

“Evaluation of neurovascular conflict in Trigeminal Neuralgia”



***Dissertation submitted for the partial fulfilment
for the requirement of the degree of
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DECLARATION

This thesis titled “**Evaluation of neurovascular conflict in Trigeminal Neuralgia**” is a consolidated report based on a bonafide study of the period from January 2021 to December 2021, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfilment of rules and regulations of Post doctoral fellowship in Cerebrovascular Neurosurgery.



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CERTIFICATE

This is to certify that the thesis entitled “**Evaluation of neurovascular conflict in Trigeminal Neuralgia**” is a bonafide work of Dr Shah Shreykumar Pravinchandra and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram (SCTIMST) under my guidance and supervision.


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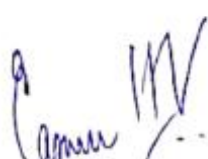
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Abbreviations :

CSF- Cerebrospinal fluid

SCA- Superior cerebellar artery

CT- Computed Tomography

MRI- Magnetic Resonance imaging

MRA- Magnetic resonance angiography

MVD- Microvascular Decompression

STL (Standard Triangle Language)

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INTRODUCTION

Trigeminal neuralgia (TN), often cited as one of the most painful conditions known to mankind. Before the introduction of effective treatment for TN, it was known as the “suicide disease”. Today, that sobriquet is all but a thing of the past due to advances in medical and surgical therapeutic options. Trigeminal neuralgia is the most common facial neuralgia characterised by episodes of paroxysmal sharp and shooting electric shock like pain, which usually lasts for few seconds to few minutes more often involving the maxillary and mandibular branch of the trigeminal nerve. Neurovascular compression is a major cause of TN, which is defined as an "abnormal" contact between an artery and the root entry zone of a cranial nerve. The root entry zone is the transition zone of the central to the peripheral myelin. Neurovascular compression syndrome is defined as a direct contact with mechanical irritation of cranial nerves by blood vessels. Success rates for MVD, however, depend on a number of clinical features and the imaging findings. Paroxysmal pain, the presence of trigger points, and a positive response to carbamazepine all portend a good outcome, whereas patients with a constant aching pain have less-successful outcomes [1,2]. Although vascular compression or contact may occur at one or more points along the nerve's cisternal segment, not all vascular compression of the nerve is equally clinically relevant [2-5]. Thus, it is important for clinicians to understand not only which imaging techniques are optimal for detecting neurovascular compression but also which segments of the trigeminal nerve are vulnerable to symptomatic vascular compression. Understanding the importance of a neurovascular contact is crucial for classical trigeminal neuralgia aetiology. Moreover, it is important for clinical management because transposition of a blood vessel in microvascular decompression is generally considered first choice surgical treatment in medically refractory classical trigeminal neuralgia

AIMS OF THE STUDY

Objectives:

1. To study : anatomical factors affecting the neurovascular conflict in trigeminal neuralgia in radiological studies.
2. To study the clinical profile among patients who underwent microvascular decompression for trigeminal neuralgia

REVIEW OF LITERATURE

Historical background

Although facial pain is mentioned in texts from ancient Egypt, Greece and medieval Persia, the first case description of what we can now be fairly certain was TN, was penned in detail by John Locke, as he had witnessed an attack of excruciating facial pain in the Countess of Northumberland.⁶ The comprehensive report included description of an episodic unilateral facial pain that also included the mouth and the tongue. The term *tic douloureux*, which for a long time was the most common term for what we today call TN, was coined by André in 1756, based on a report of five cases (of which probably only two would be diagnosed with TN today), and was used to not only describe the extreme pain, but also the grimaces associated with it.⁷ Another synonym used for the disease has been Fothergill's disease, after John Fothergill published an extensive, widespread and on many accounts accurate description of the disease in 1773 that in most regards holds true today for clinical diagnosis.⁸ In the early 1820s, Bell succeeded to differentiate the functions of the trigeminal nerve and the facial nerve respectively, and thereby confining the disease to the trigeminal nerve, ultimately leading to the term trigeminal neuralgia.⁹ Perhaps the most revolutionary finding regarding the pathogenesis of TN was presented by Dandy in the early 1930s.¹⁰ Initially mentioned only in passing in one of his meticulous descriptions of the surgical technique, he had noted a high frequency of gross lesions in association with the trigeminal root.¹¹ The most common lesion was an arterial loop, which was found in one third of the patients. This notion was later developed into theories on how pressure injures the nerve, thereby causing TN.¹² By the late 1960s, the collective evidence for a peripheral etiology i.e., compression of the trigeminal root, was plentiful.¹³ It was however, for quite some time, rivaled by those advocating the theory of a central etiology.¹⁴ The subsequent surgical developments during the 1970s did however provide more evidence for a peripheral, or at least a first order sensory neuron, etiology than for a central one.

ANATOMY

After afferent fibers converge from each of the nerve's three main sensory distributions within the Meckel cave, the nerve passes through the porus trigeminus, traverses the cistern, and then enters the pons. Along the cisternal portion of the nerve, the myelin sheath surrounding the nerve transitions from that derived from Schwann cells (i.e., peripheral myelin) to that derived from oligodendrocytes (i.e., central myelin). The portion of the nerve along which the peripheral myelin transitions to central myelin may be referred to as the transition zone. The point where the nerve enters the pons is the root entry point. Peker et al. [15] described a detailed

analysis of trigeminal nerve microanatomy. They performed a histologic analysis of 100 trigeminal nerves derived from 50 cadavers. Staining with Luxol fast blue (SigmaAldrich) was performed to determine the length and morphologic features of the centrally myelinated portion of the trigeminal nerve. For all 100 nerves, the authors calculated the fraction of the cisternal segment of the nerve that was centrally myelinated. The authors found that, although in some nerves central myelin was present in less than onequarter of the cisternal length, the maximum observed length of the centrally myelinated segment was 48% of the cisternal segment of the trigeminal nerve [16]. This metric expressing the length of the centrally myelinated portion of the trigeminal nerve as a fraction of the nerve's entire cisternal segment length is particularly useful because the entire cisternal portion of the nerve can be well appreciated on steady-state free precession (SSFP) MR images [16]. By dividing the cisternal segment of the trigeminal nerve into proximal (posterior) and distal (anterior) halves, clinicians can determine whether any encroaching blood vessels are likely to fall on the central myelin (proximal half) or peripheral myelin (distal half) (Fig. 2). Proximal vascular compression of the cisternal segment of the trigeminal nerve is considered more likely to be clinically relevant, whereas distal compression is less likely to be the cause of a patient's symptoms.

Vascular Compression

Vascular compression may occur anywhere along the cisternal segment of the trigeminal nerve, but not all trigeminal nerve compression is symptomatic [17]. Early pioneers of MVD surgery noted that, to achieve pain relief, particular attention ought to be paid to the dorsal root entry zone, which is the portion of the trigeminal nerve surrounded by central myelin [18, 19]. Other authors have supported the importance of the centrally myelinated segment of the trigeminal nerve as the site of clinically relevant vascular compression [20, 21]. Although Jannetta et al. [21] suggested that the dorsal root entry zone can be variable in length and may extend to the porus trigeminus, Peker et al. [15] have refuted this by showing that the central myelin never extends beyond the midpoint of the trigeminal nerve. In a study of 579 patients who underwent MVD for TN, Sindou et al. [20] showed that only 9.8% of patients had compression along the most distal portion of the cisternal trigeminal nerve. A number of histologic studies have shown that vascular compression of the trigeminal nerve can be associated with focal demyelination that is restricted to the proximal centrally myelinated portion of the nerve [22, 23]. Although the reasons that the proximal portion of the nerve appears more susceptible to compression are poorly understood, central myelin is thinner than peripheral myelin relative to axon diameter and may be less capable of damage repair than peripheral myelin [24].

