CASE STUDY

Going under the gamma knife: A case of intractable trigeminal neuralgia

Nessa Timoney *(Fourth Year Medicine, TCD)*

CLINICAL POINTS

- Trigeminal Neuralgia (TN) is the most common cause of facial pain in individuals older than 50 years of age.
- The pathophysiology consists of chronic irritation of the trigeminal nerve due to compressive or inflammatory causes.
- Diagnosis of idiopathic TN is based on clinical presentation, whereas secondary causes of TN may be confirmed by imaging techniques such as MRI, MRI with or without contrast, MR angiography, and 3D reconstructed MRI.
- It is estimated that more than 80% of patients respond initially to medical treatment but as time passes, medications may lose their efficacy, even when part of multiple drug therapy regimens.
- Surgical treatment is reserved for patients who have failed to achieve pain relief after adequate trials of two or three pain medications, when pain relief is attained but the patient is experiencing significant drug toxicity, or in the presence of symptomatic TN with a surgically amenable structural lesion.

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PRESENTATION OF CASE

KS, a 58-year-old male patient, presented to the neurology out-patient clinic in autumn 2008 at the University of Louisville where he was being followed for ongoing facial pain, having a three-year background history of Trigeminal Neuralgia (TN). At the time of presentation, he reported an eight month history of recurring facial pain despite pharmacotherapy, and was becoming increasingly concerned about the side effects of his medication, oxcarbazepine (Trileptal), which had become intolerable. The site of his pain was in the distribution of the maxillary (V_2) and mandibular (V_3) divisions of the right trigeminal nerve. Pain was intermittent, each episode lasting approximately 5 to 10 minutes on average and episodes occurring several times daily. KS described the pain as "stabbing", and rated the severity as 10 out of 10. He further reported that on six to seven occasions, he experienced an aching pain that lasted up to 25 minutes. His facial pain had gradually worsened over the last six months, with a more rapid deterioration of pain tolerance over the preceding one to two months. Pain was precipitated by chewing, brushing of teeth, talking, and combing hair. In addition, KS complained of TN associated headaches that "felt as though his head was in a vice constantly."

After several months of medical therapy with high-dose oxcarbazepine, which had been increased at a previous outpatient visit to alleviate worsening symptoms, KS had felt "terrible, doped up, and like a zombie." He reported being more clumsy, bumping into walls and was aware of a general decrease in his gross motor skills. He also reported finding himself isolated and increasingly depressed. This was particularly concerning for KS, who had a past history of bipolar disorder for which he was being treated. He worried that the isolation, pain, and depression would exacerbate his bipolar disorder.

At the time of the current presentation, KS's medications included: oxcarbazepine, an anticonvulsant, 600 mg three times daily and clonazepam, a benzodiazepine derivative with anticonvulsant, muscle relaxant, and anxiolytic properties, 1 mg daily for TN, sertraline hydrochloride (Zoloft), an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, 50 mg daily and lamotrigine (Lamictal), an anticonvulsant, 200 mg twice a day for bipolar disorder, and finasteride (Proscar), a 5-alpha reductase inhibitor, 5 mg daily for benign prostatic hyperplasia. KS noted he had an allergy to gabapentin.

Past drug history included 1600 mg carbamazepine (Tegretol), an anticonvulsant, taken daily when KS was first diagnosed with TN in 2005. He found temporary relief from the carbamazepine but pain persisted a few months thereafter despite dosage increase. Other drugs were added individually to the pharmacological regime over a nine month period. These agents included gabapentin (Neurontin), which he subsequently had an adverse reaction to, and ba-

clofen (Lioresal). He was then tapered off the carbamazepine, which was substituted for oxcarbazepine (Trileptal) at a 600 mg dose daily as carbamazepine had been ineffective for pain relief. On his next visit, despite pharmacological intervention, he complained of persistent pain. As a result, oxcarbazepine was prescribed up to a dose of 2400 mg daily at which dosage side effects became intolerable and still failed to achieve adequate pain relief. At this point, surgical intervention was considered.

