OVERVIEW

Trigeminal neuralgia is a well-known condition; neuroscientists working in the fields of neurology and neurosurgery are well acquainted with the syndrome. The diagnosis is made nearly entirely based on the patient’s history. It should be a simple matter for physicians to make the proper diagnosis, but it is not. In a survey of patients with TN, 90% had experienced pain for more than 1 year before receiving an accurate diagnosis, whereas 13% went 10 years without a diagnosis. With an incidence of four cases per 100,000 in the US, individual practitioners in medicine and dentistry will see very few cases of TN in their careers. The rarity of the cases contributes to the rates of misdiagnosis and inappropriate treatment. Indeed, Tew and van Loveren found that 33% of their 1100 patients with TN had undergone unnecessary dental extractions.

First described in the 1600s, the clinical picture is one of pain and symptoms confined to the facial area; there are no systemic components to TN. Wartenberg suggested that the hallmarks of TN would be paroxysms of pain confined to one or more of the three divisions of the trigeminal nerve. The pain is predominantly unilateral, and is described as electric, lancinating, focal, and sharp. It can last for seconds to minutes initially, and sometimes lasts as long as 1 hour. Usually the patient is symptom free between attacks. Later in the course of the disease, patients report dull, aching, constant pain in the same distribution as the paroxysms.

Most patients experience a cyclic history of the pain, with the interval between attacks lasting weeks, months, and occasionally years (most patients experience a shortening of the interval between attacks in the course of a decade). Often, the interval between attacks is marred by an increasing level of paresthesias in the nerve. If questioned, patients will frequently report sensations of clicking in the ipsilateral ear, possibly related to the motor innervation of the tensor tympani. There can be pain in the external auditory canal, in the area subserved by the trigeminal nerve. The external auditory canal is innervated by the ninth, 10th, and fifth cranial nerves and by the geniculate ganglion. The trigeminal and vagolymphatic nerves supply the majority of the external auditory canal; this is the correlation with the auricular pain.

The pain can be triggered by nonnoxious stimuli (chewing, talking, wind on the face, cold, and light touch). The classic trigger(s) will produce pain in divisions beyond the one so stimulated. The trigger represents allodynia in facial pain. This is due to central sensitization in addition to the peripheral initiator. Allodynia is the result of A-beta fiber activity with neuronal reorganization at the level of the dorsal root ganglion and rostrally. Many patients will describe a sense of pulling, fullness, and flushing in the affected area of the face. The patient usually can describe the first attack in detail, as to the time, place, associated events, and pain course. The pain can also be triggered by positional changes of the head. Typically, lying down on the side of the pain will provoke an attack, whereas rolling to the other side can minimize it. Patients will attribute pain at night more to these positioning phenomena than to contact with bedsheets in sleep. This correlates with the same position-provoked pain during the day.

There can be a family history in approximately 5% of patients with TN. Five percent of patients will experience bilateral sequential pain. More women may present than men (7.2 compared with 4.7 per 100,000), with the peak decade of presentation being the sixth. The age range at presentation in my experience is 22 months to 94 years. There is some controversy about the frequency of side of presenta-
tion. White and Sweet reported right-sided pain in 61%, left-sided in 36%, and bilateral in 4%. Investigators in other studies did not find a propensity for one side or another.

Systemic illnesses such as multiple sclerosis, Lyme disease, and Charcot-Marie-Tooth disease can be part of the cause of the pain. Chiari malformations may exacerbate the pain of various cranial nerves, including the trigeminal nerve, as can other pathological phenomena discussed in the Differential Diagnosis section. These conditions can produce sequential pain on the contralateral side, or increased incidence of bilateral pain. Most often the pain is due to vascular cross-compression of the root entry zone (Fig. 1) of the main sensory root of the trigeminal nerve, the portio major, in the posterior fossa. This can include the area of the mixed motor and sensory fibers of the motor root, the portio minor. It may well be that cross-compression in this latter region produces the symptoms of facial pulling, facial fullness, and heaviness that some patients report. The innervation that the fifth cranial nerve supplies to the sinus cavities underscores the confusion in attributing pain ascribed to this area. The branches of the V1 supply the anterior dura, allowing for referred pain in this region.

