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Original Research Article

Study on the Association of Nerve Atrophy and Severity of Pain in Trigeminal Neuralgia

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Abstract:

Introduction: Trigeminal neuralgia (TN) is a painful condition that is often brought on by the construction of a blood artery. TN is a possible symptom of MS. Demyelination close to the compressed area can generate shock-like pains during epaptic transmission. Although healthy persons can experience neurovascular compression, it can be relieved surgically. The brains of those with TN show anatomical changes.

Aims and Objectives: This study examines the relationship between trigeminal nerve atrophy and pain severity in trigeminal neuralgia patients.

Methods: In this investigation, diagnostic criteria from ICHD-3 were used to evaluate 80 participants, 40 with primary "trigeminal neuralgia (TN)" and 40 matched controls. The study was conducted from September 2023 to August 2024. MRI data were gathered to look at "neurovascular compression (NVC)" and changes in brain anatomy, and the VAS and SF-MPQ were used to measure the level of pain experienced. This study seeks to better comprehend the pathophysiology of TN by exploring the relationships between NVC, brain plasticity, and clinical factors.

Result: This study's primary "trigeminal neuralgia (TN)" patients shared demographics with healthy controls, but their pain and emotional impact were much higher. An analysis found lower GMVs in some brain areas in TN patients. Numbers were higher in contralateral trigeminal nerve cases. Mediation study shows that trigeminal nerve morphology most affects pain severity. The study revealed direct effects of trigeminal nerve morphology on pain severity in primary TN patients.

Conclusion: This study concluded that individuals with primary trigeminal neuralgia (TN) have significantly reduced grey matter volume (GMV) and ipsilateral trigeminal nerve (TGN) size.

Keywords: Trigeminal neuralgia (TN), neurovascular compression (NVC).

Introduction

"Trigeminal neuralgia (TN)", sometimes referred to as tic douloureux, is a persistent pain disorder distinguished by recurring, transient episodes of electric shock-like sensations that impact the trigeminal nerve, responsible for innervating the forehead, face, and lower jaw. This pathological state often manifests unilaterally and may affect one or many branches of the trigeminal nerve. Trigeminal neuralgia is a clinical condition distinguished by episodes of intense facial discomfort. The designation "tic douloureux" was used by the French physician Nicolaus Andre in 1756 to describe the facial spasms that may occasionally accompany episodes of intense pain [1,2]

The trigeminal nerve is categorised as the fifth cranial nerve. The trigeminal nerve is responsible for delivering sensory innervation to the facial region, as well as giving both sensory and motor innervation to the muscles that are involved in the process of mastication [3]. The trigeminal nerve arises from the pons area of the brainstem and later divides into three separate branches:

- The ophthalmic division (V1) of the trigeminal nerve is responsible for innervating the eye, upper eyelid, and forehead.
- The maxillary nerve (V2) is responsible for innervating various anatomical structures including the nostril, lower eyelid, upper gum, upper lip, and cheek.
- The mandibular branch (V3) of the trigeminal nerve is responsible for innervating the jaw, lower lip, muscles, and lower gingiva involved in mastication [4,5].

The trigeminal nerve originates from the pons. The majority of instances of trigeminal neuralgia arises by compressing of the trigeminal nerve root in close proximity to its point of entry into the pons, typically within a few millimeters. The etiology of the majority of "trigeminal neuralgia (TN)" cases, ranging from 80% to 90%, can be attributed to the compression exerted by a neighboring artery or vein. The superior cerebellar artery has been predominantly implicated in approximately 75% to 80% of the instances [6]. Additional blood arteries that have been identified as potential contributors to trigeminal neuralgia (TN) are the petrosal vein, the vertebral artery, and the anterior inferior cerebellar artery [7]