KS's past surgical history included Gamma Knife Radiosurgery (GK-RS) at the University of Kentucky, in May 2006 (two years priors to current presentation). The GK-RS was performed due to a lack of symptom resolution with maximal pharmacotherapy for several months following initial presentation in 2005. Immediately following this surgical intervention, the patient was maintained on oxcarbazepine at a dose of 300 mg daily and remained pain-free for two years. During this pain-free period, KS was re-evaluated in the clinic for ongoing management of his condition in September 2007. At that time his TN was well controlled on 300 mg of oxcarbazepine daily and this dose was being tapered gradually since the patient had reported no pain in the preceding several months. Although his medications remained effective for several months at tapering doses, KS eventually began to experience recurrence of TN symptoms that led to his current presentation to the neurology outpatient clinic.

As previously mentioned, KS also suffers from bipolar disorder in addition to TN, and there was nil of note when asked about his family history. Social history revealed that KS is currently not working due to the distressing pain associated with his condition. He is, however, trained as a psychologist in a school setting. KS has no children

Classical TN	Symptomatic TN
A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of trigeminal nerve and fulfilling criteria B. and C.	A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes with or without persistence of aching between paroxysms, affecting one or more divisions of trigeminal neuralgia and fulfilling criteria B. and C.
B. Pain has at least one of the following: • intense, sharp, superficial or stabbing • precipitated from trigger areas or by trigger factors	B. Pain has at least one of the following: • intense, sharp, superficial or stabbing • precipitated from trigger areas or by trigger factors
C. Attacks are stereotyped in the individual patient	C. Attacks are stereotyped in the individual patient
D. No clinically evident neurological deficit	D. A causative lesion, other than vascular compression, has been demonstrated by special investigations and/or posterior fossa exploration
E. Not attributed to another disorder	

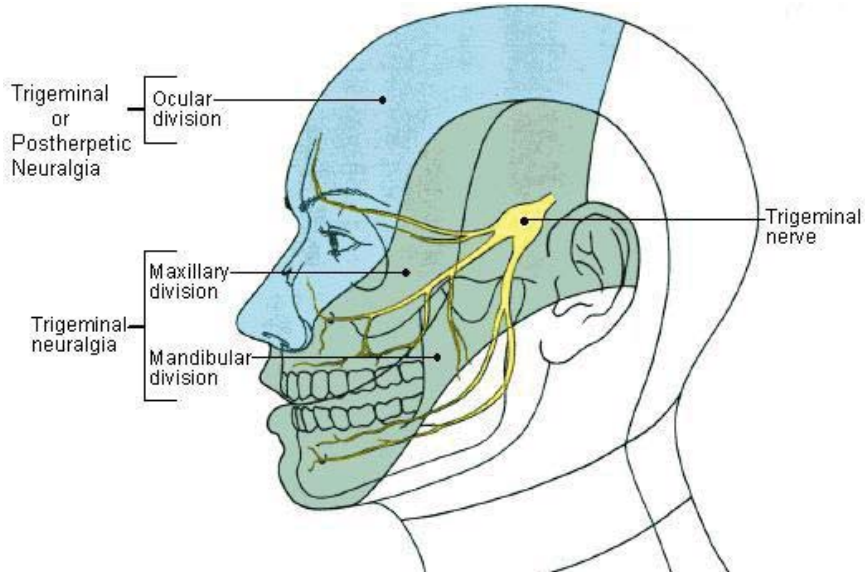
▲ **Table 1:** ICHD-II Trigeminal Neuralgia Classification © International Headache Society 2003/5

and no spouse or significant other, and he denies current or past use of tobacco, alcohol, or recreational drugs.

Review of systems was non-contributing. As would be expected in a patient with TN, no signs were elicited upon physical or neurological exam[5]. If there had been positive findings upon physical examination, this may have been suggestive of a diagnosis other than TN[1].

Investigations and Diagnosis

Diagnosis of idiopathic TN is typically made clinically because there is no routine and definitive laboratory, electrophysiologic, or radiologic testing indicated for a diagnosis of TN. Due to the characteristic symptoms associated with TN, a diagnosis can



▲ **Figure 1:** Facial distribution of TN.

be made based on the clinical picture alone. Evidence-based reviews have demonstrated that clinical or laboratory testing is of limited use in the diagnosis of TN. In addition, routine neuroimaging may only identify an underlying cause for the TN in up to 15 percent of patients with TN-like symptoms[2]. As a result, such investigations are not carried out routinely unless the patient has failed a trial of medication and is a candidate for surgical intervention[2].