Normally, the SCA courses posteriorly in the perimesencephalic cistern, encircling the brain stem in the groove between the pons and mesencephalon, above the trigeminal nerve 2 (Fig. 1). In its proximal portion, it is separated from the PCA by the oculomotor nerve and runs medial to the anterior half of the tentorial edge. Distally, it passes beneath the tentorium cerebelli to reach the superior surface of the cerebellum above the origin of the trigeminal nerve from the pons. Usually, the artery makes a shallow caudal loop and courses inferiorly for a variable distance on the lateral side of the brain stem s

Epidemiology

Population-based studies indicate an incidence of TN of 4.7-26.7/100.000 person-years.²⁵ This represents roughly one third of the incidence of all facial pain conditions (excluding toothache).²⁶ Women are affected more often than men by a factor of approximately 2:1.²⁶ The maxillary branch is most commonly affected, while the ophthalmic branch is the least commonly affected, but the pain is often distributed over more than one branch.²⁷ The incidence of TN is positively correlated to age, with a peak incidence in the eighth decade of life onwards, and since it is a chronic disease the prevalence can further be assumed to accumulate in the later decades.^{26,27} The lifetime prevalence has been reported to be 0.4-0.7 %.¹⁵³ There is an association between MS and TN. 4 % of the total incidence of TN occur in MS patients, meaning a relative risk of 20 for MS patients to develop TN.²⁷ Conversely, the prevalence of TN among MS patients is 2 %, ^{28,29} TN can in a small number of patients be the first symptom of MS.⁹⁹ While MS is a risk factor for developing TN, TN is in turn a risk factor for developing depression, anxiety or sleeping disorder with a hazard ratio of approximately 2-3 for each.³⁰

Pathophysiology

The pathophysiology behind TN is incompletely understood. The current theories all require a basic understanding of the sensory trigeminal anatomy.³¹⁻³³ Peripheral sensory stimuli is converged into, and conducted through, three principal trigeminal nerve divisions innervating an area from the anterior scalp to the chin; the ophthalmic nerve (V1), the maxillary nerve (V2) and the mandibular nerve (V3). Each of these contains the peripheral axons of pseudounipolar nerve cells. The axons are an even mixture of myelinated and unmyelinated ones, with the former measuring up to 1.3 micrometers in diameter and the latter measuring up to 11 micrometers in diameter. The nerves enter the intracranial space through the superior orbital fissure (for V1), the foramen rotundum (for V2) and the foramen ovale (for V3). The nerve cell bodies are located medially in the middle fossa in the trigeminal ganglion, organized in clusters, with a somatotopic organization, from V1 superomedially to V3 inferolaterally. The trigeminal ganglion is surrounded by a dural pouch, Meckel's cave, which connects to the posterior fossa through the porus trigeminus, a dural tube riding over the petrous ridge. Centrally to the ganglion, the rootlets containing the axons of these same neurons gradually converge into the trigeminal root, which leads through the porus trigeminus and the prepontine cistern to the pons. Just before entering pons, in the trigeminal root entry zone, there is a transition from peripheral myelin (Schwann cells) to central myelin (oligodendrocytes). Within the brain stem, the axons extend to three different nuclei; the mesencephalic nucleus where muscular proprioception is directed, the principal nucleus where the majority of the tactile sensory signals are connected to second order sensory neurons, and the spinal nucleus, extending

from pons to the upper spinal cord, where most of the thermal and nociceptive sensory signals are connected to second order sensory neurons. From there, signals are conducted to the third order sensory neurons in the contralateral thalamus and onwards to the primary somatosensory cortex. For our understanding of pathophysiological theories explaining TN, the most important part of this anatomy is the retroganglionic part of the first order sensory neurons and the structures surrounding it.

Two findings are strikingly often demonstrated in TN; demyelination in the trigeminal root and a vascular compression of the root.³⁴ Often the former is assumed to be a result of the latter, and there is evidence of correlation between neurovascular conflicts and pathologic changes including demyelination in TN patients.^{35,36} Of all the cranial nerves, the trigeminal nerve is the one most frequently affected by a hyperactive dysfunctional syndrome (in this case TN), and it is also the cranial nerve with the largest portion of central myelin.⁸⁸ The central myelin has been reported to extend up to 9 mm from pons (mean 3½ mm).³⁷ It has been suggested that it is the large volume of central myelin subjectable to compression that makes the trigeminal nerve particularly vulnerable to compression that in some cases leads to TN.³⁸ Neurovascular conflict involving the trigeminal root can be graded according to the Sindou classification: 0 = no contact, I = contact without affection, II = displacement, and III = indentation.³⁹ Arterial neurovascular conflict with the trigeminal nerve is most commonly caused by the superior cerebellar artery, followed by the anterior inferior cerebellar artery or an unspecified small artery.⁴⁰ Though most neurovascular conflicts in TN involves arteries, there is also a significant number of patients with a venous contribution to the conflict, and in 8-16 % of the patients, a vein is the only offending vessel.⁴¹ These patients also have good effect from MVD, indicating causality.^{41,42} Case-control studies on MRI findings indicate that neurovascular contact in the root entry zone and/or anatomical changes have strong correlations to TN.⁴³ However, in studies on healthy subjects or on asymptomatic sides in TN patients, neurovascular conflicts involving the trigeminal root are very common compared to the low prevalence of TN.⁴⁴⁻⁴⁶ In other words, neurovascular conflicts are likely to be more commonly asymptomatic than associated with TN, which leads to the conclusion that it is not the only factor of importance for developing TN.

Demyelination of the trigeminal nerve has also been demonstrated in TN associated with compression of the nerve from a tumor in the cerebellopontine angle, resulting in TN.⁴⁷ Further, in the early years of decompressive surgery, it was suggested that nerve root compression could be caused by the trigeminal nerve riding over the petrous ridge, thereby causing TN.⁴⁸ This theory has only recently been tested, generating preliminary evidence suggesting that the angle of the petrous ridge may be a factor associated with TN, with a more acute angle having a positive correlation with prevalence of TN.⁴⁹

Apart from compression, the other common cause of trigeminal demyelination is MS. Of MS patients with TN (MS-TN) At least 84 % of MS-TN patients have an MS-lesion on MRI that can explain their TN.⁵⁰ MS-lesions associated with TN are confined to the first-order afferents, while lesions in the region of second-order neurons are associated with sensory disturbances other than TN.⁵⁷ Similar findings are however reported in a general MS population with a frequency of 23 %, without association to trigeminal neuralgia.⁵¹ In addition

to that, neurovascular conflicts are more common than expected in MS-TN, leading to the hypothesis of a dual concurrent mechanism explaining MS-TN.⁵²

