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Project Title: The Incidence of Medically Refractory Trigeminal Neuralgia: A 10-year Prospective Population Based Study

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SUMMARY: (no more than 250 words single spaced)

Trigeminal neuralgia (TN) is regarded as one of the most painful conditions afflicting humans. It is a relatively rare disease with an estimated incidence of 4/100,000/year. While TN progresses in severity over time, it is not known what proportion of sufferers go on to develop pain refractory to standard medical therapy and then require neurosurgical interventions.
A prospective database was established at our center that provides the exclusive neurosurgical services for a relatively constant provincial population of 1.25 million people. Baseline demographics and disease characteristics were recorded for all patients undergoing their first TN surgery between 2001-2010, and any subsequent surgeries for recurrent TN pain up to 2014. Rate of first surgical intervention for TN was calculated as well as rate of failure, defined as patients undergoing subsequent surgery for recurrent TN pain.
During the 10 year enrollment period, 163 patients underwent their first surgery with 113 having follow-up of greater than 1 year for TN that had become refractory to standard medical therapy, a rate of 1.4/100,000/year. There was significant difference between ages at time of first surgery between MVD and Rhizotomy procedures at 57.2+/-11.9 versus 74.5+/-9.7 years of age respectively. MVD experienced repeat procedures for 13/87 patients while rhizotomy procedures required 29/76 procedures to be repeated.
Over one-third of TN sufferers will develop pain refractory to medical therapy requiring surgical treatment. MVD first surgery for TN was associated with the lowest failure rate (14.9%) while 40% of rhizotomy procedures required additional surgery.

Student Signature **Supervisor Signature**

ACKNOWLEDGEMENTS:
I gratefully acknowledge the support by one or more of the following sponsors;
H.T. Thorlakson Foundation
Dean, Faculty of Medicine
Manitoba Health Research Council
Manitoba Institute of Child Health
Kidney Foundation of Manitoba
Leukemia and Lymphoma Society of Canada
CancerCare Manitoba
Manitoba Medical Service Foundation
Associate Dean (Research), Faculty of Medicine
Heart and Stroke Foundation
Health Sciences Centre Research Foundation
Other:

Introduction:

Classical trigeminal neuralgia (TN) is a relatively rare and severe craniofacial pain condition characterized by extreme, brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve.(1) Pain attacks last seconds to minutes, with no clinical signs or symptoms between attacks. TN is considered to be one of the most painful conditions to afflict humans. It is generally accepted that the cause is pulsatile compression of the trigeminal nerve root by an aberrant loop of artery or vein resulting in irritation of the nerve with every heart beat.(2) TN is rarely caused by multiple sclerosis (MS), when demyelinating plaques involve the trigeminal nerve projections within the brainstem.

TN differs from other craniofacial neuropathic pains such as tumor related trigeminal neuropathy that generally manifests with constant aching and burning pain, numbness as well as objective signs of deafferentation such as an absent corneal response. Another condition called idiopathic facial pain also has more constant pain elements that may extend beyond the anatomical distribution of the trigeminal nerve and is often associated with depression and anxiety symptoms. All these craniofacial neuropathic pain conditions are often collectively mis-labeled as "TN" although effective remedies for classical TN are ineffective for the other conditions.

The initial treatment of choice for TN is an antiepileptic agent such as carbamazepine or gabapentin. (3,4) These medications are so effective that some practitioners consider initial pain relief as a diagnostic test to confirm the diagnosis of TN. Conversely, analgesics including opiates are usually ineffective for TN pain. Unfortunately, as TN progresses in severity and frequency over months to years, pain may become refractory or dose related side effects intolerable as medication requirements increase. Once this occurs surgical treatment options include a variety of rhizotomy techniques or microvascular decompression surgery (MVD). The rhizotomy techniques include balloon compression rhizotomy (BCR) or percutaneous glycerol rhizotomy (PGR). These techniques involve inserting a needle directly through the cheek and foramen ovale into Meckel's cave. There injury is produced by either injection of neurolytic glycerol solution or direct mechanical compression by temporary inflation of a balloon, providing rapid pain relief.(5,6) Another increasingly utilized rhizotomy technique being employed is radiosurgery (RS), most frequently with a GammaKnife® (GK). RS uses a highly focused dose of radiation directed at the trigeminal nerve root and works similarly to PGR and BCR. With RS, however, there is usually a latency period of several weeks before pain relief and fewer patients achieve complete pain control when compared to

those undergoing percutaneous rhizotomies. Regardless of the rhizotomy procedure chosen there is an approximate long term failure rate of 50%, usually within the first two years post operatively.

