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Familial Trigeminal Neuralgia Treated with Stereotactic Radiosurgery: A Case Report and Literature Review

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Abstract

Background—Trigeminal neuralgia (TN) is a chronic pain condition characterized by brief episodes of lancinating pain in one or more distributions of the trigeminal nerve. Episodes of pain secondary to TN are triggered by certain stimuli, such as chewing, shaving, or touching the face. Although a common cause of TN is compression of the trigeminal nerve root entry zone by an artery or vein, many cases of TN are idiopathic. However, there have been limited reports in the literature of familial TN.

Case Presentation—A 31-year-old male presented with classic TN symptoms in the right V1/V2 distribution that recently progressed to the V3 distribution a case of familial TN. His father and brother both have TN. Carbamazepine, oxcarbazepine, and rhizotomy did not improve his symptoms. He was treated with stereotactic radiosurgery (SRS) with a dose of 85 Gy delivered to the proximal trigeminal root with improvement in his pain. We also review and summarize the over 160 cases of familial TN found in the literature.

Conclusions—This is the first reported case of familial TN treated with SRS. Patients with familial TN are more likely to have bilateral disease, to present with earlier onset, and to become refractory to medical therapy and may require more aggressive approaches. We propose that SRS is a good treatment approach for these patients.

Keywords

trigeminal neuralgia; trigeminal nerve; radiation; stereotactic radiosurgery

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COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution.

Conflict of interest: Ryan A. Denu declares that he has no conflict of interest. Stephen A. Rosenberg declares that he has no conflict of interest. Steven P. Howard declares that he has no conflict of interest.

Informed consent: Informed consent was obtained from all participants included in the study.

BACKGROUND

Trigeminal neuralgia (TN), formerly tic douloureux, is a common cause of facial pain characterized by brief episodes of lancinating pain in one or more distributions of the 5th cranial nerve. These episodes of pain are triggered by certain stimuli, most commonly chewing, shaving, touching the face, and breezes. The most common identifiable causes of TN are compression of the trigeminal nerve root entry zone or the midthird of the nerve by an artery or vein.[1–3] However, most cases of TN are idiopathic. TN is first treated pharmacologically, typically with carbamazepine; refractory cases are often treated with percutaneous procedures, surgery, or radiation therapy. Most patients lack a family history of TN, although there have been reports of over 164 cases of familial TN (Supplementary Table 1). There are currently no specific diagnostic criteria for familial TN. Herein we present an additional family with TN and describe treatment of the index case with stereotactic radiosurgery (SRS). Further, we summarize all previous cases of familial TN, and provide recommendations for how to treat and counsel patients with familial TN and their families.

CASE PRESENTATION

A 31-year-old male presented with intense, shooting, short-lasting facial pain in the right V1/V2 distribution that recently progressed to the V3 distribution. His pain was most often triggered by a breeze, shaving, and/or trauma (e.g. young child striking his face). However, eating does not exacerbate or trigger his pain. The patient's past medical history is significant for migraines with aura. He has no history of hypertension, diabetes, heart disease, autoimmune disease, or cancer. He shows no signs of multiple sclerosis or other demyelinating disease. He was worked up with complete history and physical and an MRI of the brain. No lesions, vessels loops, or other structural causes of his pain could be identified (Figure 1). Interestingly, both his father and brother have TN (Figure 2). Furthermore, his father and brother both have right-sided TN with similar symptoms, triggers, and distribution. He was diagnosed with TN and was started on a course of carbamazepine, which provided no relief. He was then switched to oxcarbazepine, which was also unsuccessful. The addition of ketorolac to his treatment regimen provided some relief and has been his most successful medical therapy to date. Unfortunately, he still experienced episodes of pain. Because of unsuccessful medical management, he underwent a rhizotomy that provided no improvement to his symptoms. Subsequently, he had a neurosurgery consult regarding microvascular decompression, but opted not to pursue this. He was referred to our institution for a consult regarding radiation therapy to alleviate his TN. We recommended stereotactic radiosurgery (SRS) with a dose of 85 Gy delivered to the proximal trigeminal root, which would have been performed at an outside institution (see Supplemental Figure 1 for timeline of this case); this falls within the recommended 70–90 Gy for TN.[4]

CONCLUSIONS

TN, formerly tic douloureux, is characterized by shooting pain in the distribution of the fifth cranial nerve and is significantly debilitating for afflicted patients. These episodes of pain are triggered by certain stimuli, such as chewing, shaving, or touching the face. Most cases

of TN are idiopathic, although some cases are caused by compression of the trigeminal nerve root entry zone or midthird by an artery or vein.[1–3] TN affects females slightly more than males (3:2 ratio), and onset usually occurs in the sixth decade.[5, 6] TN is not typically thought of having a genetic or family history component, with past studies demonstrating that 1–6% of patients with TN have a family history of TN.[7–10] Our analysis of the literature reveals 164 cases of TN with a family history, including the patients discussed in this report (Supplementary Table 1). This case presents a novel example of a family (father and two sons) experiencing very similar patterns of classic TN. This points to a potential genetic component for at least some cases of TN.

There have been a number of reports of familial TN in the literature,[5, 7–30] and we reviewed all 164 reported cases. Some studies have suggested familial TN is characterized by earlier onset (usually by 45 years), a greater occurrence in females,[14, 31] and a greater incidence of bilateral TN.[8, 32, 33] The case presented herein follows the trend of earlier onset, but none of the family members with TN were female and none of them had bilateral TN. Our review of 164 cases of familial TN in the literature reveals that there is actually a slightly higher incidence in males (of the cases where gender was reported, 53% were males and 47% were females). Furthermore, our analysis confirms the increased incidence of bilateral disease, as 19% of cases that described disease distribution were bilateral compared to 81% unilateral (most reports of TN show that 5% of patients have bilateral disease). Our review also confirmed the earlier age of onset in familial TN, as we observed the average age of onset to be 43 years. Additionally, patients with familial TN are potentially less likely to respond to initial medical therapy, as about 1/3 of patients were not relieved by initial medical therapy and typically pursued more aggressive therapies; however, some of the case reports we reviewed lacked detailed information to assess this, limiting the power and confidence in this conclusion.

The causes of TN, especially familial TN, remain elusive. Previous pedigree analyses of patients with familial TN have provided some clues. Some studies report that familial TN follows an autosomal dominant inheritance pattern,[10] but these data are far from conclusive and contradicted by others.[13] It is possible that there are multiple genes that could contribute to familial TN, some of which display autosomal dominant inheritance while others display autosomal recessive inheritance. Additionally, it is possible that some of these genes are incompletely penetrant. Another interesting genetic phenomenon associated with familial TN is anticipation; in multiple reports, the age at onset in one generation was earlier than it had been in the prior generation.[10, 15, 16] This indicates either a clinical ascertainment bias or a true biological mechanism, perhaps related to trinucleotide repeat expansion, which is seen in other cases of genetic anticipation such as Huntington's disease, whereby the trinucleotide repeat (e.g. CAG in Huntington's) increases in number with each generation due to slippage during DNA replication. Regarding the underlying pathophysiology of TN, multiple mechanisms have been proposed. The possibility of some premature atherosclerotic change leading to familial TN was originally proposed by Kirkpatrick.[11] Others hypothesize that the cause could be biochemical, which is supported by the sizable number of reported cases of simultaneous occurrence of TN and Charcot-Marie-Tooth disease, suggesting an underlying biochemical abnormality that affects nerves either centrally or peripherally.[14, 25] Familial vascular malformation is another potential

cause and has been reported, but this is not seen in all cases of familial TN. Animal studies have suggested the possible involvement of genes encoding calcium channels[34] and the potential involvement of proenkephalin A in trigeminal sensory transmission of pain.[35]

With regard to treatment of TN, generally response to drug therapy, namely carbamazepine, is good, as over 80% of patients responding. Surgical interventions are also used with much success, but are usually reserved for younger patients in good health because of their greater associated risks. There are multiple surgical techniques used to address TN including radiofrequency trigeminal gangliolysis (PRTG), percutaneous balloon microcompression (PBM), and percutaneous retrogasserian glycerol rhizotomy (PRGR). Percutaneous interventions are effective at resolving pain initially, but may be less efficacious long-term; there are often technical obstacles during the procedure,[36] and side effects include dysesthesia and sensory deficits. Other surgical procedures used in the treatment of TN include MVD of the trigeminal root and retrogasserian rhizotomy. MVD provides long-lasting pain reduction in about 84% of patients, but complications include facial numbness and/or palsy, CSF leaks, hearing deficits, and infections at the site of incision.[37–39] Stereotactic radiosurgery has also been established as a treatment for patients who do not respond to optimal medical management. Studies show that 67–88% of patients experience initial pain relief with SRS.[40–44] Long-term follow-up of these patients indicate, 78%, 74%, 68%, and 53% remain pain-free without medication at 3, 5, 7, and 10 years of follow up. There may be less risk of side effects compared to MVD and rhizotomy.[45] An analysis of 36 patients treated with SRS, 80.5% of whom experienced early pain relief, revealed that 67% of patients were still pain free after at least 3 years of follow-up.[46]

In conclusion, we have reported a family with three men affected by right-sided TN and, to our knowledge, the first reported case of using SRS to treat a patient with familial TN. Due to a lack of precise genetic information on familial TN, we do not recommend routine genetic referrals for this patient population. Our extensive review of all known cases of familial TN demonstrates that that patients with familial TN are more likely to have bilateral disease, to present with earlier onset, and to become refractory to medical therapy and may require more aggressive approaches. We propose that SRS is a good treatment approach for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

MVD	microvascular decompression
SRS	stereotactic radiosurgery

TN trigeminal neuralgia

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Figure 1. Brain MRI

Axial T2-weighted MRI image demonstrating no vascular compression at the entry root of the trigeminal nerve.

Figure 2. Pedigree of the patient's immediate family

Filled objects represent individuals affected by TN. The arrow represents the index case described in this case report.