The list of clinical characteristics of TN that must be explained by a hypothesis on the pathogenesis of TN on a physiological level is extensive, including for example the triggering by non-noxious stimuli, the length of the paroxysms and the response to various treatments. The ignition hypothesis elegantly explains nearly all characteristics of TN.⁵³ It builds on the revelation that oscillations in membrane potentials that normally occur in only a small portion of neurons are far more common in injured neuronal structures. This is what ignites a chain reaction, recruiting a large number of axons including nociceptors, based on two principles; 1) ephaptic cross-talk i.e., a spreading of electric discharge from one axon to the neighboring ones, aided by the lack of insulation in the demyelinated nerve, and 2) crossed after discharge, a non-synaptic release of potassium ions and/or neurotransmitters into the interstitial space, exciting neighboring neurons. The potassium ion release eventually causes a hyperpolarization, causing the discharge to stop followed by a refractory period. After discharge has been recorded microneurographically in a TN patient.⁵⁴ While the ignition hypothesis is arguably the most interesting theory on the pathogenesis of TN, in that it is based on solid preclinical data and that it so comprehensively explains the disease, it also remains to be thoroughly verified in animal models or in TN patient. A verified animal model that reproduces the clinical characteristics of TN has not yet been presented in the literature. While the ignition hypothesis explains the clinical features of TN, there are also unexplained structural and functional changes in the central nervous system associated with TN.⁵⁵ These changes occur in gray and white matter in many parts of the brain that are directly or indirectly involved in various aspects of pain. To what extent these changes are the cause or the effect of TN remains to be investigated, but it is likely reasonable to expect them to in some way at least contribute to the perception of the TN pain.

Diagnosis

Fothergill's description of the clinical characteristics of TN, first published in 1773, is considered to have stood the test of time.^{56,57} Add to this that the diagnosis (without regards for underlying cause) can be made almost entirely based on patient history, and it would seem that virtually no TN patient should have to be misdiagnosed.^{58,59} Yet, this has been frequently occurring, both historically and in modern days.⁶⁰ In 69 patients who underwent MVD, 58 % had previously received dental treatment for the same condition, and of those initially seeing a dentist, only 7 % were directly referred to a physician.⁶¹ Cluster headache is, despite its longer lasting pain and autonomous symptoms, sometimes also confused with TN, and in 144 patients with cluster headache, 22 % were initially diagnosed with trigeminal neuralgia.⁶² Other differential diagnoses include glossopharyngeal neuralgia and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), both though with traits that clearly separates them from TN.⁶³

According to a recent consensus between the International Headache Society and the International Association for the Study of Pain, TN is diagnosed based on the following criteria in the International Classification of Headache Disorders, 3rd edition (ICHD-3):⁶⁴

A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.

B. Pain has all of the following characteristics:

1. lasting from a fraction of a second to two minutes
2. severe intensity
3. electric shock-like, shooting, stabbing or sharp in quality

C. Precipitated by innocuous stimuli within the affected trigeminal distribution.

D. Not better accounted for by another ICHD-3 diagnosis.

In addition to that, some patients may exhibit sensory deficits in the affected region, ipsilateral muscle contractions and mild autonomic symptoms such as lacrimation. Following an attack of pain, there is usually a refractory period of time during which pain cannot be triggered. TN is further subdivided by demonstrated etiology:

1. Classical TN: no apparent cause other than neurovascular compression. Without or with persistent background facial pain.
2. Secondary TN: caused by an underlying disease. These causes include MS, space occupying lesion or other disease.
3. Idiopathic TN: no significant abnormalities on either MRI or electrophysiological tests.

This classification of etiology is however newer than the inclusion of patients in the cohorts in this study, and for all practical purposes in relation to PBC, the Burchiel classification from 2003 is more useful.⁶⁵ It subdivides TN into:

1. TN, Type 1 (TN-1): corresponding to classical or idiopathic TN with a persistent background pain of <50 %.
2. TN, Type 2 (TN-2): corresponding to classical or idiopathic TN with a persistent background pain of >50 %.
3. Symptomatic TN (MS-TN): corresponding to secondary TN in MS patients.

Of these, TN-1 (most often without any background pain at all) and MS-TN are considered for treatment with PBC. Clinically, MS-TN differs from TN-1 in at least three important regards; it is more often associated with sensory and electrophysiological disturbances, it is more often bilateral, and it presents significantly earlier, typically in the fifth decade of life.⁵² It is worth noting though, that with regards to age and to sensory and electrophysiological disturbances, there is considerable overlapping between the two groups.⁶⁶ The type of pain or the way it is triggered by stimuli does however not differ depending on the underlying cause, which again brings us back to talking to the patient.⁶⁷

Modern workup also most notably includes an MRI, since the positive finding of a likely structural underlying

cause, such as a severe neurovascular conflict, an MS-lesion or a tumor, is likely to have implications on the choice of treatment for a particular patient. A significant portion of the more current literature on TN relates to advancing the science on MRI protocols and findings. Factors other than the underlying cause e.g., trigeminal nerve atrophy, increased diffusion and reduced fractional anisotropy have been associated with TN, but there also seems to be a good amount of correlation between these factors, and it is therefore not currently clear which of these parameters that really add diagnostic value to the preoperative work-up.⁶⁸

Medical Treatment

The evidence for the treatment of TN is stronger in medical treatment than in surgery, and among the drugs, carbamazepine has the strongest evidence and is therefore considered the gold standard for the initial treatment of TN.⁶⁹ The use of oxcarbazepine for TN has, with the lack of high-quality randomized controlled trials (RCTs), weaker evidence, but there is consensus to support it as an alternative to carbamazepine as a first-line treatment.⁶⁹ Both these drugs stabilize axonal membranes, by inhibiting voltage-gated sodium channels, and more so related to high-frequency trains of action potentials in neurons with depolarized action potentials.⁷⁰ The potential advantage of oxcarbazepine over carbamazepine is that the former may exhibit less adverse effects, a factor that often limits the use of carbamazepine.⁶⁹ Common side effects include, but are not limited to, tiredness, dizziness, nausea, memory problems, headache, skin rash, leukopenia and hyponatremia.⁷¹

Other drugs lack sufficient high-quality evidence of effect on TN, but are nonetheless considered as second- or third-line drugs. These include lamotrigine, baclofen and gabapentin.⁶⁹ Anticonvulsants acting purely synaptically without a membrane stabilizing effect e.g., barbiturates, have not been proven to have an effect on TN.⁷² Recently, evidence supporting the efficacy of injections of botulinum toxin A for the treatment of TN have emerged, but large well designed studies are needed to confirm these initial reports.⁷³

In MS-TN patients specifically, there is not enough evidence to support any drug over others, and therefore it has been recommended to use a similar first- and second-line treatment strategy as in a general TN population.⁷⁴ Drug therapy for MS-TN is complicated by MS patients being considered to be more sensitive to the side effects of antiepileptic drugs, especially carbamazepine.⁷⁵ However, it is also in many TN-1 patients difficult to achieve adequate reduction of pain and frequency of attacks, while maintaining the side effects on acceptable levels. For carbamazepine, the numbers-needed-to-treat is 1.7-1.8 and the numbers-needed-to-harm is 3.4-24 (depending on the severity of harm).⁷³ After at least two failed attempts at sequential monotherapies and possibly one failed attempt at polytherapy, it is time to refer the patient for surgical intervention.⁷⁶ The lifetime risk of TN patients having to undergo surgery has not been established for modern treatment modalities, but is likely a moving target due to advancements in therapy. There are further no high-quality studies comparing medical to surgical treatment.⁷⁷

