Role of the neurologist in the evaluation and treatment of patients with trigeminal neuralgia

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The neurologist, although not usually the first healthcare provider to evaluate a patient with trigeminal neuralgia (TN), is often involved in confirming the diagnosis and managing the patient's pain with medications. The neurologist has several other important roles for patients with TN: assessing and reducing the individual's pain, patient and family education, and encouraging referral to a neurosurgeon for pain-reducing procedures when appropriate. In general, surgical procedures for TN should be considered when the patient does not attain pain relief after adequate trials of two or three medications, or when pain relief is attained but the patient requires medication dosing at levels that result in significant drug toxicity. There is emerging evidence that surgical procedures for TN are more effective if performed earlier in the course of the patient's pain.

KEY WORDS • trigeminal neuralgia • neurologist • neuropathic pain

The evaluation and treatment of patients with TN often involves healthcare professionals from a number of disciplines, and recognition of the proper diagnosis often takes years. Patients may seek the help of family physicians, dentists, or oral surgeons and may have undergone a number of dental procedures before the diagnosis is suggested and then confirmed by a neurologist or neurosurgeon. Problems arise because of several factors: the patient's pain resembles that of a variety of dental problems, the pain is not constant, and TN is not a commonly encountered condition for any of the primary or specialty healthcare professionals who initially evaluate these patients. This review focuses on the role of the neurologist in the evaluation and treatment of TN. I review the situations in which the neurologist may be of help to the patient: in making the diagnosis, performing a workup, proper selection and use of medications for pain control, educating the patient and family, and knowing when it is time to refer to a neurosurgeon for a pain-reducing procedure.

Making the Diagnosis

Although the neurologist is not usually the first physician to see the patient with TN, they may be the first to evaluate the patient thoroughly and to confirm the diagnosis. The differential diagnosis of unexplained facial pain may be extensive, with an overlap of symptoms (Table 1). Important questions about the patient's history include the following. Is the pain clearly in the distribution of the trigeminal nerve (most commonly the second division)? Is it unilateral? Does it have a lancinating quality? Are there

triggers? Is there any sensory loss? Does the patient fit the proper demographic category? If it is TN, then what subtype is it? Are there atypical features?

After the differential diagnosis is considered, it is important to look for an underlying source of the pain. For a younger patient or one in whom the pain is bilateral, it is important to exclude MS. Nevertheless, for many patients with typical symptoms, there is usually no secondary cause for TN.

Assessment of the Severity of the Patient's Pain

It is my experience that patients present to the neurologist at various stages in the history of their TN. These stages include the newly or recently diagnosed patient, the one who has already been diagnosed and who seeks another opinion, or the patient with a long history of TN who has received medical (and possibly surgical) intervention and who is not doing well. Furthermore, each of these subgroups can be broken down into those in crisis (pain) and those in remission.

For those in pain crisis, it is often apparent on initial assessment. Most patients will readily tell you if they are in pain. Others may have painful attacks (tics) in the examination room. It is important to ask about the type of pain that they have. Is it a sharp, shooting, lancinating type of pain? How long does it last (seconds)? How frequent are the attacks? Is there pain in between bouts? Has there ever been a (spontaneous) remission? What triggers an attack? Has the patient discovered any tricks to reduce the pain? Has the patient tried any over the counter or complementary medical treatments? Has the patient tried prescription medication?

It is helpful to use an analog scale for a more "objective" assessment of pain. This can be as simple as asking the patient to rate the pain on a scale of 1 to 10, or it may be more

Abbreviations used in this paper: AED = antiepileptic drug; MR = magnetic resonance; MS = multiple sclerosis; TN = trigeminal neuralgia.

TABLE 1

Differential diagnosis of predominantly unilateral facial pain

dental & sinus pain
temporomandibular joint disease
cluster headaches
SUNCT
atypical facial pain
Tolosa–Hunt syndrome
giant cell arteritis

formal, using written instruments such as the Wong–Baker Faces pain rating scale. Alternatively, the short-form McGill pain questionnaire¹⁰ may be helpful. These measures provide a consistent method to assess the patient's pain from one visit to the next.