Additional factors that can contribute to nerve compression encompass epidermoid cyst, albeit infrequently, acoustic neuroma, meningioma, and arteriovenous malformation or saccular aneurysm [8].Multiple sclerosis has been identified as a risk factor for trigeminal neuralgia, with a reported prevalence ranging from 2% to 4% among patients diagnosed with trigeminal neuralgia. The multiple sclerosis causes demyelination of trigeminal nerve nucleus is a contributing factor in this case[9].The majority of instances of trigeminal neuralgia can be attributed to the compression of the trigeminal nerve. There is a prevailing belief that trigeminal neuralgia (TN) is associated with the demyelination of nerves in the vicinity of the compressed area. The precise process by which demyelination contributes to the manifestation of symptoms in trigeminal neuralgia remains unclear [10]. The prevailing hypothesis posits that the presence of a demyelinated lesion leads to the formation of ectopic impulses, which subsequently results in ephaptic transmission. The potential explanation for the occurrence of shock-like pains in the facial trigger zone due to light tactile stimulation lies in the ephaptic connection between pain-generating fibres and fibres responsible for transmitting light touch sensations [11].

The presence of a provoked event, subsequent refractory intervals, and the elicitation of painful feelings from a solitary stimulus suggest the potential involvement of the central pain mechanism in trigeminal neuralgia. The presence of modified grey matter within the sensory and motor cortex has also been documented [12].Certain hypotheses propose that demyelination might occur as a result of vascular compression of the nerve root caused by convoluted or abnormal arteries. The close proximity between the trigeminal nerve root and these arteries has been proven through radiologic and pathologic studies. The primary artery involved in this context is predominantly the superior cerebellar artery. The aforementioned notion gains further support from the observed alleviation of symptoms subsequent to surgical procedures aimed at anatomically separating the implicated blood vessels from the affected nerve [13,14].

Based on the bio-resonance hypothesis, it is proposed that the occurrence of facial pain is attributed to the destruction of trigeminal nerve fibers caused by the convergence of vibration frequencies between the trigeminal nerve and its surrounding structures. This damage disrupts the normal transmission of impulses, ultimately leading to the manifestation of facial pain [15].

As the condition advances, individuals diagnosed with primary trigeminal neuralgia frequently encounter intermittent episodes characterised by sudden and severe escalations in attack frequency and length. These episodes are typically followed by periods of relief from pain [16].

Regrettably, the comprehensive investigation of the fundamental causes of TN remains incomplete. There is a growing body of research indicating that around 90% of primary trigeminal neuralgia (TN) cases are characterised by the presence of Neurovascular Compression (NVC). This refers to a condition in which the trigeminal ganglion (TGN) comes into direct touch with or is displaced by nearby blood vessels. Microvascular decompression (MVD) is a surgical intervention that involves the relocation of the problematic blood artery from the trigeminal ganglion (TGN) root through the utilisation of a small sponge or Teflon pad [12]. Microvascular decompression (MVD) has been identified as the most efficacious therapeutic intervention for primary trigeminal neuralgia (TN), as evidenced by a substantial proportion of patients, exceeding 98%, expressing immediate relief from pain following the surgical procedure. Moreover, a noteworthy 68% of patients have reported enduring positive outcomes in terms of pain alleviation at a 10-year postoperative assessment [14]. Nevertheless, the presence of Neurovascular Compression (NVC)is not limited to persons with trigeminal neuralgia (TN). Neuroimaging investigations have revealed that 25-49% of healthy individuals and 14-39% of cadavers exhibit this structural variation, even in the absence of any prior TN diagnosis. Therefore, it is insufficient to merely assign descriptors such as suspected contact, contact, and nerve displacement and indentation when defining NVC and its severity [15].

In recent years, there has been a recognized association between peripheral nerve injury and subsequent alterations in brain structure and function. Multiple studies have documented changes in grey matter volume (GMV) in individuals with primary trigeminal neuralgia (TN). Nevertheless, there has been a lack of research exploring the potential relationship between atrophy of the trigeminal ganglion (TGN) and any associated alterations in "grey matter volume (GMV)" among

individuals diagnosed with primary trigeminal neuralgia (TN) [17].