Surgical Treatment

There are currently five different surgical procedures in widespread use for TN; MVD, SRS, RFT, PRGR and PBC. Evaluations of results after surgery vary in the literature. Most analyses use a dichotomous measure of an acceptable/unacceptable pain relief to evaluate efficacy. This is a statistical requirement both for reports of recurrence rate, which has become less commonly used recently, and for survival/actuarial analysis, which has been used increasingly during the 21st century. As with the diagnosis itself, the evaluation of efficacy relies heavily on self-reports, but in interaction with a researcher or health care provider.⁷⁷

Based on observational data, MVD is considered the gold standard in surgery for TN, and it is the only procedure aimed at correcting the presumed pathology behind the pain i.e., a pathological neurovascular conflict.⁷⁸ MVD is therefore often the first choice for TN patients suitable for open surgery. TN patients are often elderly, and while elderly patients often have more comorbidity, an advanced age is in itself no contraindication to MVD.⁷⁹ The success rate of MVD is dependent on the grade of neurovascular conflict, with more severe conflicts being correlated to better outcomes.³⁹ The existence of a neurovascular conflict on preoperative MRI has a very high positive predictive value, but the grade of conflict is often underestimated in comparison to operative findings.⁸⁰ A neurovascular conflict on preoperative MRI therefore speaks in favor of MVD, given that the patient is otherwise suitable for open surgery. According to the ignition hypothesis, the removal of mechanical stimulus from the injured trigeminal root, reduces the triggering of the ectopic pacemaker behind the pain paroxysms, which leads to an immediate pain relief, while also facilitating longer-term repair of the compressed neuronal tissue.⁷² The mortality rate of MVD is 0.3-0.4 %.^{15,81} Since it is a non-ablative technique, side effects from lack of function of the trigeminal nerve are not expected, but they do occur.⁸² Serious complications include cerebrospinal fluid leaks, infections, injuries to the cerebellum and affection of the seventh and eighth cranial nerve.⁸³ There are, however, data supporting that some of these complications have decreased in recent decades, presumably due to a more refined technique and more experienced surgeons.⁸⁴

In the two most recent decades, publications on an endoscopic variant of MVD, so called E-MVD, have emerged. In a newly published meta-analysis, results after E-MVD are better than MVD when it comes to complications rates, while no significant difference can be found in published data on immediate pain relief and recurrence between the two techniques.⁸⁵ While MVD is the only non-ablative technique for TN, it is sometimes combined with a partial sensory rhizotomy (PSR). The frequency of PSR in MVD was 3.4 % in the US in 1996-2000.⁸¹ Partial rhizotomies can also be performed without MVD, if no neurovascular conflict is found during posterior fossa exploration. The results in terms of pain-free rate are possibly lower than in MVD, and with the addition of a predictable sensory loss.⁸³

For many patients with TN, MVD is not the best option due to comorbidities making open surgery less suitable. Three ablative percutaneous techniques i.e., PBC, PRGR and RFT, have therefore been part of the standard repertoire for the treatment of TN since the early 1980s.⁸⁶ They all have their advantages and disadvantages, but the several decades of parallel use is an indication that neither has turned out to be viewed as clearly superior or inferior to the others. Though there are obvious similarities in that they all access the

trigeminal ganglion or root by cannulating the Härtel trajectory, their means of ablation have implications for slightly different effects and side effects. RFT is the most anatomically selective technique, while PBC is selective to large myelinated fibers. As they are all trigeminally ablative, they all carry a risk of hypoesthesia, masticatory weakness and dysesthesia.⁸⁷

The least invasive surgical technique, in that it leaves no external scar, is SRS. Using a single-session radiation highly focused on the trigeminal nerve, it creates, just like the percutaneous techniques, a lesion that can potentially cure the symptoms of TN. A downside to SRS is that for a majority of patients it takes months for the treatment to have full effect.⁸⁸ About half the patients undergoing SRS are pain free without medication when the treatment takes full effect, with a majority of the rest being able to control the pain with medication.⁸⁸ While there are different techniques for generating and delivering the radiation, none has so far proved more efficient than the other.⁸⁸ The main side effect is hypoesthesia, while other side effects and complications are rarely reported, though single cases have raised the suspicion of radiation damage to nearby vascular structures, mainly the superior cerebellar artery.⁸⁸

Other surgical techniques, some with a long history, such as peripheral alcohol injections and peripheral neurectomy, have been reported to some extent even in modern days, but they are not part of the standard repertoire at most neurosurgical centers.⁸⁹ The current literature on these techniques does not seem to be strong enough to either discard them or to motivate a more widespread use of them. Deep brain stimulation of the posterior hypothalamus for the treatment of MS-TN has also been reported, but should be considered experimental.⁹⁰

High-quality studies comparing various surgical modalities for TN are lacking in the literature. For single center studies, patient selections for various modalities are almost always different or not reported, making accurate comparisons difficult. In addition to that, for pooled analyses, the inconsistency in reporting results poses a challenge.

MATERIALS AND METHODS

DESIGN:

Retrospective Hospital based observational study of patients with trigeminal neuralgia, in the Neurosurgery Department of Sree Chitra Institute of Medical Sciences and Technology (SCTIMST). A formal clearance was obtained after the evaluation of the study by Institute Ethics Committee (IEC).

DURATION OF THE STUDY: 1 year

FUNDING: There were neither external sources of funding nor conflicts of interest in the current study

ETHICAL COMMITTEE CLEARANCE - The study protocol was presented to the SCTIMST ethical committee and scrutinised at various angles regarding aim of the study and the safety of the patients involved in it. The study was started after the formal clearance from the IEC.

Methdology

94 cases with unilateral trigeminal neuralgia who have undergone MR Imaging of Head with 3D CISS and MRA sequence and microvascular decompression were analysed for neurovascular conflicts. All cases were included in a sequential manner irrespective of gender, ethnic, class, race or caste. The follow-up after discharge was recorded from the hospital records. The records of these patients, including their case files and outpatient follow-up files were retrospectively analyzed. Data regarding age; sex; duration of symptoms; side of pain; site of pain and post operative follow-up were collected from the files. Imaging investigations done at that time included MRI CISS and MR angiography. The patients underwent microvascular decompression depending on imaging findings. A few patients had postoperative complications such as hematoma or cerebrospinal fluid leak, which merited another procedure and were also recorded.