It is also important to determine the impact of TN and the patient's pain on activities of daily living (or quality of life). Important questions to ask of patients include the following. Are they able to eat? Are they losing weight? Are they able to wash their face? Are they able to brush their teeth? Are they able to sleep? Can they go outside when it is cold or windy? Do they avoid a social life? Have they avoided going to the dentist for routine evaluation or cleaning? Have they become anxious and depressed? The more affirmative answers obtained the more clear it is that the condition is even more severe than might be realized from a pain rating scale.

Workup of the Patient With TN

The most important test in the evaluation of TN is MR imaging. This modality serves a number of functions: it can be used to identify a structural lesion, such as fifth cranial nerve or brainstem meningioma or a cavernous malformation;⁷ it can be used to identify white matter lesions within the brainstem or the subcortical white matter, which helps to make the diagnosis of MS; and it may aid in the identification of vascular structures around the fifth cranial nerve that may be implicated as the cause of TN, and that may be amenable to surgical treatment.

Patients often present to the neurologist after having undergone a brain MR imaging session. Often the MR images have been interpreted by the neuroradiologist as “normal.” Nevertheless, it is important for the neurologist to review the actual MR imaging films (or their digital equivalent). The MR imaging protocols vary among institutions, and are continuously evolving.⁵ The following questions should be raised. Is the quality of the film adequate? Was a contrast agent used? Were thin (1-mm) sections obtained through the fifth cranial nerve? If the answer to any of these questions is no, then it may be important to repeat the study to correct the deficiency. This often changes the result from “normal” to identification of the origin of the pain.

If a patient has typical TN, and a vascular loop is found with no other pathological entities, then further evaluation is not necessary. Rarely the MR image may reveal tumor, infarct, or a persistent primitive trigeminal artery. For patients with atypical features, further diagnostic tests are often performed. If MS is a possibility, then a lumbar puncture to look for oligoclonal bands, and evoked potential

studies may be helpful. For others, a workup to assess for Lyme disease or sarcoidosis may be indicated if other features are present.

Education of the Patient With TN

Unfortunately, for many patients TN is an ongoing and often progressive condition. The neurologist needs to provide ongoing education to the patient and family about what to expect with regard to the underlying disease and treatment. In our current reimbursement environment, this is quite difficult because it is time-consuming. Nevertheless, it is time well spent because there will be greater patient satisfaction and better outcome, because education often improves compliance.

Although the goal of treatment should be the resolution of pain and return to normal function, this is not always attainable. More commonly, the result is significantly reduced pain, with ongoing use of medication(s) and (hopefully) few adverse effects. Although the eventual outcome is not easily predictable, for many patients TN is a condition of painful crises and remissions. In my practice, many patients have painful crises that last up to 6 weeks, and although they may not be completely free of pain afterward, there is often significant improvement.

There are other patients with painful crises and partial remissions who are clearly dependent on medication to avoid significant pain. Many patients who say they are “doing well,” however, will report that under certain daily conditions they will get a mild twinge or reminder of their severe pain, although it never quite progresses to a full shock.

Patients should be taught about neuropathic pain and how it differs from nociceptive pain. They may have already realized the difference, because they may have tried “nonneuropathic” drugs such as acetaminophen and nonsteroidal antiinflammatory medications, without success.

A great deal of education needs to be done with regard to medications. Patients are usually not familiar with the classes of medications used for TN or neuropathic pain. Because these medications may be AEDs or antidepressant agents, patients should be informed that they are not prescribed for those purposes, but that they work for TN pain. Appropriate information should be given with regard to potential side effects of the medication(s) chosen and how they might be minimized. The possible need for laboratory testing should also be explained.

Experienced physicians realize that most patients are unable to retain all of the information given to them with regard to their diagnosis and treatment the first time it is explained. For that reason, education is an ongoing process in the course of treatment. This is particularly true for patients with TN, who may be older and can have coexistent memory problems.

A helpful resource is the Trigeminal Neuralgia Association (www.tna-support.org). They have an excellent, up-to-date website as well as written materials, telephone support, and patient support groups. Their recently revised layperson's guide, *Striking Back!*,¹² is an excellent resource. The Trigeminal Neuralgia Association holds national and regional patient education meetings.