TN is a syndrome characterized by recurrent but brief, lancinating, paroxysmal attacks of facial pain. This pain is superficial, usually unilateral and restricted to the facial somatosensory distribution of the trigeminal nerve and its branches (Figure 1)[3]. Similar to the presentation of KS, TN tends to affect the right side of the face more commonly than the left, a finding that is believed to be due to the narrower foramen rotundum and foramen ovale (conduits for the maxillary and mandibular nerve, respectively) on the right[1]. TN pain is classically shock-like, stabbing, or sharp and usually lasts only seconds. Attacks may occur infrequently or as often as 100 times a day, with patients generally being asymptomatic between episodes. KS, however, noted an aching type of pain between episodes. As demonstrated in KS's case, non-noxious triggering factors may include smiling, talking, brushing teeth, and eating[1, 4]. Small areas in the nasolabial fold and/or chin may be trigger areas, particularly susceptible to precipitation of pain. Although pains usually remit for variable periods, the amount of time spent in remission tends to diminish as the disease progresses[5].

In the past, terminology for TN was problematic as attempts were made to classify the neuralgia based on its aetiology. However, in the first revision of the 2nd edition of the International Headache Society Guidelines, difficulties in proper classification were clarified and criteria for specific subtypes were explicitly outlined. Neuralgia caused by compression of the nerve by a vascular loop demonstrated during open surgery, is described as *secondary trigeminal neuralgia* (see Figure 2). Aetiology unrelated to vascular loop compression is classified as either *classical trigeminal neuralgia* or *symptomatic trigeminal neuralgia,* and may be differentiated based on the International Headache Society Guidelines in Table 1[5].

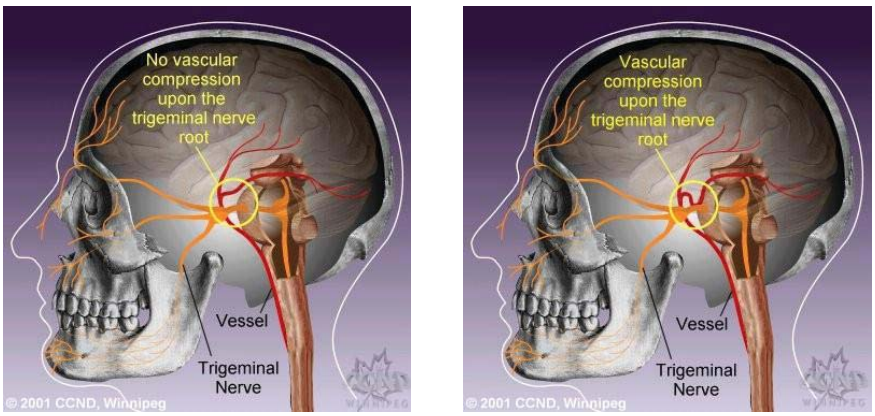


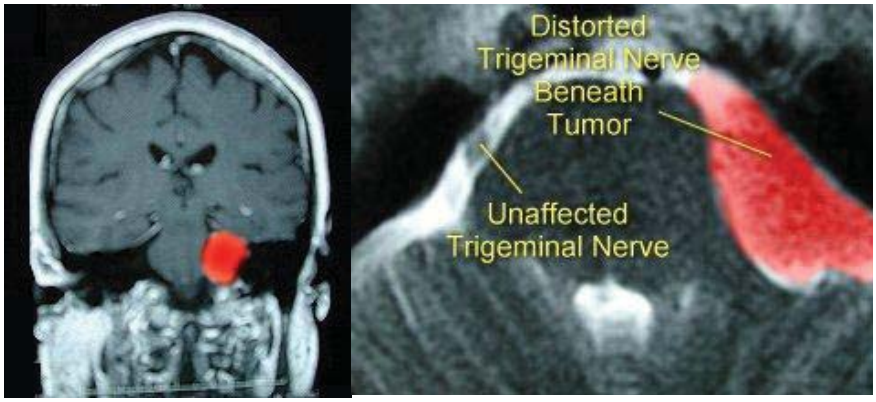
Figure 2
a) In people without TN, there is usually no vascular compression upon the trigeminal nerve root
b) In most sufferers of typical TN, vessels compress the trigeminal nerve root.