Inclusion criteria

1. 94 cases with unilateral trigeminal neuralgia who have undergone MR Imaging with 3D CISS sequence and MRA shall be analysed
2. Patients who have undergone microvascular decompression
3. Patients having neurovascular conflict only due to superior cerebellar artery

Exclusion criteria

1. Patients who have undergone MRI from outside and films only uploaded at SCTIMST
2. Patients with MR imaging without 3D CISS imaging or MRA
3. MR imaging in which the trigeminal REZ cannot be reported upon properly
4. Patients who have bilateral trigeminal neuralgia
5. Patients having neurovascular conflict due to other causes except superior cerebellar artery compression and secondary trigeminal neuralgia

Investigations

3D Slicer is a medical image processing software used for multimodal image reconstruction of 3D models from various data formats(Slicer (2021)). It is an open-source, multi-platform free software available for use in the biomedical field for the visualisation of internal anatomy. It can import MRI and CT scan data in DICOM format and perform segmentation on the data. Models can be segmented and reconstructed using fully or semi-automated tools like threshold, level tracing, grow from seeds, paint etc. The reconstructed models can be exported as an STL (Standard Triangle Language) file for applications such as 3D printing. The software has additional extensions which can tackle specific problems with the help of artificial intelligence (AI) (Slicer (2021))

Image Processing

The cerebrovascular and neural data of patients with Trigeminal Neuralgia is available in the form of high-resolution 3D Time of Flight Magnetic Resonance Angiography (TOF MRA) and Fast Imaging Employing Steady-state Acquisition (FIESTA MRI). The vasculature of arteries are clearly visible in a TOF MRA and the nerves and brainstem are clear in the FIESTA MRI. To reconstruct the 3D model of any part we need to segment the sequence of 2D data from the MRI. This is done with the help of software. Here the segmentation is done in an open-source software called 3D Slicer.

An illustrated flow chart regarding the 3D reconstruction of trigeminal neuralgia is shown

in figure 2.5. The TOF MRA and FIESTA data of the patient is imported into the software in DICOM format. Using the Crop Volume module the region of interest is selected and cropped. The image is also made isotropic in the same module. A new segment is created using the Segment Editor module and renamed as an artery. The contrast of the image is adjusted suitably using the adjust window/level of volume option from the top toolbar. Using the Threshold function the regions of arteries are assigned to the new segment. The 3D model is then constructed from the segmentation. The Scissors function is used to remove unwanted regions in the 3D view. The model is then saved as a .mrml file. Similar steps are followed for the reconstruction of the trigeminal nerve however the segmentation is done on the FIESTA data file. Both the models are now opened in a single window. From the Data module we create a transformation for the trigeminal nerve to move it to the correct position with regard to the circle of Willis. The position of the nerve is adjusted such that the segmentation region matches the trigeminal nerve region in the MRI data. The transformation is hardened (fixed) and the model can be exported as a .stl file for further analysis. The geometry of the flow domain and the solid wall needs to be obtained as a ComputerAided Design(CAD) model before the governing equations can be applied to the region and be discretised. The data from the segmentation of the TOF-MRA data in 3D Slicer is used for this. The model is exported to an STL model. The STL model opened in Solidworks window

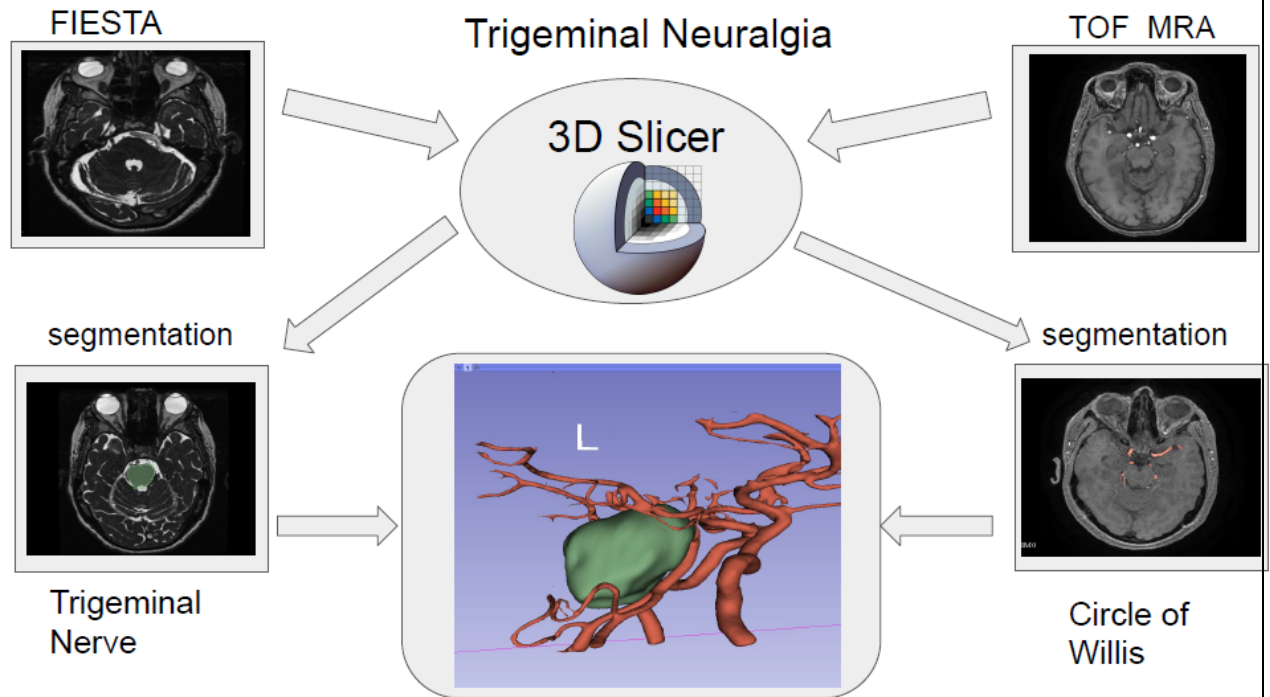


Figure 1 showing flow chart for 3D reconstruction for trigeminal neuralgia

Statistical analysis

The data were entered in SPSS (Statistical programme for social sciences) version 17. Data was checked again to avoid any error. Frequencies with percentages were computed for categorical variables like sex, site involvement, grade of NVC whereas mean $\pm$ S.D was utilized for numerical variables like age and length of SCA. Stratification was done with regards to age, sex, NVC, length of SCA type to control the effect on these outcome variables. Through paired T test, p-value ≤ 0.05 was taken significant.

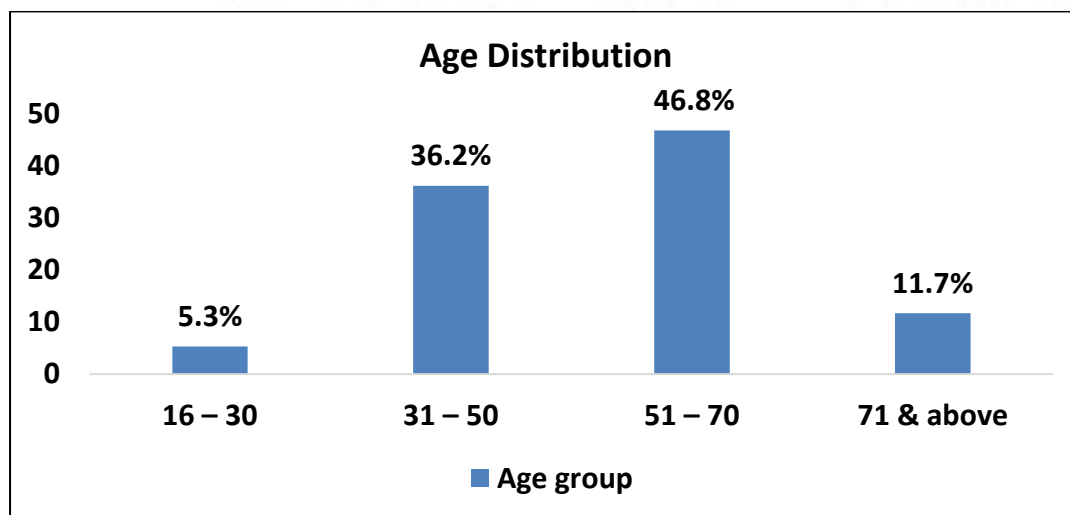
RESULTS

Age

Table 1- showing age distribution among the participants

Age(years)	Number	Percentage
16 – 30	5	5.3
31 – 50	34	36.2
51 – 70	44	46.8
71 & above	11	11.7
Total	94	100.0