Symptoms will predominate in the V1 (15%), or V2 (17%), and the combination of V1 and V2 (32%), and rarely start in only the V3. All three divisions are affected in 17% of patients at onset. The use of medications may add to the diagnosis. There are reports of the unique sensitivity of TN to carbamazepine, and this is sometimes preferred as a fundamental part of the essential history. Carbamazepine will reduce or alter the pain in 70 to 90% of patients with TN, but also in 67% of patients with related head and neck pain.18 There are no convincing reports that carbamazepine reduces trigger zone hyperalgesia. The response to this drug will not eliminate the diagnosis, but it may presage an improved surgical outcome (PJ Jannetta, personal communication, 2003).

PAIN EVALUATION IN TN

Pain Rating Instruments

Pain evaluation in TN is sometimes difficult. It is the opinion of many patients with TN that the apparent mismatch between their physical appearance and their reports of pain leads to a diagnostic disconnection. In my institution we use the McGill Pain Questionnaire; coupled with the visual analog scale (Scores 1–10) and the Wong–Baker Faces pain rating scale, it aids in the evaluation of the type and intensity of the various pain components. The McGill Pain Questionnaire is one of the most extensively used and validated scales. It was created by patients and physicians specifying sensory, affective, and evaluative descriptors. Melzak, et al.,13 organized them in a quantifiable way to produce a pain rating index. Completion of the 78-word test takes 5 to 10 minutes. It has been suggested that the McGill Pain Questionnaire can give a reliable indication of the affective stress. Melzak and Zakrzewska have each used this questionnaire to distinguish different types of facial pain, including dental pain, burning mouth syndrome, and TN.21 The visual analog scale is based on a 10-cm scale with descriptors at either end. The scale is used to rate the pain at the patient’s first visit and subsequently, and it can be used to monitor response to medications or treatments. The reproducibility of results is reasonably good. If one adds descriptors between either end (such as in the Wong–Baker Faces pain rating scale), one gets a version of a verbal rating scale. Verbal scales are simple, but somewhat insensitive to small changes.

Examination of the Fifth Cranial Nerve

Corneal Reflex. The evaluation of the fifth cranial nerve is conducted as part of the general neurological examination. The fifth cranial nerve is the largest of the nerves, and its functions are both sensory and motor. The corneal reflex is elicited with the fine tip of a cotton swab, touching but not dragging the wisp of cotton over the cornea. Both the upper and lower cornea are tested; the upper half of the cornea is innervated by V1, the lower by V2.

Sensory Examination. The sensory examination of the three divisions is conducted with light touch (cotton wool), pinprick, vibration, and hot/cold sensation, ending with deep pressure. In this fashion, all the modalities are sequentially evaluated. Half of the 125,000 fibers in the human trigeminal nerve are myelinated (in the spinal dorsal roots, that figure is 20%). The relative increase in myelinated fibers increases the number of potential sites for large-fiber dysfunction, which is related to neuropathic pain. In 1938, Lewy and Grant1 published that 25% of patients with TN had sensory abnormalities, a figure confirmed in subsequent papers.49 This sensory loss will often be unnoticed by the patient. It may be found in only one of the modalities tested, as suggested by Nurmikko.12 Loss of vibratory sense (128-Hz fork) is equated with loss of A-beta fibers, loss of pinprick sensation is related to loss of A-delta fibers, and vasomotor and sudomotor abnormalities are seen in C fiber dysfunction. Temporal summation is related to sensitization of the wide dynamic receptors of the unmyelinated C fibers. The deficits may involve both small- and large-fiber activity.12 Distal small-fiber loss with neuropathy produces the report of burning pain.