Method

Research Design

In this cross-sectional analysis, 80 participants were chosen as the cohort. The participants in this study were 40 participants who had been diagnosed with primary trigeminal neuralgia (TN) and 40 matched controls (in terms of age, gender, education, and dominant hand). The study recruited the patients from the People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh. Using the criteria provided by the International Classification of Headache Disorders, Version 3 (ICHD-3), a diagnosis of primary trigeminal neuralgia (TN) be made. Unilateral pain within the trigeminal nerve's distribution was present in all cases. The Visual Analogue Scale (VAS) and the shortened McGill Pain Questionnaire (SF-MPQ) were used to quantitatively evaluate pain in patients with primary trigeminal neuralgia (TN). In addition, we collected MRI information to investigate the phenomena of neurovascular compression (NVC) of the trigeminal nerve. Voxel-based morphometry (VBM) analysis was also performed to look for changes in brain structure. This study used correlation and mediation analysis to explore links between NVC, neural plasticity, and clinical variables. The current study aims to further our understanding of the pathophysiology of TN and its resultant implications in a clinical setting; the Research Ethics Review Board has approved it.

Inclusion and Exclusion Criteria

Inclusion

- Primary trigeminal neuralgia (TN) patients are diagnosed by ICHD-3.
- Primary TN patients must have a confirmed illness duration of 2 years.
- Unilateral trigeminal nerve pain with stabbing or electric-like paroxysms is required.
- Neurological or sensory deficiencies not caused by TN must be absent to be included.

Exclusion

- Secondary TN caused by neurological disorders or other reasons is eliminated.
- Participants with pain problems or diseases other than TN that may impair study outcomes are excluded.
- Participants with serious psychological illnesses that could affect pain or brain structure are excluded.

Statistical Analysis

The statistical analysis in this study will encompass the utilisation of descriptive statistics to provide a concise summary of crucial variables, such as age, disease duration, VAS pain ratings, and SF-MPQ pain rating indices (total, sensory, and affective). The frequencies and percentages of categorical data, such as gender and medication consumption, will be reported. In order to evaluate the importance of disparities in pain ratings between primary TN patients and healthy controls, independent sample t-tests will be utilised, with a significance level of $\alpha = 0.05$. This study aims to describe the presence or absence of neurovascular compression (NVC) in patients with trigeminal neuralgia (TN), and to quantify the level of interobserver agreement. The purpose of these statistical studies is to offer a thorough comprehension of the pain characteristics and neurovascular compression (NVC) status within the study group. This will contribute to the exploration of aspects connected to trigeminal neuralgia (TN) and their potential connections to alterations in brain structure.

Ethical Approval

The present study acquired clearance from the Research Ethics Review Board of People's College of Medical Sciences & Research Centre, Bhopaland written informed consent was collected from all subjects involved in the research.

Result

Table 1 shows the demographic and clinical characteristics of 65 primary “trigeminal neuralgia (TN)” patients and 65 healthy controls. Interestingly, the two groups had similar sex, age, and education levels. However, TN patients had left/right pain laterality, a mean pain duration of 7.06 years, and frequent attacks (5.81 times per day) lasting 1.41 minutes resulting in a VAS Pain Rating of 5.75. TN patients also had higher ratings on the SF-McGill Pain Questionnaire, indicating more severe sensory and affective pain, and on emotional evaluation measures (HAMA and HAMD), suggesting a potential emotional impact. Brain VBM measurements showed no significant variations in TIV, GMV, WMV, or CSF between groups, but GMV and WMV differences were identified. These findings highlight the clinical differences and potential emotional impact of primary TN compared to healthy controls in the research cohort.

Table 1: Demographics and clinical characteristics of the study population

	Primary TN patients n=65	Healthy controls n=65	P value
Sex, n (%)			
Female	40 (61.53%)	40 (61.53%)	
Male	25 (35.46%)	25 (38.46%)	
Age (years)	53.71 ± 7.83	53.79 ± 8.11	0.991
Education (years)	11.49 ± 3.64	13.25 ± 4.17	0.841
Disease characteristics			
Pain laterality (left/right)	25/40	0	
Pain duration (years)	7.06 ± 5.30	0	
Attack frequency (times per day)	5.81 ± 5.91	0	
Duration of attack (min)	1.41 ± 0.80	0	
VAS Pain Rating	5.75 ± 1.80	0	
SF-McGill Pain Questionnaire			
SF-MPQ-Total	13.40 ± 6.79	0	
SF-MPQ-Sensory	8.09 ± 4.09	0	
SF-MPQ-Affective	5.11 ± 2.65	0	
Emotional assessment			
HAMA	4.12 ± 3.41	0	
HAMD	4.31 ± 4.41	0	
Brain VBM			
TIV	1.389 ± 0.109	1.439 ± 0.111	0.091
GMV	0.671 ± 0.050	0.681 ± 0.039	0.071
WMV	0.521 ± 0.045	0.529 ± 0.049	0.239
CSF	0.231 ± 0.041	0.241 ± 0.030	0.281