Figure 2- showing age distribution among the participants



The maximum number of patients were in the age group of 51-70 years 44 patients out of 94 (46.8%) followed by 31-50 years 34 patients out of 94 (36.2%) and minimum in 16-30 years of age 5 out of 94.(5.3%)

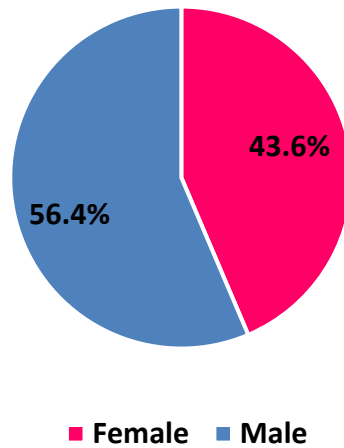
Gender

Table 2- showing the gender distribution among the participants

Gender	Number	Percentage
Female	41	43.6
Male	53	56.4
Total	94	100.0

Figure 3 - showing the gender distribution among the participants

Gender Distribution

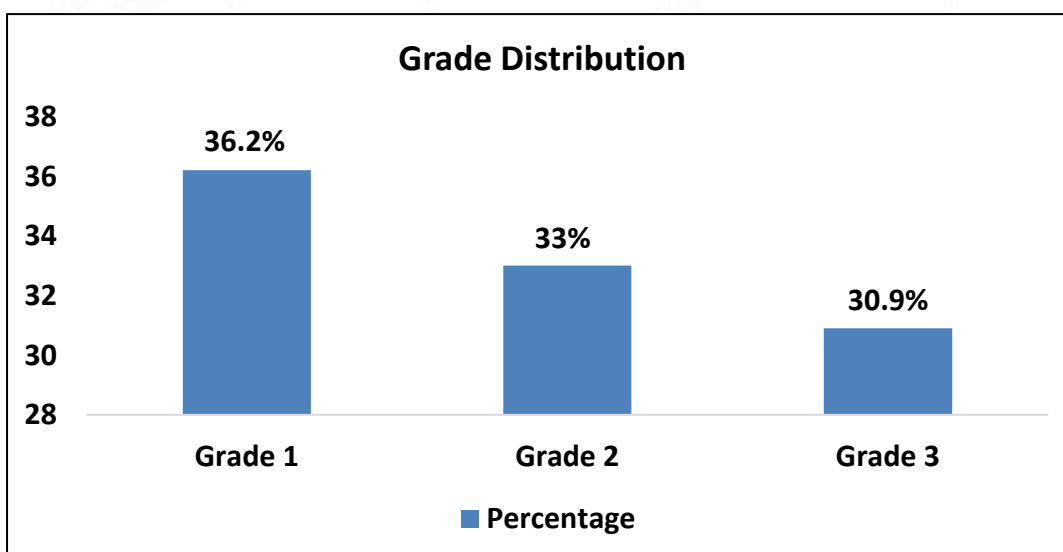


There were 53 males and 41 females (male/ female ratio 1.29:1).

Table 3: Grading of neurovascular conflict

Grade	Number	Percentage
1	34	36.2
2	31	33.0
3	29	30.9
Total	94	100.0

Fig 4: Distribution of participants based on severity grade



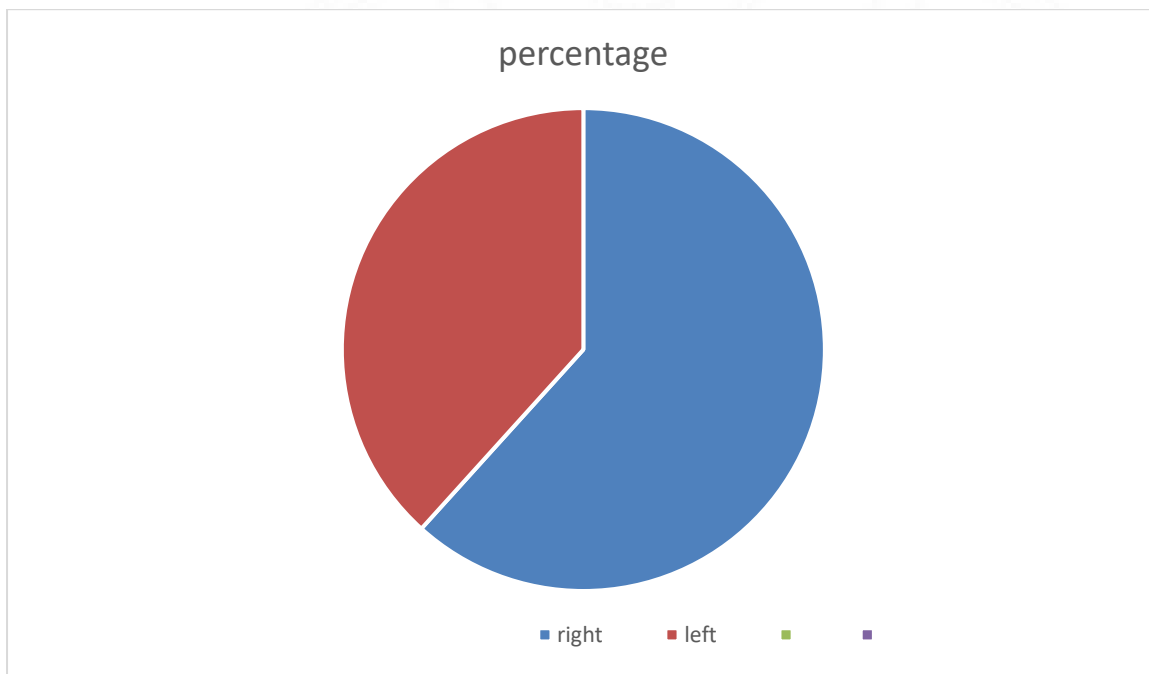
36.2% patients had presented with neurovascular conflict grade 1 while 33% and 30.9 % patients had

neurovascular grade 2 and 3 respectively

Table 4 Showing the distribution of trigeminal Neuralgia

Side of Trigeminal Neuralgia	Number	Percentage
Right	58	61.70
Left	36	38.30
Total	94	100

Figure 5 showing the distribution of trigeminal neuralgia



61.7% patients had right sided trigeminal neuralgia and 38.3 % patients had left sided.

Table 5: Distribution of participants based on site of facial pain

Site of facial pain	Number	Percentage
v0	13	13.8
v1	03	3.2
v2	20	21.3
v3	10	10.6
v1,v2	11	11.7
v2,v3	33	35.1
v1, v2, v3	04	4.3
Total	94	100.0

35.1 %patients had symptoms in v2,v3 distribution which was maximum followed by pain distribution in v2 segment which was 21.3%

Table 6: Length of SCA on symptomatic and asymptomatic side

Length of SCA	Mean	Number	Std. Deviation
Symptomatic side	21.776	94	3.1918
Asymptomatic side	16.206	94	3.1230

The Average length of SCA on the side with symptoms was 21.776mm whereas on the asymptomatic side was 16.206mm with average difference of 5.61mm.