The sensory loss may not always be in the area with the most pain reports. Jannetta described a high incidence of hypesthesia to cotton wool in the area of the nasolabial fold ipsilateral to the pain. Nurmikko showed that electrophysiological investigations uncovered sensory abnormalities
in modalities of the trigeminal nerve that corresponded to the triggered zone. The trigemino-ocular response is transmitted through the afferent V, or V, branch, with the efferent mydriasis then miotic response through the sympathetic and parasympathetic nervous systems. The trigemino-depressor response consists of bradycardia and hypertension followed by reflex hypertension. It is mediated by sympathetic inhibition and parasympathetic stimulation. The demonstration of these reflexes with low-level electrical stimulation further characterizes the dysfunction in the affected side.

**Trigeminal Evoked Potentials**

Lunsford, et al., first described the trigeminal evoked potential. He related nerve fiber dysfunction to the pain, finding that 86% of patients had an abnormality. He also reported that 83% improved following microvascular decompression. Szapiro, et al., noted that patients with sensory loss did less well, a finding disputed by Zakrzewkska. Evaluation of the jaw musculature in TN is less clear. There is a body of literature that looks at the effect of trigeminal dysfunction on the inhibitory reflex in the masseter muscle, concluding that the R, reflex originates from the trigeminal nucleus, whereas the R, reflex has its efferent loop in the C-1 region of the spinal cord. Both are mediated through A-delta fibers. Taken together, these modalities are powerful tools with which to supplement the clinical examination, perhaps to expand the therapeutic window by directed treatments.

The trigger areas are an interesting topic for further research. Several authors have shown that the tactile and temperature thresholds are raised in these areas, and have also observed hyperalgesia to thermal stimuli. There is often temporal summation (abnormal increases in intensity of pain to constant-strength stimulus, radiation of pain from the stimulus, after-sensation). Temporal summation of pain is a hallmark of central hyperexcitability to pain. Allodynia and hyperalgesia are the hallmarks of neuropathic pain. These findings implicate peripheral fibers (A-delta, A-beta) as well as neuronal pools in the pain of TN. Better understanding of the relative contributions in an individual patient may allow for better timing of interventions. The natural history of TN indicates progressive large-fiber loss, making certain therapeutic interventions less likely to succeed.

**Diagnostic Imaging**

Imaging studies in TN have included skull x-rays, computerized tomography, and now MR imaging. Standard MR imaging is ordered in these patients to evaluate other causes of the syndrome (vide infra). The sensitivity of MR imaging alone for determining the vessel(s) or site of compression is poor (PJ Jannetta, personal communication, 2003). When MR imaging is coupled with MR angiography, Patel, et al., at Frenchay Hospital in England report 90.5% sensitivity with 100% specificity as to vessel compression. Nevertheless, they found a correlation in only 76 of 92 patients. There were eight false-negative and seventeen false-positive findings.

Fukuda, et al., have advocated MR tomographic angiography in their series, but reported only a 67% correlation with intraoperative findings. They found that small arteries, veins, and thickened arachnoid membrane reduced the sensitivity of the test. Yoshino, et al., looked at MR imaging with the constructive interference in steady state feature, citing a success rate of 12 (80%) of 15. Nevertheless, researchers in other centers found that the combination of three-dimensional MR fast imaging employing steady-state acquisition with three-dimensional fast–spoiled gradient–recalled acquisition sequences only yielded a 71% accuracy rate. The available imaging possibilities are legion, but lack the accuracy to define the exact vessel(s) involved, nor do they exclude patients without demonstrated vessels.

An interesting new development in the imaging cascade is the use of functional MR imaging. In this application, the patients stimulated with pinprick touch in the trigger areas demonstrate activation of the trigeminal ganglion, nuclei, and other central structures. Finally, in a new application of the positron emission tomography scan, opioidergic imaging shows a decrease in the binding of the thalamus receptors in chronic facial pain, including TN. All of these neurophysiological investigations serve to provide us with a full picture of the range of dysfunction in the trigeminal system.

**Electrophysiological Tests**

Electrophysiological investigations into the trigeminal nerve have yielded consistent results, but they have not been widely used. They are a good complement to a careful sensory examination. Indeed, there is close correlation between these electrophysiological investigations and the clinical examination, which can specify the type of sensory neuropathy.