KS fulfilled most of the criteria for a diagnosis of classical TN, with the exception of the duration of his episodes, which lasted longer than two minutes (criterion A).

Imaging studies such as Brain MRI with or without contrast, MR angiography (MRA), and 3D reconstructed MRI can help distinguish secondary causes of TN from the idiopathic form of the condition. Thus, in addition to ruling out secondary TN (vascular loop), MRI also permits detection of symptomatic TN caused by lesions such as tumours or Multiple Sclerosis (for explanation, refer to Discussion: pathophysiology). Imaging is indicated in patients presenting with the condition when younger than 60 years of age, primarily to exclude tumour (see Figure 3)[6]. On initial presentation, KS underwent MRI with and without contrast as well as MRA, and no aberrant vascular loop or other lesion was identified, thus ruling out both secondary and symptomatic TN. Further confirming his diagnosis was the significant pain relief he experienced while on carbamazepine, an anticonvulsant, which according to some, is a good diagnostic trial medication for classical idiopathic TN[1]. A lack of response in his case would have suggested symptomatic TN or another diagnosis, both of which are less likely to respond to the drug[1]. Therefore, the negative findings on MRI in addition to the patient's response to a trial of carbamazepine confirmed the diagnosis of classical persistent idiopathic TN.

MANAGEMENT

Upon his current presentation to clinic, KS was instructed to continue oxcarbazepine at 600 mg three times daily (1800 mg) to mitigate the intolerable side effects that he had previously experienced when on the higher dose (2400 mg). Given the failure of previous pharmacological



▲ **Figure 3:** In these MRI images, a tumour responsible for compressing the trigeminal nerve is highlighted in red.

regimens prior to his first surgery and the patient's concerns about the side effects of high-dose oxcarbazepine and his current pharmacological regimen, he was then referred for surgical reevaluation at the University of Kentucky. KS discussed the surgical options with his neurosurgeon and opted for a second GK-RS rather than an open surgical modality. This decision was based on the patient's familiarity with the GK-RS procedure, his desire for a less invasive procedure and its improved safety profile as compared to the more invasive open-surgery modalities such as microvascular decompression (MVD).

Outcome and Follow-up

GK-RS provides safe and effective treatment of TN for certain patient prototypes. Currently, it is the least invasive surgical treatment for TN and side effects are usually limited to persistent trigeminal paraesthesias[5]. Despite its safety profile, pain recurrence after initial GK-RS treatment is a major concern and it would not be uncommon to undergo a second procedure, as in KS's case[8]. It has generally been considered a viable therapeutic option for the management of medically refractory idiopathic TN[9]. Following his second GK-RS, KS denied post-surgical numbness, and he was counseled about long-term outcome and possible recurrence. Thus far, he has had an excellent result. Since this second surgical intervention, KS has been maintained on the lower dose of Trileptal (1800mg per day) and instructed to follow-up with University of Louisville neurologists for routine visits or earlier if problems develop.

Discussion

Introduction

Trigeminal Neuralgia (TN) is a relatively rare but well-known cause of facial pain with a prevalence of 15.5/100,000 cases[4]. It can occur at any age but is more common in the elderly, with approximately 90 percent of cases occurring in those over the age of 40[4]. For reasons unknown, cases of TN are twice as likely in women as men (ratio of 2:1)[4]. Certain subgroups of the population are more likely to be affected. For example, TN has a prevalence of between one and two percent in patients with Multiple Sclerosis (MS), and a slightly higher prevalence in patients with hypertension than in the general population[1] (for explanation, refer to Discussion: pathophysiology).