Choice of Medication

The neurologist often chooses the pain medication for the

patient with TN. Sometimes the first medication is effective, but often there is a second or third trial. Sometimes the decisions involve combinations of medications. In the last 10 years, for many neurological conditions, there have been a number of large, randomized, multicenter, double-blind, placebo-controlled studies that have provided evidence-based medicine and that have helped physicians make an informed choice regarding treatment. For TN, this is mostly not the case. For older medications, the studies that exist are usually not double-blind or placebo-controlled, or they have small numbers of participants and do not match the current standards of investigation. There are few studies for newer medications; most are case reports or series, or have small numbers of patients with short follow-up durations. As a result, the physician faced with choosing a medication for TN has little objective information to follow.

The most commonly used first-generation AEDs are carbamazepine and phenytoin (Table 2). Carbamazepine has been shown to be effective in the treatment of TN in a number of older studies,⁴ and it has been a mainstay in this capacity for a number of years. Key adverse effects include the following: leukopenia, hyponatremia, rash, and elevation of liver enzymes. More recently, long-term treatment has been associated with elevation of components of the lipid profile⁸ and deleterious effects on bone health.¹¹ Phenytoin is also used for chronic TN, although it is less well studied, and may not be as effective.²

Advantages of first-generation AEDs include the physician’s familiarity with the drug, its lower upfront cost, its reasonable degree of efficacy, and the fact that these medications are present in most formularies. Disadvantages of first-generation AEDs include complicated pharmacokinetics (often nonlinear), higher levels of protein binding, narrow therapeutic indices, appreciation of subtle but often progressive chronic toxicities (cosmetic, bone health, cholesterol, brain atrophy), and drug–drug interactions.

The more commonly used new generation of AEDs include gabapentin, oxcarbazepine, and lamotrigine. Gabapentin is often tried after carbamazepine, although there are few studies to support its use. There was a small trial with positive results in patients with TN who had MS.⁹ Occasionally, patients who respond to gabapentin have not responded to other AEDs. Most patients tolerate gabapentin well, although adverse effects include somnolence, weight gain, and peripheral edema.

Oxcarbazepine is structurally related to carbamazepine, although it has a number of properties that make it a different medication. Oxcarbazepine is reduced via cytosolic en-

zymes to an active metabolite, a pathway that does not involve P450 isoenzymes. Oxcarbazepine and carbamazepine are both voltage-dependent sodium channel blockers, although they have differential effects on calcium channels. There are a number of case series in which it has been suggested that oxcarbazepine is effective in TN.^{6,14} There are also two clinical trials comparing the efficacy of oxcarbazepine and carbamazepine for TN (in newly diagnosed patients in one and in those with chronic TN in the other), and in both of them the researchers suggested no difference in efficacy, although oxcarbazepine was better tolerated.³ Possible adverse effects of this drug include sedation, nausea, and hyponatremia.

Lamotrigine is also used for TN. In a small trial, there was a positive effect in pain reduction in patients with refractory TN when lamotrigine was added to the existing drug regimen.¹³ This medication is usually well tolerated; however, there were early reports suggesting an increased risk of serious rash such as Stevens–Johnson syndrome. A lower starting dose and slower titration rate seems to reduce that possibility.

Overall advantages of second-generation AEDs include the following: efficacy at least as good as first-generation AEDs, new or different mechanisms of action, lower levels of protein binding, fewer drug–drug interactions, and the suggestion that they have a better adverse event profile, with some having been shown to have fewer negative effects on bone health.¹¹ Disadvantages of newer AEDs include their upfront cost (although the overall cost may be less due to fewer complications and less of a need for laboratory monitoring) and less information about potential chronic toxicity.

Other older agents that are considered include baclofen, opioids, and antidepressants (amitriptyline, nortriptyline). Other newer agents that are tried include other AEDs (zonisamide, topiramate, levetiracetam), antidepressants (venlafaxine, duloxetine), and topical agents (lidocaine, capsaicin). Pregabalin, which has received an approval letter from the Food and Drug Administration, and is related to gabapentin, may also prove to be a helpful medication. The details of these medications are beyond the scope of this review.

