesthesia when the electrode is moved to the target and then again at the moment of the lesion. Hence, patients must be awakened in between because they must report in what areas of the face they feel the paresthesia evoked by electric impulses delivered from the tip of the electrode to prevent damaging the wrong trigeminal division. The electrode is moved slightly until the evoked paresthesia is coincident with the painful division, and then the patient is anesthetized again before the actual thermocoagulation begins.

Sophisticated methods have been developed, including the intraoperative recording of trigeminal evoked potentials. In any event, however, the electrode cannot be aimed at the first trigeminal division because the damage to small fibers entails corneal deafferentation and keratitis. Balloon compression and glycerol injection are devoid of the risk of corneal keratitis because they damage large myelinated fibers only. Regarding the general pros and cons of the percutaneous ganglion lesion techniques, the pain relief is immediate and complete in a high percentage of cases, and follow-up studies report a variable duration of pain relief, persisting in about 70%, 60%, and 50% at 1, 3, and 5 years, respectively. The success of “pulsed” radiofrequency, in contrast, is not supported by evidence. In fact, one study reported that in all patients submitted to pulsed radiofrequency, the original pain returned by 3 months. The major risks of all percutaneous ganglion lesion procedures are piercing of the maxillary artery (which is close to the trajectory toward the foramen ovale), and that of the dura mater covering the Meckel cave, with various possible consequences, from burning of an oculomotor nerve to infusion of glycerol into the CSF of the middle cranial fossa. Almost unavoidable are trigeminal sensory deficits, which are usually transient with balloon compression and glycerol injection and more severe and longer lasting after radiofrequency (Figure 3-8).

Stereotactic radiosurgery (gamma knife) is the most recent type of intervention applied to trigeminal neuralgia and therefore the one with the fewest number of patients who have been treated. However, the amount of favorable evidence is increasing rapidly. Naturally, the main problem is the same as for all stereotactic radiosurgery interventions (ie, the reliability and accuracy of the methods of finding the exact coordinates of the trigeminal root just before its entrance into the pons, where the radiation beams should collimate). A randomized controlled trial studied whether expanding the irradiated area more distally along the root would increase the rate of responders: the total success rate was 68% regardless of the length of the irradiated area. Only the occurrence of facial numbness or paresthesia correlated with the length of the irradiated area. This study (one of the very rare randomized controlled trials of stereotactic radiosurgery in trigeminal neuralgia) is very interesting because it conveys strong evidence that the root entry zone is the key spot in the origin and maintenance of trigeminal neuralgia. Unlike the other types of intervention, the pain-relieving effect of gamma knife therapy is not immediate and generally requires 6 to 8 weeks to develop.

Continuum (Minneap Minn) 2017;23(2):396–420 ContinuumJournal.com

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According to the 2008 AAN/EFNS guidelines on trigeminal neuralgia, at 1 year after gamma knife therapy, complete pain relief with no medication occurs in up to 69% of patients. This falls to 52% at 3 years. Facial numbness is reported in 9% to 37% of patients (although it tends to improve with time), and troublesome sensory loss or paresthesia is reported in 6% to 13%, whereas anesthesia dolorosa is practically absent. No complications outside the trigeminal nerve have been reported. The most recent Cochrane Review does not add to the 2008 guidelines. A recent meta-analysis of gamma knife interventions, however, found that, because about 34% of patients do not reach 1 year of pain relief, repeated administration of radiations were necessary. With the increasing number of interventions, the rate of success and the pain-free time increase significantly. Unfortunately, toxicity also increases, with facial hypesthesia persisting in 50% of patients at 1-year follow-up.

Although microvascular decompression is the only causal cure and huge numbers of patients have undergone this procedure, no reported trial meets the minimal criteria of evidence to be considered in a Cochrane Review. Microvascular decompression is the only type of surgery for trigeminal neuralgia that cannot be done as an outpatient surgical procedure. It requires general anesthesia, intubation, craniotomy, cutting the dura mater, shifting the cerebellar hemisphere, and microscopy to adequately visualize the nerves emerging from the cerebellopontine angle. The neurosurgeon may then disentangle the looping artery and leave a small sponge to keep the pulsating artery separated from the trigeminal root. Naturally, a placebo intervention or blinded operators are unthinkable. Importantly, in about 11% of patients, no complications outside the trigeminal nerve have been reported. The most recent Cochrane Review does not add to the 2008 guidelines. A recent meta-analysis of gamma knife interventions, however, found that, because about 34% of patients do not reach 1 year of pain relief, repeated administration of radiations were necessary. With the increasing number of interventions, the rate of success and the pain-free time increase significantly. Unfortunately, toxicity also increases, with facial hypesthesia persisting in 50% of patients at 1-year follow-up.

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referred for this type of intervention, the surgeons do not find any neurovascular compression\textsuperscript{9,14} or they find a mere contact that apparently is not damaging the nerve. Most surgeons in these latter cases interpose the separating sponge anyway, but they report a greater rate of failure, hence the need to establish MRI criteria that ensure that morphologic changes of the trigeminal root are observed.\textsuperscript{14}

Allowing for the lack of evidence-based data, still the meta-analyses of the largest studies make microvascular decompression the most efficacious of the surgical interventions for classic trigeminal neuralgia: according to the AAN/EFNS guidelines,\textsuperscript{6} 90\% of patients obtain pain relief. More than 80\% of patients 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\%. Up to 4\% of patients incur major problems such as CSF leaks, infarctions, or hematomas. Aseptic meningitis is the most common complication (11\%). Diplopia is usually transient, and facial palsy is rare. Sensory loss occurs in 7\% of patients. The major long-term complication is ipsilateral hearing loss (Figure 3-9).

In conclusion, percutaneous gasserian ganglion lesions, gamma knife, and microvascular decompression may all be considered, with microvascular decompression offering the longest duration of pain relief.

When the decision is difficult, the best option is referral to a large center that is led by experienced neurosurgeons. Insufficient evidence exists to support or refute the effectiveness of the surgical management of trigeminal neuralgia in patients with MS. The author, however, believes that MS patients with evidence of drug-resistant trigeminal neuralgia should be offered the surgical option. The recent demonstration of the concurring pathophysiologic role exerted by neurovascular compression would seem to favor the choice of microvascular decompression in the posterior fossa.\textsuperscript{52} However, positive reports occur with all the main types of intervention, including percutaneous ganglion lesions and gamma knife.\textsuperscript{54}

**CONCLUSION**

The diagnosis of trigeminal neuralgia, with or without concomitant continuous pain, must rely on clinical grounds only. Diagnostic tests are necessary to distinguish three etiologic categories: idiopathic trigeminal neuralgia (nothing can be found), classic trigeminal neuralgia (an anomalous vessel produces morphologic changes of the trigeminal root near its entry into the pons), and secondary trigeminal neuralgia (due to major neurologic disease such as MS or tumors at the cerebellopontine angle). Oxcarbazepine and carbamazepine are still the first-choice medical treatment, although many patients experience significant side effects, and those with concomitant continuous pain respond less. A new sodium channel blocker that is selective for the Na\textsubscript{1.7} receptor has promise of efficacy without inducing side effects related to CNS depression. Three categories of surgical interventions (percutaneous ganglion lesions, gamma knife, and microvascular decompression) are all very

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<td>Percutaneous ganglion lesions and gamma knife are efficacious in the treatment of trigeminal neuralgia and can be repeated in cases of relapse.</td>
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efficacious. Precise MRI criteria for differentiating a real neurovascular compression from an irrelevant contact will be of benefit in better selecting patients for microvascular decompression. The treating neurologist should work in a collaborative fashion with the patient and the neurosurgeon to determine when and what type of surgical procedure to try.

REFERENCES