Table 2 highlights the specific brain regions where patients with primary trigeminal neuralgia (TN) have smaller grey matter volumes (GMVs) compared to healthy controls. The insula, the right hippocampus, the left somatosensory cortex 2, the right anterior cingulate cortex, the right inferior temporal gyrus, the left middle temporal gyrus, the left and right temporal poles, the left precuneus lobe, and the right precuneus lobe. Each region is described in terms of its Brodmann's area, number of voxels in the cluster, and MNI coordinates, with peak voxel t-values showing the degree of GMV reduction also provided. These results point to anatomical variations in these brain regions that might be linked to the pathophysiology of primary TN and its associated symptoms, illuminating prospective areas of interest for further inquiry into the neural basis of this disorder.

Table 2: Regions of reduced grey matter volume in primary TN patients compared to healthy controls

Anatomical regions	Side	Brodmann's area	Voxels in cluster	MNI coordinates			Peak voxel t-value
				X	Y	Z	
Insula	L	15	251	−40	15	1	5.6
Hippocampus	R	34	359	290	−29	−5	5.14
Somatosensory cortex 2	L	39	141	−40	−09	21	4.18
Anterior cingulate cortex	R	25	109	9	15	29	4.25
Inferior temporal gyrus	R	19	209	49	−29	−24	4.03
Middle temporal gyrus	L	19	441	−61	3	−19	4.68
Temporal pole	L	41	199	−40	−3	−39	3.93
Temporal pole	R	41	191	40	0	39	4.41
Precuneus lobe	L	8	261	−16	−71	41	3.74
Precuneus lobe	R	7	181	19	−49	29	4.36

Figure 1 shows nerve volume (mm3) under various situations. The "Ipsi-TGN-Major NVC" disease has moderate nerve tissue with 63-mm3 nerve volume. "Ipsi-TGN-Minor+No NVC" has 75-mm3 nerve volume, slightly higher. In the "Contra TGN" condition, nerve volume is highest at 89 mm3. These findings reveal that the contralateral TGN condition has a significantly higher nerve volume than the ipsilateral circumstances, suggesting that nerve density and growth patterns may vary in different neurological situations.

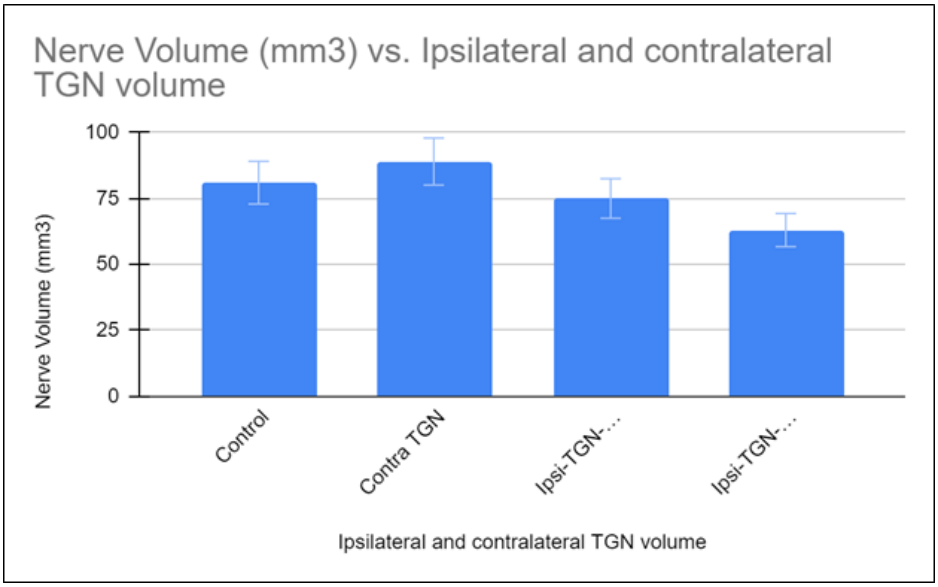

Figure 1: Comparisons of ipsilateral and contralateral TGN volume between primary TN patients and controls.

The relationship between ipsilateral TGN volume, GMV of the left insula, and pain rating index in Figure 2. The mediation analysis demonstrated that the trigeminal nerve morphology, not the left insular GMV, had a largely direct effect on the pain severity in primary TN patients.

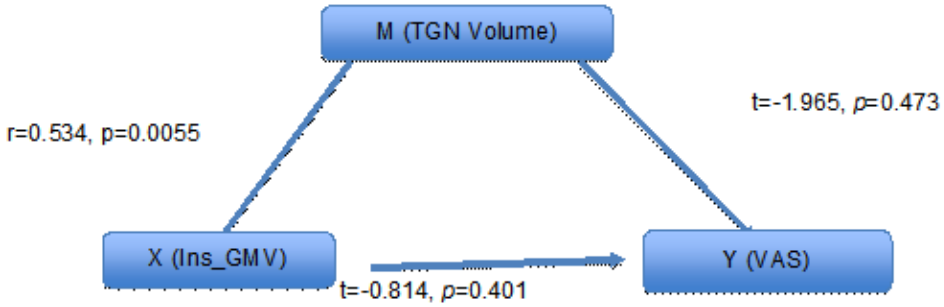

Figure 2: The link between ipsilateral TGN volumes, GMV

Discussion

Recent neuroimaging investigations have documented structural changes in the grey matter of individuals diagnosed with primary trigeminal neuralgia. Nevertheless, there is a scarcity of research that has specifically examined the quantitative assessment of trigeminal nerves and the correlation between the volume of these nerves and brain morphology, specifically in relation to grey matter volume[16]. The present study aimed to examine the association between trigeminal nerves and alterations in grey matter volume among individuals diagnosed with primary trigeminal neuralgia, in comparison to a group of healthy individuals serving as controls. Furthermore, we investigated the correlation between the anatomy of trigeminal nerves and grey matter with the pain clinical data that were gathered. The research findings shown a primarily direct correlation between trigeminal nerve atrophy and clinical pain characteristics in individuals diagnosed with primary trigeminal neuralgia. The study offers novel perspectives on the underlying mechanisms of the condition [18].

The objective of this study was to conduct a prospective assessment of the degenerative alterations in trigeminal nerves (TGNs) by utilising measurements of volume (V) and cross-sectional area (CSA) derived from high-resolution 3-T MR images acquired from individuals diagnosed with unilateral trigeminal neuralgia (TN). Additionally, the study aimed to establish correlations between these data and patient demographics, neurovascular compression (NVC) characteristics, as well as clinical outcomes. The findings of the study indicate that high-resolution imaging can effectively illustrate the atrophy of the trigeminal ganglion (TGN) in patients diagnosed with trigeminal neuralgia (TN). The aforementioned data indicate that there is a correlation between the severity of compression and clinical outcomes with atrophic alterations in TGNs. These findings suggest that the

assessment of such atrophic changes could potentially serve as a predictive factor for long-term prognosis following vascular decompression [19].

Trigeminal neuralgia is frequently correlated with nerve atrophy, alongside vascular compression. The researchers conducted an evaluation to determine if the cross-sectional areas of various segments of the trigeminal nerve on preoperative imaging could serve as a predictive factor for the result following microvascular decompression (MVD) [17]. Trigeminal neuralgia is characterized by the degeneration of the root entry zone of the afflicted nerve, which is notably smaller in size compared to the unaffected side. However, it is important to note that the extent of volume loss in various segments of the nerve carries distinct prognosis consequences. The occurrence of proximal atrophy is linked to vascular compression and exhibits a positive correlation with enhanced outcomes subsequent to microvascular decompression (MVD). Nevertheless, there is a notable correlation between distal atrophy and a considerably poorer prognosis following microvascular decompression (MVD) [20].

The objective of the study was to assess the enduring effectiveness of microvascular decompression (MVD) and to ascertain the variables that influence the outcome in individuals undergoing treatment for primary trigeminal neuralgia (TN). Only the instances that exhibited a distinct neurovascular conflict, characterized by vascular contact and/or compression of the root entrance zone of the trigeminal nerve, were identified during surgery and subsequently treated with "pure" microvascular decompression (decompression of the root without any extra lesioning or cutting of the neighboring rootlets), were included in the study. The administration of pure microvascular decompression (MVD) has been found to provide individuals suffering from primary trigeminal neuralgia (TN) with a 73.41% likelihood of achieving long-term (15 years) remission from neuralgia. The identification of a distinct and evident vascular compression during surgical intervention, and potentially, though not yet consistently, on preoperative magnetic resonance imaging, is indicative of a success rate over 90.1% [21].

There is a limited number of scholarly articles available that discuss the treatment of primary Trigeminal Neuralgia by the method of microvascular decompression (MVD). These publications often lack extensive data from large sample sizes and long-term observation periods. Additionally, the utilization of Kaplan-Meier (K-M) analysis is infrequently employed in these studies. No specific focus was given to the comparative analysis of the efficiency of Microvascular Decompression (MVD) in treating Trigeminal Neuralgia with typical (characterized by paroxysmal pain only) and atypical features (characterized by the presence of a constant background of pain). Pure microvascular decompression (MVD) presents a viable treatment option for individuals suffering from Trigeminal Neuralgia caused by vascular compression, resulting in a durable resolution in 75% of instances. Both conventional and atypical presentations have positive responses to microvascular decompression (MVD), which challenges the traditional belief that an atypical presentation negatively impacts surgical outcomes [22].

A retrospective study was undertaken to assess the dimensions of the trigeminal nerve on magnetic resonance imaging (MRI) scans of individuals diagnosed with unilateral trigeminal neuralgia. The findings suggest that noninvasive imaging techniques can be used to visualize the degeneration of the trigeminal nerve in individuals diagnosed with trigeminal neuralgia [23].

Idiopathic trigeminal neuralgia (TN) is attributed to neurovascular compression and is frequently associated with morphological alterations in the trigeminal nerve. The objective of this study was to objectively assess the extent of atrophic alterations in trigeminal nerves among patients diagnosed with trigeminal neuralgia (TN). Additionally, the study aimed to explore whether the presence of nerve atrophy has any impact on the effectiveness of microvascular decompression (MVD) as a treatment method. Traction neuritis (TN) is characterized by the presence of atrophy on the nerve that is impacted by the condition. Moreover, a stronger degree of nerve atrophy is correlated with a more pronounced trigeminal nerve indentation and a more favorable long-term prognosis after microvascular decompression (MVD) [24].

Prior research has established a strong correlation between classical trigeminal neuralgia (TN) and severe Neurovascular Compression (NVC) that leads to displacement or atrophy of the trigeminal nerve. There is a lack of research examining the correlation between the clinical attributes of trigeminal neuralgia (TN) and severe neurovascular compression (NVC). The occurrence of severe neurovascular compression (NVC) was found to be more common in men compared to women. Women, on the other hand, may exhibit a higher likelihood of having alternative disease aetiologies that either cause or contribute to trigeminal neuralgia (TN). There was no observed correlation between severe Neurovascular Compression (NVC) and either age or disease duration [25].

Conclusion

This study concluded that individuals with primary trigeminal neuralgia (TN) have significantly reduced grey matter volume (GMV) and ipsilateral

trigeminal nerve (TGN) size. Our findings suggest a possible link between cranial nerve function and cerebral cortex anatomy by establishing a convincing correlation between the ipsilateral TGN and GMV in the left insula. Furthermore, our results show that TGN volumetric measurements are linked to different aspects of pain in TN patients. These findings suggest a possible imaging biomarker for monitoring therapy responses in this condition and add to our understanding of the complex nerve system abnormalities seen in primary TN, providing important insights for future research and clinical care.

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