**Table 7: Differences between the length of SCA on Symptomatic and Asymptomatic side
Using Paired t test**

Length of SCA	Mean	Std. Deviation	t	95% Confidence Interval of the Difference	P value
Symptomatic side – Asymptomatic side	5.5691	3.4779	15.525	93(4.856 – 6.281)	<0.001

The above table shows that there was a difference between the length of SCA on symptomatic and asymptomatic side and this difference was statistically significant with p value <0.001.

DISCUSSION

At present, the pathogenesis of PTN is very controversial, many literatures speculate that neurovascular compression in the root entry zone (REZ) is the main etiological factor. The nerve compression will cause local demyelination, and chronic stimulation makes nerve produce abnormal impulses [91]. MVD is performed to separate the nerve and blood vessel with a Teflon pad following which the pain is improved after the nerve compression is released. Therefore, it is important to detect the presence of offending vessel in patients with TN not only for the diagnosis of these diseases but also for determination of a treatment strategy and prediction of clinical outcomes. It is the key to the success of the operation multimodal image based 3D reconstruction provided more details about the individualized anatomy of the REZ area in each case, including not only the offending vessel and its location but also the shape of vessels and nerves, the severity of compression, and the spatial relationship between the brainstem and its surrounding structures. All this detailed information is essential for the prediction of the clinical outcome, but to perform the 3D reconstruction of multimodal images, it is often necessary to select an image postprocessing software. 3D Slicer is an open source software for medical image informatics, image processing and 3D visualization. It has powerful 3D reconstruction, multimodal image registration and fusion, model segmentation, and surgery stimulation and other functions, and it can be run on a variety of systems, bringing convenience of powerful medical image processing, visualization and data analysis to clinicians and researchers [92,93]. With the software, images can be processed conveniently on personal computer, no matter when and where, without the need for a dedicated MRI platform. In this study, 3D-TOF MRA sequence and 3D-FIESTA sequence were used to distinguish blood vessels and nerves. Different from the previous way of assessing the neurovascular relationship with two-dimensional imaging, in this study, the open source 3D Slicer software was used to reconstruct the brain stem, nerves, and blood vessels, which accurately shows the offending vessel and the degree of nerve compression. This new method is accurate, flexible, convenient and easy to learn. The research result proves that the method of predicting the neurovascular relationship in PTN based on 3D Slicer multimodal image reconstruction is feasible, effective and low-cost. The 3D-FIESTA sequence can delineate the blood vessel and the nerve as low-signal intensity structures, whereas the cerebrospinal fluid is a high signal-intensity structure. However, it is difficult to make an accurate prediction of neurovascular relationship because the sequence alone is not sufficient to distinguish among the arteries and nerves [94]. Considering this matter a 3DTOF MRA sequence, which can provide obvious intensity contrast between arteries (high signal intensity) and nerves (intermediate signal intensity), to reconstruct the artery. By registering and reconstructing these two MRI scan sequences, the neurovascular relationship in the CPA can be better displayed in a three-dimensional view.

Under the premise of not increasing the consumption of medical resources and the economic burden of

patients, it can make full use of the existing examination resources to realize the 3D visualization of CPA through the 3D reconstruction of multimodal images, which can help the surgeon better understand the local anatomy. In addition, the 3D model can be used as a tool for preoperative conversation and doctor-patient communication, it is clear and easy to understand, and it is worth promoting.

Compared to 3D-TOF-MRA and 3D-FIESTA, image reconstruction has the main advantages that a 3D model can accurately show the position of nerve compression, the shape of blood vessels and one can measure distance, angle, volume by model at will. This 3D model in the preoperative conversation can help patients understand better the cause for their symptoms and the effect and need for the surgery. This also can help us understand the local anatomy and basic pathogenesis and etiological factor for the neurovascular conflicts.

Sunderland 95 stated that the SCA "frequently" loops downward to the upper surface of the trigeminal nerve and may indent or even perforate it, but he did not supply precise statistics. Jannetta 96 studied 56 autopsy cases without seeing any evidence of trigeminal nerve compression by vessel at or near the pons.

Dandy 97 described the SCA as "usually" sending out a branch that dangles freely in the lateral cistern before reaching its destination. This, he said, may pass between the nerve root and the brain stem or along the lateral surface of the sensory root, and in 30.7% of his 215 cases of trigeminal neuralgia, the SCA in some way affected the nerve. He noted that lower facial tic (V2 and V3) was most commonly associated with compression of the superomedial side of the nerve by the SCA and that upper facial tic (V1) was most commonly associated with compression of the lower margin of the nerve). This study confirms the observations of Dandy and Sunderland that the SCA or one of its major branches frequently loops caudally in the ambient cistern and makes contact with the trigeminal nerve. 95,97. Then why do some patients develop these symptoms and others don't. Jannetta 98 suggested that age-related "brain sagging" and "arterial elongation" account for the aberrant location of the compressive vessels. Although Jannetta does not explicitly define "brain sagging" or arterial elongation, he mentions that these processes are "seen routinely" in aging patients. Dandy 97 also discussed arterial elongation caused by age and arteriosclerosis, which we assume to refer to the accepted age-related increase in vessel tortuosity

The above observations reflect from the fact that the specimens were from elderly adults in whom the intracranial vessels are likely to be tortuous and elongated. Therefore it seems likely that with increasing tortuosity and elongation, the SCA, being prevented by the tentorium cerebelli from expanding cranially, will tend to expand caudally toward the region of the trigeminal nerve. With Trigeminal nerve being a relatively fixed structure during its anatomical course as it passes through the Meckel Cave this extra length of SCA and tortuosity will have little space to anatomically lie and hence they tend to groove the nerve. Any study of cadaver specimens must be of limited value in discussing the etiology of pain producing conditions such as trigeminal neuralgia, but the frequency with which some degree of neurovascular contact occurs makes it possible that vascular compression and distortion of the trigeminal nerve root may indeed be important in the

etiology of this painful condition. In this study, we found that the length of superior cerebellar artery on the symptomatic side was longer than the asymptomatic side and it was statistically significant. It was also found that the vessel making contact with the nerve was usually the main trunk of the SCA rather than a smaller branch formed by its bifurcation, and, in life, pulsation in arteries of this size would be likely to have some further distorting effect on the nerve.

The presence of neurovascular relationships in the root entry zone of the V nerve, in the absence of trigeminal neuralgia, is quite common, with incidences varying from 13 to 60%. The SCA is the vessel that has more often contact with the V par, followed by the AICA. In 3.8%–28.2% of the cases where there is contact between them, causes nerve compression with distortion and grooving of the nerve. It is understood that the neural compression leads to irregular demyelination within the sensory root, which is responsible for neuralgia [99-101]. The vascular compression increases after the fifth decade of life, when the arterial tortuosity increases due to the process of atherosclerosis. However, the anatomical variations associated with the origin and course of the SCA are the ones that facilitate the contact and compression with the related nerves.