MVD as pioneered by Jannetta(7) offers higher potential for disease cure with an atraumatic alleviation of the culprit neurovascular compression on the trigeminal nerve root through a retromastoid craniectomy. Reports of initial pain relief are 95% and long term complete pain relief described in about two-thirds. The risks of surgery have been variable reported but are generally very low when performed at centers with a high volume of experience.

The epidemiology of TN is not well known. The estimated incidence rate is approximately 4/100,000/year for classical TN (8,9). The proportion of those who develop medically refractory TN, however, is currently unknown. Also not well established are the comparative merits of each of the potential surgical options in terms of patient selection, safety and success.

The aim of the present study was to determine the incidence of medically refractory TN as identified by the rates of first surgery for TN. The study was conducted in Manitoba, a Canadian province with a relatively fixed population, over a 10 year longitudinal period. The success and safety of the various procedures were also examined.

Methods:

The Center for Cranial Nerve Disorders (CCND) in Winnipeg is a neurosurgical subspecialty clinic providing all surgical treatment for TN in Manitoba, a Canadian province with a population of 1.25 million people. While patients do have the option to travel to other Canadian centers for medical and surgical treatment under the Canadian Health Act, our center has a uniquely large annual volume of experience with cranial nerve surgery and receives referrals from across the country. As such, few or no patients from Manitoba would be expected to seek neurosurgical treatment for their TN elsewhere.

From a prospectively maintained clinical database, all Manitoba patients seeking neurosurgical consultation at our CCND for a 10-year period between 2001-2010 were identified by their home address and telephone area code. Classical TN was diagnosed with criteria consistent with the IHS II classification, including those with a unilateral brief electric shock like pains, abrupt in onset and termination with pain limited to one or more divisions of the trigeminal nerve with pain usually remitting for variable periods of time (1) These patients were identified and followed through the study recruitment period to determine first neurosurgical procedure for TN. Those with MS related TN or other craniofacial pain conditions were excluded.

Patient demographics and disease data obtained at first CCND visit were obtained from the database. Date and type of first TN procedures were noted. Any subsequent neurosurgical procedures for TN were similarly noted up to June 2014. Short term follow-up and complication occurrences were obtained from review of patients clinical and hospital charts. Long term and most recent follow up were determined by direct telephone interview for all patients who could be reached and by chart review for those who could not be contacted.

Postoperative outcome measures were also recorded utilizing the Barrow Neurological Institute (BNI) Pain Intensity Scale as well as the BNI Numbness scale. Descriptive statistics are reported as mean +/- standard deviation and ranges, and comparative statistics are considered significant at $p<0.05$. The medical ethics research committee at the University of Manitoba approved this study.

Results:

During the 10-year study period from 2001-2010, 272 Manitoba patients with surgically naïve TN were referred to our center, 115 men and 157 women. Among these, 163 subsequently underwent first time surgical intervention for TN during the same time interval. This included 91 women and 72 men aged 66.2 +/- 12.5 (38-87) years at the time of first surgery. Their average age at onset of symptoms was 60.5 +/- 14.3 (30-85) years and duration of disease at time of surgery was 7.2 +/- 6.9 (1-31) years.

Annual number of first surgeries for TN in Manitoba was 15 per year. Based upon a provincial population of 1.25 million, the annual rate of first surgery for TN was 1.4/100,000/year.

The first surgical procedure was MVD for 87 and BCR, PGR or GK in another 76 patients. Comparison between the patients undergoing these two categories of surgery, MVD versus rhizotomies, revealed a significant difference in age at time of first surgery; 57.2 +/- 11.9 versus 74.5 +/- 9.7 years of age, respectively ($p=0.0001$) There was no significant difference comparing gender or duration of disease between the groups.

Of the 87 patients initially treated surgically with MVD, 13 (14.9%) went on to require subsequent surgeries for persisting or recurrent TN pain. Of these, 11 had rhizotomies and 2 had repeat MVD.

Of the 76 patients initially treated surgically with rhizotomy, 29 (40%) went on to require subsequent surgeries for persisting or recurrent TN pain. Of these, 8 eventually had an MVD (at some time) while 21 underwent only additional rhizotomies. There was a significant difference between rates of

reoperation required between those initially treated with MVD versus rhizotomy ($p<0.05$)

Regarding rhizotomy procedures, prior to 2003, only PGR and BCR were available at our center. Thereafter, the first GK in Canada became available at our center and since then was selected as the choice of initial type of rhizotomy procedure in 74.2% of rhizotomy cases. There was no significant difference in the age or gender of those choosing GK over PGR/BCR rhizotomies. There was also no change in the ratio between the number of MVD versus rhizotomy over the study period.

Long term follow-up, greater than one year after initial TN surgery, was available for 113 at 5.5 +/- 3.4 (1-12) years.; 77 were contacted by phone and 36 by chart review alone as they could not be reached. The remainder had no records of clinic or chart follow-up beyond one year after surgery. At the time of this study, 20 patients were noted to have died.

The long term BNI Pain Intensity Scores at most recent follow up are tabulated in Table 1. Among the 87 individuals who underwent first time surgical intervention utilizing and MVD procedure, 67 had long term follow up. Of these, 41 (60%) had excellent pain control requiring no medications (I-II), 12 (18%) had good pain control with medication use (IIIa and IIIb), and 14 (22%) had poor control after MVD, 9 of whom underwent additional surgeries. When considering results after all surgeries, 47 (70%) were excellent, 14 (21%) were good and 6 (9%) were poor, by the BNI pain intensity scale regarding their initial TN pain.

Among the 73 individuals who underwent first time intervention utilizing PGR, BCR or GK rhizotomy procedures, 46 had long term follow up. Of these, 15 (32%) had excellent pain control requiring no medications (I-II), 9 (20%) had good pain control with medication use (IIIa and IIIb), and 29 (63%) had poor control after rhizotomy, 20 of whom underwent additional surgeries. When considering results after all surgeries, 25 (54%) were excellent, 16 (35%) were good and 5 (11%) were poor by the BNI pain intensity scale regarding their initial TN pain.

Long term BNI numbness scores after a single rhizotomy were available for these 26 patients; 16 (61.5%) reported no postoperative numbness (I), 6 (23.1%) reporting mild numbness that was not bothersome (II), 3 reported numbness that was somewhat bothersome (III), and 1 reported numbness that was very bothersome (IV).

The long term BNI numbness scores for the 53 patients who had one or more rhizotomies included 11 (21%) who reported numbness that was somewhat bothersome (BNI Numbness Score III), and 6 (11%) who reported numbness that

was very bothersome (BNI Numbness Score IV). No grade III or IV numbness was attributed to MVD procedures.

All patients were seen for early follow up postoperatively. A search for surgical complications was conducted by thorough review of clinic and hospital records. No patients died or had major permanent complications related to their TN surgeries. Long term rhizotomy complications were limited to deafferentation complications noted above and graded in the BNI numbness scale. From the MVD group, one patients required readmission to hospital for a CSF leak that required placement of a lumbar drain complicated by drain related meningitis; she recovered without sequale. Two patients also reported slight hearing loss (but could use a telephone with the affected ear) and four patients reported some early postoperative bouts of vertigo. Two patients reported some pain at the site of the MVD incision and another two requiring postoperative antibiotics for superficial wound infections.

Discussion:

As a disease, unfortunately TN is known to always be severe and progressive in nature. Epidemiological data is sparse with published incidence rates of 4-4.5/100,000/year(8,9). We identified that the number of TN patients evaluated at our centre was 2.7/100,000/year, approximately half the incidence number. We also found the number of TN suffers undergoing their first surgery was 1.4/100,000/year. This suggests that approximately one third of the TN sufferers eventually progressed to a medically refractory state of disease to undergo surgical intervention at our CCND. It bares emphasis that the study population had classical TN, as defined by IHS II; our results should not be extrapolated to other non-TN craniofacial pain conditions.

The choice between MVD and rhizotomy as a surgical first procedure was found to be most closely related to patient age at the time of surgery. The elderly were more likely to undergo rhizotomy, particularly the minimally invasive GK procedure. The choice of MVD versus rhizotomy appears to also have been closely related to future survival, as death in the follow-up period was noted in 4% of the MVD group and 21% in the rhizotomy group. Not surprisingly, a procedure with better potential for long term disease control will be preferred for those with anticipated longer survival. It should be noted that none of these deaths were associated to the surgical interventions.

The outcomes of surgery can be assessed with respect to the requirement for additional subsequent surgeries. Despite a greater proportion of survivors among the MVD group, future surgery for persistent or recurrent TN was performed for 13 patients (15%) versus 29 (40%) for those first treated with

rhizotomy.

When long term pain relief outcomes were assessed after the first procedure for TN, there was a significant difference in excellent results between MVD and rhizotomies, 60% VS 32 % respectively. When most recent outcomes were assessed after single or multiple procedures, those first treated with MVD or rhizotomy had similar chances of excellent or good results (5 each). There was however significant differences between these two groups, with excellent result's in 70% versus 54% in the MVD and rhizotomy groups respectively. This is clinically important as excellent results denote pain control without need for medications, and medication use for TN has been shown to usually cause side effects that impact on patient quality of life.

Another clinically relevant difference between patients first treated with MVD, who do not need further surgery 85% of the time, and those treated initially with rhizotomy that requires additional treatment in 40% is the incidence of rhizotomy induced deafferatation pain. Among the rhizotomy first group, 21% developed treatment related bothersome dyesthesias and another 11% developed painful deafferentation complaints. Among those who underwent more than 1 rhizotomy, these complaints were reported in 50%. Therefore a strategy of less invasive rhizotomy procedures is associated with a significant incidence of new deafferatation pain compared to initial MVD surgery.

The outcome advantages of MVD surgery must be considered in light of surgical risks. In our experience, no patient had a life altering complication related to MVD, as opposed to the new serious pain complaints inflicted upon the rhizotomy patients. These results, however, are not necessarily universally applicable as our CCND is unique in North America. Our surgeon has performed over 800 MVD surgeries for TN and HFS over a 20 year period. In contrast, the average number of MVD performed per year among surgeons performing this operation annually in the USA was 3. In recent years, our centre performs approximately half of all the estimated 120 annual MVDs in Canada, representing a large out of province patient group travelling here for their surgery. Any potential advantages of MVD over rhizotomy procedures is dependant upon a high rates of surgical success and safety.

Conclusion:

Central to this study is ascertaining information that can be used in resource planning regarding anticipated number of procedures and subspecialist requirements on a regional and national level. This can only be accomplished by determining an accurate rate of medically refractory TN in the population. At

our center, our findings suggest that 50% of patients seen at our CCND are referred to surgery with this accounting for approximately one third of all TN patients. There was an equal mix of MVD procedures versus rhizotomy procedures performed with the most important determining factor being that of patient age at the time of initial surgical intervention. Higher failure rates in the rhizotomy group were seen with respect to repeat procedures and total pain relief together with bothersome to severe numbness complications post operatively. MVD was shown to be much safer and effective at alleviating patients symptoms post operatively, however, this must be considered together with the fact that we are a high volume center doing many MVD procedures on an annual basis.

Ultimately, the goal for this data is to allow for physicians to better educate patients regarding the predictive characteristics of failure which will allow for appropriate medical and surgical options for be explored early in the disease progression.

Our findings may also be able to help us determine the numbers of TN sufferers who continue to have ongoing pain or need of medication due to recurrence of TN pain post operatively, but who have not yet returned for repeat surgical procedure.

When evaluating treatment complications, our data will help determine which treatment option delivers the most permanent pain relief without new, long term complications for the largest proportion of the population possible.

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Appendix:

Table 1:
Patient outcomes after all procedures, primary and subsequent
* Follow up 5.5 +/- 3.4 (1-12) years → N=113

BNI Pain Scores	Single MVD (N=58)*	MVD + Add. Surgery (N=9)*	Single Rhizo (N=26)*	Rhizo + Add. Surgery (N=20)*
1. No Pain, No Meds	31	5	10	7
2. Some Pain, No Meds	10	1	5	3
3a. No Pain, Meds Used	4	0	2	3
3b. Some Pain, Meds Effective	8	2	7	4
4. Some Pain, Meds Ineffective	4	0	0	2
5.Severe Pain, Meds Ineffective	1	1	2	1