It has been said that the more treatments that exist for a condition, the less likely it is that any one of them works particularly well. Nevertheless, for patients with mild TN it is reasonable to try oxcarbazepine (good efficacy and favorable side effect profile), and to expect a good initial response within 48 hours. After that it is important to titrate closely to maximize efficacy and to minimize adverse effects. For patients who have a partial response, it is reasonable to raise the dose to toxicity. If side effects limit the trial, then the dose should be lowered so that another agent can be added. If the trial is successful, then tapering of the first medication can be tried. Some patients require combination therapy, and it may be rational to pick drugs from different therapeutic categories (for example, AED plus antidepressant).

When to Refer for Neurosurgical Intervention

Although in some patients TN is controlled over the long term with low doses of a single medication, for many it is a progressive disorder. It is not infrequent that TN attacks be-

TABLE 2
First- and second-generation medications for TN

First-Generation	Second-Generation
carbamazepine	gabapentin
phenytoin	oxcarbazepine
valproate	lamotrigine
baclofen	zonisamide
amitriptyline	topiramate
nortriptyline	levetiracetam
	venlafaxine
	duloxetine

come more severe, last longer, and require increased doses and numbers of medications. One consequence is that in taking drugs to reduce pain, the patient experiences side effects. There may be strategies to reduce adverse events (for example, split the total dose by increasing the frequency), but often they are not sufficient.

When the diagnosis of TN is made, it is reasonable to try at least two medications in sequential monotherapy. If that fails, then one or two trials of polytherapy, in which agents from different classes are combined, can be tried. This may help the pain by affecting more than one mechanism of action. It is important that medications are used properly; that is, adequate dosing is delivered and titrated to maximize pain control, while minimizing adverse effects. If a patient has an intolerance of a medication or a rash appears at a nontherapeutic dose, then that cannot be counted as an adequate trial. The same can be said about noncompliance (whether that consists of under- or overdosing). Many patients suffer because their distrust of medication is stronger than their experience of pain.

If a patient continues to have breakthrough pain or has intolerable adverse effects after two or three medication trials, then surgical intervention should be considered. In my experience, only approximately half of the patients are willing to consider surgery after only two or three medication trials. This is mostly because they have a strong fear about the potential complications of procedures. Continuing education helps, but this is a process. The neurologist's concern is that if surgical intervention does not occur within 7 years, then the outcome may not be as good.¹ In addition, it is usually easier for the patient to undergo a procedure when they are younger and otherwise healthier.

The positive side is that most patients with intractable pain eventually accept referral to a neurosurgeon. It is particularly helpful for patients to meet with the neurosurgeon when they are not in the middle of a painful crisis, so that they are more able to make proper decisions. Patients should be referred to neurosurgeons with special expertise in the surgical management of TN. Recently I had the experience of referring a patient to several neurosurgeons experienced in TN procedures. Nevertheless, because of a restrictive health insurance plan, the patient went to the only neurosurgeon within the provider network. This surgeon was not familiar with TN treatment procedures, and advised the patient not to have surgery. The patient became confused and continued to suffer needlessly.

There is now enough experience, especially with microvascular decompression, to justify earlier intervention.¹ If a patient is not a candidate for microvascular decompression, then the other available procedures should be considered (radiofrequency lesioning, glycerol injection, gamma knife surgery). The neurologist needs to be well versed about the procedures used to treat TN, and to help advise the patient in making the proper decision, both before and after the neurosurgical consultation.

CONCLUSIONS

The neurologist plays an important role in the treatment of TN, first by making or confirming the diagnosis. Second, the neurologist should oversee the workup to ensure that it

is done properly. Third, the neurologist is often the one who initiates appropriate treatment, and who monitors that therapy. Fourth, the neurologist should also be the patient advocate, and educate as part of an ongoing process. Last, the neurologist should be proactive in guiding the patient toward the decision to seek neurosurgical intervention under the following conditions: 1) when the patient does not respond to medication; 2) when unacceptable side effects arise; or 3) when there are untoward compromises in the patient's quality of life. For that reason, neurologists need to be informed about the procedures performed for treatment of TN to provide the best advice for their patients.

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Manuscript received March 17, 2005.

Accepted in final form April 8, 2005.

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