Historical Perspective

Also known as "tic douloureux" or Fothergill disease, TN was first described in 1688, by Drs. Johannes Michael Fehr and Elias Schmidt as "*a sharp shooting pain in the maxilla which prevents eating solid food, varying in time – the person died of malnutrition*[10]." The syndrome was then described in greater detail by Dr. John Fothergill, a British physician who scrupulously described the symptoms and nature of the pain, onset, duration, aggravating factors, and predilections for certain age groups and gender[10]. It was not until 1820, however, when Sir Bell investigated the fifth cranial nerve, that the term "Trigeminal Neuralgia" was introduced. The distinguishing symptomatology, therapeutic debate, and evolution of recent therapeutic options, make this complex pain syndrome uniquely intriguing[11].

Pathophysiology

Walter E. Dandy demonstrated in 1925 that if the trigeminal nerve was sectioned in TN patients, relief of pain was noted. After performing over 500 operations, he consistently observed an anomalous vascular loop compressing upon the nerve[10]. Upon further scrutiny, it was noted that the pulsating nature of the compressing artery was traumatic enough to cause demyelination of the axon. This focal demyelination results in an abnormal conduction or ephaptic transmission, more simplistically referred to as a "short-circuit". Consequently, these demyelinated axons are prone to ectopic impulses, which in the case of TN, may be directly responsible for the typical characteristics of the pain experienced in those with the facial pain syndrome described as episodic, electric, lancinating pain[1]. The strong association of MS and TN further emphasizes demyelination as an underlying cause of the pain[11].

MEDICAL MANAGEMENT

The medical management of TN has evolved as its pathophysiology has been further elucidated and both imaging technology and surgical techniques have advanced. At the onset of the disorder, pharmacotherapy works extremely well and approximately eighty percent of patients achieve almost complete control of their symptoms on medication alone. Initial first line treatment is therefore medical[1, 4]. A derivative of phenytoin, used first in 1942, was later replaced by carbamazepine in 1962.

Carbamazepine is now the mainstay of medical treatment of TN based on recommendations of the European Federation of Neurological Societies and the Quality Standards Subcommittee of the American Academy of Neurology[12]. Carbamazepine is an anti-epileptic that acts by reducing sodium-conductivity thereby decreasing the responsiveness of peripheral mechanoreceptors. Eighty percent of patients benefit from this therapy and ninety-four percent report relief from symptoms in the first 48 hours[13]. Lack of efficacy or side effects such as nausea, vomiting, dizziness, drowsiness, or unsteadiness, may indicate the need to substitute carbamazepine for oxcarbazepine, a derivative of carbamazepine, but with a more favourable side effect profile[7,14]. Should a patient's TN pain be refractory to oxcarbazepine or if the patient finds the side effects of the indicated medications intolerable, alternative agents such as phenytoin, gabapentin, pregabalin, lamotrigine, topiramate, and baclofen may be added or substituted[4,7]. For fifty percent of medically treated TN patients, it is inevitable that drugs will progressively lose their efficacy because of drug resistance or drug tolerance necessitating increased doses, and thus surgical intervention must be considered[15].

SURGICAL MANAGEMENT

Referral to neurosurgery is imperative when the diagnosis is consistent with TN and the pain is refractory to pharmacotherapy. Surgical procedures consist of either open or percutaneous modalities. The most commonly used surgical procedures for TN patients include microvascular decompression, percutaneous radiofrequency rhizotomy, percutaneous glycerol rhizolysis, percutaneous balloon microcompression, and stereotactic radiosurgery using Gamma Knife. Each surgical procedure has its merits and limitations, and approaches must be based on the individual and what is best in their particular case.

Open techniques involve posterior fossa exploration such as partial trigeminal rhizotomy and microvascular decompression (MVD). These procedures carry a small risk of serious adverse events such as stroke, meningitis, and death. First introduced by Dr. Peter Jannetta in 1967, MVD is still considered the gold standard for treatment of TN as it provides the highest rate of long-term patient satisfaction with the lowest rate of pain recurrence[3, 11]. Complications of surgery are rare when the team is experienced but may include: cerebellar injury, hearing loss, cerebrospinal fluid leakage, facial weakness, and lower cranial nerve dysfunction[3, 11].

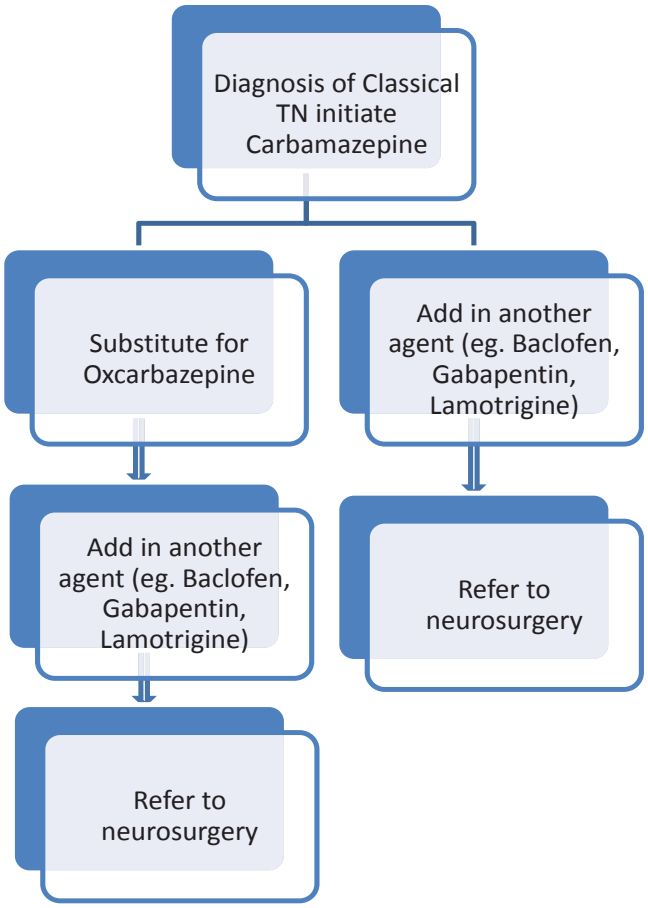


Figure 4: Algorithm for the diagnosis and treatment of TN.

Percutaneous techniques include glycerol injection, balloon compression, radiofrequency rhizotomy, and Gamma Knife Radiosurgery (GK-RS). These less invasive procedures carry reduced health risks and a shorter hospital stay compared to open procedures[3]. However, less invasive procedures do not provide as long lasting relief as that of the open procedures and have a higher incidence of sensory loss[1]. A summary of the diagnosis and treatment of TN is depicted in Figure 4[14].

MVD provides a higher and longer duration of relief than any of its counterparts. More than 70 percent of patients report consistent relief at 10 years post MVD[1]. Although both MVD and GK-RS result in pain relief, MVD is more likely to result in complete pain relief[16]. However, MVD may not be appropriate for all TN patients and is the surgery of choice for younger patients who are less likely to be at risk of complications. As a result, this procedure should be avoided in the elderly[17]. Furthermore, for the persistent idiopathic TN patient with continuous aching pain, MVD does not provide a favorable outcome. In this patient profile type of TN, GK-RS may be a better alternative to MVD. At the University of Maryland Medical Center, the majority of patients with persistent idiopathic TN undergoing GK-RS reported an overall improvement in quality of life, even if the pain returned[18].

The long-term results of the GK-RS procedure remain unknown as no high-quality studies have yet been performed with a follow-up of greater than five years. Therefore, it is difficult to predict the long-term outcome of KS's second GK-RS procedure and whether or not the neuralgia will reoccur. Good prognostic factors include a lack of the following three factors: previous surgery, post-surgical numbness, and typical pain; KS denied presence of the latter two[19]. Rates of initial pain relief with GK-RS approach those of MVD or percutaneous techniques in patients without previous surgery[19]. However, MVD continues to have a lower recurrence rate and is favoured as the treatment of choice for suitable patients. Repeat GK-RS has shown success rates for pain relief comparable to initial GK-RS, but results in fewer patients able to discontinue their medications[19]. This may be a concern for KS as he was intolerant to most of the medications commonly prescribed for TN.

To conclude, the minimal invasiveness of GK-RS makes it a good option for patients who cannot or should not undergo MVD. These include the elderly, those with medical problems that preclude neurosurgery, or patients such as KS who do not wish to undergo open surgery. The low rates of complication of GK-RS, coupled with good success rates and high patient satisfaction, favour its increasing use as a primary intervention for TN[13].

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