The trigeminal evoked potential was developed by Lunsford and colleagues who reported that 86% of patients with TN had abnormal potentials, whereas 83% improved their potentials after successful microvascular decompression. This is in agreement with the physiological testing in which the electrical evoked potential measures large-fiber (A-beta) involvement. Qualitative sensory testing allows the examiner to delineate further the deficits involving the A-delta and C fibers. Modality-specific stimulation (cold, warm, hot, cold, and laser) can further subdivide the A-delta group from the C fibers. Romaniello, et al., conducted a series of examinations in humans in which they used short and ultrashort Nd:YAG laser pulses to a small and large surface area. They were able to show the correlation between the subjective report of pinprick with the short-burst laser and the A-delta scalp evoked potentials. The ultrashort, large-target laser produced a feeling of warmth, which corresponded to the C fibers. These elegant complementary studies allow us to characterize the patients with TN as to the existence of large-fiber, small-fiber, or mixed sensory neuropathy. This may lead to more precise surgical procedures in which the appropriate fiber group is targeted.

**Differential Diagnosis**

The differential diagnosis in TN is somewhat varied. The scope of related head and neck pain spans several systems; the aerodigestive system, the skeleton, the muscle/soft tissues, the dental system, and the vascular supply as well as the different peripheral, central, and autonomic nervous system components. Maxwell proposed a simple classification scheme: trigeminal group and other cranial nerves. In the former, he listed idioopathic, ophthalmic, sinus, neoplastic, inflammatory, and vascular causes.
The presence of some conditions is easily eliminated based on the examination, but the following 10 conditions pose some problems. 1) PreTN, well described by Fromm, is prodromal, dull, aching pain, toothache–like, in one division. It is paroxysmal, provoked by light touch, and cyclical. It usually progresses to classic TN. 2) Postherpetic neuralgia is pain in the trigeminal nerve division(s) after an attack of herpes zoster. This is a burning itch, which is constant, deep, and accompanied by allodynia to touch. It is commonly present in the V1 only. 3) Glossopharyngeal neuralgia encompasses severe, stabbing pain in the ear, ear and throat, or throat alone while swallowing. 4) Tic convulsif is identical to TN in its pain characteristics, except for the fact that the patient also displays unilateral tonic contractions of the ipsilateral face, which are identical to hemifacial spasm. 5) Geniculate neuralgia is characterized by severe, stabbing, “ice-pick” pain deep in the ear. There is often a deep, constant background pain as well. 6) Dental pain is sharp, elicited by local stimuli, and short lasting. It is quite similar to TN in the V3 or V1. 7) Temporomandibular disorders are a confusing lot, with many diagnostic criteria. The pain is a dull ache in the region of the joint, with an accompanying stiff, tense feeling. This can spread from the preauricular area to the associated musculature. It is provoked by jaw movement, can be intermittent, and is associated with local tenderness. There is restricted jaw opening. 8) Maxillary sinusitis produces a throbbing pain in the cheek; there is also heaviness, aching, and tenderness. It is worse in the morning, and with head-down positions. 9) Migraine is unilateral head pain. It is throbbing; pulsating but not sharp. It can be associated with an aura, nausea, vomiting, and photophobia. 10) Giant cell arteritis causes diffuse, aching pain in the temporal region, often into the neck. There can be localized tenderness over the vessels. There is malaise, weight loss, and sometimes visual loss (50%).

Trigeminal neuralgia can be a secondary type, occurring in the context of tumors (schwannomas, meningiomas, and epidermoiders), but most patients with these tumors also have vessel compression. Infiltrative lesions include amyloidomas and carcinomatosis. Small infarcts and other vascular lesions in the pons or nerve root can cause pain. Familial TN is more frequent in patients with Charcot-Marie-Tooth disease.

CONCLUSIONS

The diagnosis of TN is made based on the patient’s history; it can be made by telephone in most cases. Many patients are misdiagnosed, and undergo misguided, unnecessary procedures and ineffective treatments. Primary care practitioners, family physicians, physician’s assistants, and nurse practitioners must learn to make this diagnosis.

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