In a small number of cases of TN a congenital abnormality such as an arteriovenous malformation or a persistent primitive trigeminal artery [102,103] explain the proximity of the nerve and vessel in such a way that vascular compression is apparent. But, in the majority of cases an aging process provides the primary theoretical explanation of the juxtaposition of artery and nerve. This view is in accordance with the rather late age incidence of TN, primarily in the 4th–6th decades of life [104-108] which is in accordance with our findings.

CONCLUSION

1. Our findings demonstrate that the relative longer length of the SCA compared to its counterpart on the asymptomatic side determines the clinically apparent neuralgic pain along the division of the trigeminal nerve.
2. This study also corroborates the earlier hypothesis that longer segment of SCA leads to genesis of trigeminal neuralgia
3. Further studies in the asymptomatic patients incidentally detected to have neurovascular conflict is required to arrive at a predictive algorithm for development of symptomatic trigeminal neuralgia.

Limitations and recommendations

1. It is a retrospective study
2. The model reconstruction was performed based on DICOM format data, so the reconstruction effect is largely limited by the quality of the data used.
3. Multimodal image reconstruction is an image postprocessing technology, so the builder must be very familiar with the local anatomy structure and neuroimaging.
4. When selecting the offending vessel and evaluating degree of nerve compression, it is easy to be affected by the image of the evaluator's subjective factors.

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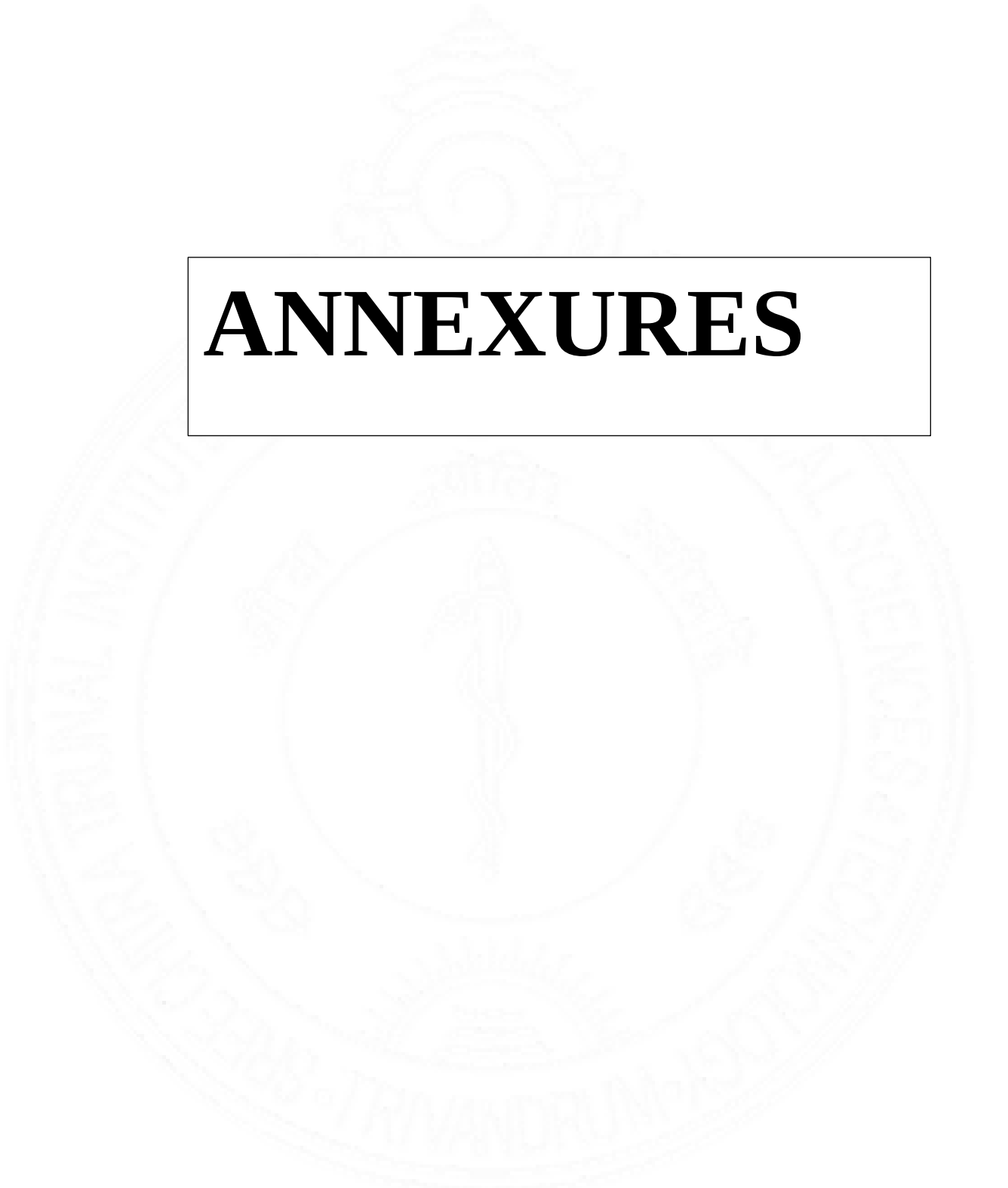
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ANNEXURES

DATA ABSTRACTION FORM

“Evaluation of Incidence of Neurovascular conflict of Trigeminal Nerve”

CODE NO: _____

GENERAL INFORMATION

Age	
Sex ^[1] _[SEP]	M/ F
Indication of MRI	

MR IMAGING (DD/MM/20YY)

Sequence	3D CISS
Conflict	Yes/ No
Grade	1/2/3
Side	Right/ Left
Length of SCA	
Angle of origin of SCA from basilar artery	
Looping pattern of SCA	

CLINICAL DETAILS

Mode of Presentation	Duration
Headache	
Facial pain	
Ear pain	
Site of Headache	1. Temporal 2. Vertex 3. Occipital
Site of Facial pain	1. V1 2. V2 3. V3 4. V1+V2 5. V2+V3

	6. V1+V2+V3
Side of Pain	Right/ Left
Typical Neuralgia	Yes/ No
Other associated features	1. Aura 2. Congestion 3. Others

AUDIOMETRY (DD/MM/20YY)

PTA L	
PTA R	
Speech Discrimination score	

EXAMINATION FINDINGS (DD/MM/20YY)

Corneal Reflex		
Schirmer's test		
Corneal haziness	Yes/ No	Yes/ No
Masseter bulk		
Facial Sensations		
Jaw opening		
Facial Deviation		

INTERVENTION DONE IF ANY

Date of intervention	(DD/MM/20YY)
Type of Intervention	1. Microvascular decompression 2. Radiofrequency ablation 3. Gammaknife/ Radiosurgery
Intraop Finding	
Relief with intervention	Yes/ No



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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1293/AUGUST/2021

20.10.2021

Dr. Jayanand Sudhir
Associate Professor
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Jayanand Sudhir,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "EVALUATION OF INCIDENCE OF NEUROVASCULAR CONFLICT OF TRIGEMINAL NERVE (IEC/1293)" on 18th August, 2021.

The following members of the Ethics Committee were present at the meeting held on 18th August, 2021 at Residences and Offices of IEC Members via Video Conference

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. Achuth Sankar S. Nair	Ph.D (i.Engineering ii.Music)	Male	Social Scientist	No
6.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes