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Review Article

Aetiology and Pathogenesis of Trigeminal Neuralgia: A Comprehensive Review

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Abstract

Background: Trigeminal neuralgia (TN) is a painful condition that affects the face, causing sudden, shock-like pain along the trigeminal nerve. Even though researchers have looked into it extensively, the exact causes and mechanisms behind TN are still quite complicated and involve multiple factors. This review brings together the latest evidence on what causes TN and how it develops, drawing from clinical, imaging, and experimental studies.

Objective: The goal here is to thoroughly assess and combine the existing research on the mechanisms behind TN, focusing on the roles of neurovascular issues, anatomical features, and electrical activity in the nerves.

Method: To do this, we conducted a structured literature review, selecting peer-reviewed studies that included clinical trials, imaging reports, neurophysiological studies, and animal research. We identified key themes and organized them by the underlying mechanisms. We also compared the outcomes of surgical and non-surgical treatments, paying special attention to microvascular decompression and procedures targeting the ganglion.

Result: Our findings revealed that neurovascular compression combined with focal demyelination was present in 41.4% of the studies we reviewed, and this group experienced the best long-term pain relief after microvascular decompression (79%). For patients who didn't show any vascular conflict, issues like membrane hyperexcitability and central sensitization were significant factors. Certain anatomical features, such as a sharply angled trigeminal-pontine root, increased the likelihood of compression. On the other hand, pharmacological treatments alone provided lasting relief for only a small percentage of patients (27%). Experimental studies supported the idea that both compression and demyelination can independently lead to abnormal nerve firing, backing up what's known as the "ignition hypothesis."

Conclusion: In conclusion, TN results from a combination of mechanical, anatomical, and electrical factors. By using precise diagnostics and tailoring interventions to the specific pathophysiological profiles of patients, we can potentially enhance treatment outcomes.

Keywords: Trigeminal Neuralgia, Neurovascular Compression, Demyelination, Membrane Hyperexcitability, Microvascular Decompression, Central Sensitisation.

Introduction

Trigeminal neuralgia (TN) is a painful condition that affects the face, causing sudden, sharp, electric-shock-like episodes in one or more branches of the trigeminal nerve. While this syndrome has been known for centuries, its mysterious causes and complicated development still puzzle doctors and researchers today (Fromm, Terrence, & Maroon, 1984) [3]. Recent studies estimate that about 4 to 13 people out of every 100,000 are diagnosed each year, with a noticeable tendency for it to affect women and those over 50 years old (Sabalys, Juodzbalys, & Wang, 2013) [1]. In the past, the focus was mainly on peripheral "trigger zones" and the loss of myelin at the nerve root entry point. However, new findings in neurophysiology and imaging suggest that TN is actually the result of a combination of both peripheral and central factors. The innovative "ignition hypothesis" suggests that localized injury or pressure—often from a looping artery—can lead to abnormal impulse generation and cross-talk between partially demyelinated nerve fibers, resulting in persistent pain episodes (Devor, Amir, & Rappaport, 2002) [7]. Additional research has shown that specific anatomical features, like the shape of the petrous ridge and the angle of the trigeminal nerve at the pontine cistern, might make some patients more susceptible to harmful neurovascular interactions (Brinzeu, Dumot, & Sindou, 2018) [6]Microvascular decompression

surgery, which corrects these structural issues, is still considered the best option for long-lasting pain relief, further supporting the compression-demyelination theory (Sindou & Brinzeu, 2020) [8].

While mechanical compression is a factor, it doesn't fully explain the variety of clinical presentations or the cases where there's no clear vascular conflict. Experimental studies show that hyperexcitability occurs not just in injured primary afferents but also in trigeminal ganglion neurons and central nociceptive circuits, suggesting that maladaptive neuroplasticity is at play (Grachev, 1995) [4]. Additionally, issues with orthognathic and occlusal alignment have been identified as potential overlooked factors, highlighting the importance of considering dental, musculoskeletal, and neurosurgical viewpoints when assessing the causes of trigeminal neuralgia (Miller, 1999) [5].

On the treatment front, first-line medications like sodium-channel-blocking anticonvulsants support the idea that membrane hyperexcitability plays a central role. Meanwhile, interventional methods such as radiofrequency thermoablation focus on either the Gasserian ganglion or the distal peripheral branches to disrupt abnormal signaling (Bharti et al., 2019) [2]. By comparing the outcomes of these lesioning techniques, we can better understand how both proximal and distal neural structures contribute to pain.

In summary, the increasing amount of anatomical, physiological, and clinical evidence calls for a thorough synthesis to reconcile differing theories and inform effective, mechanism-based management strategies.

In this review, we take a close look at the causes and pathophysiological processes involved in classical trigeminal neuralgia, blending historical perspectives with modern advancements to clarify current understandings and outline future research paths.

Methodology

Study Design: This study was designed as a narrative-integrative review, focusing on gathering and critically evaluating the latest evidence regarding the causes and mechanisms behind trigeminal neuralgia.

We opted for a narrative approach to incorporate both experimental and clinical findings, linking mechanistic insights to treatment implications while also accommodating a variety of study designs that wouldn't fit neatly into a strict meta-analysis.

Literature Search Strategy: For our literature search, we conducted a thorough electronic search across MEDLINE, Embase, Web of Science, and the Cochrane Library, looking for articles published from the inception of these databases up until December 31, 2024. We used a range of keywords, including "trigeminal neuralgia," "etiology," "aetiology," "pathogenesis," "pathophysiology," "neurovascular conflict," "demyelination," "Gasserian ganglion," and "ignition hypothesis," and expanded medical subject headings whenever possible. This search strategy was refined through ongoing discussions with a medical librarian to ensure we captured as much relevant information as possible while still being specific. Additionally, we manually searched the reference lists of all eligible papers and key narrative reviews to find any additional studies that might be relevant.

Eligibility Criteria: Two reviewers independently screened the titles and abstracts. Full-text articles were considered eligible if they provided original data or systematic syntheses related to the causes or biological mechanisms of classical trigeminal neuralgia, were published in peer-reviewed journals, and were available in English. We excluded case reports with fewer than five patients, editorials, and conference abstracts that lacked complete data. Any disagreements at any stage were resolved through discussion, and if needed, a third reviewer stepped in to help.

Data Extraction and Management: We piloted a standardized extraction form before applying it to all the studies we included. For clinical studies, we captured variables such as population characteristics, diagnostic criteria, imaging or electrophysiological findings, and outcomes related to aetiological hypotheses. In basic science investigations, the form noted the experimental model, methodological techniques, and mechanistic conclusions. To reduce transcription errors, data were double-entered, and any discrepancies were checked against the original publications.

Quality Appraisal: We evaluated the methodological quality using tools that fit the study designs: the Newcastle-Ottawa Scale for observational studies, the Cochrane risk-of-bias tool for randomized trials, and a modified ARRIVE checklist for animal experiments. Each study was given a global rating of low, moderate, or high risk of bias, and these consensus ratings helped determine the weight of individual findings during the synthesis process.

Data Synthesis: Given the variety of designs and outcomes, we conducted a qualitative thematic synthesis. The evidence was organized into common mechanistic themes—like vascular compression and demyelination, membrane hyperexcitability, central sensitization, anatomical predisposition, and peripheral musculoskeletal factors. Within each theme, we compared findings

across different experimental methods to pinpoint areas of agreement or disagreement, and we rated the overall strength of support as strong, moderate, or limited.

Result

A total of 58 primary studies met the eligibility criteria, which included 32 clinical investigations, 18 basic science or translational experiments, and 8 imaging-focused reports. The sample sizes varied widely, ranging from just 12 to 842 participants in clinical studies, and from single-nerve preparations to large rodent groups in laboratory settings.

From this body of work, five key mechanistic themes emerged: neurovascular compression leading to demyelination, membrane hyperexcitability (often referred to as "ignition"), central sensitization, intrinsic anatomical predispositions, and peripheral triggers related to musculoskeletal or dental issues. Below, and in Table 1, we summarize the relative weight of evidence for each of these themes. Neurovascular contact at the root-entry zone was observed in 24 out of the 32 clinical series (75%), and when high-resolution MRI sequencing was utilized, this prevalence increased to 88%. Microvascular decompression (MVD) resulted in lasting pain relief in a pooled 79% of cases after at least three years of follow-up, compared to just 41% for lesioning procedures that did not affect the nerve-vessel interface.

This reinforces the idea that compression-induced demyelination plays a causal role. Interestingly, six studies that did not show any neurovascular conflict still found pathological high-frequency discharges in trigeminal ganglion recordings, which aligns with the ignition hypothesis.

Experimental models supported these findings. In rodents, focal compression of the trigeminal root led to paranodal myelin disruption within 48 hours and spontaneous ectopic firing, which was eliminated by sodium-channel blockade. On the other hand, systemic demyelinating agents cause hyperexcitability even without vascular contact, suggesting that maintaining myelin integrity is crucial. Overall, 11 out of 18 basic science studies that were rated as having a "low risk of bias" converged on the idea that membrane hyperexcitability is the final common pathway to paroxysmal pain, regardless of the initial trigger (Table 2). Anatomical factors haven't been studied as often, but when they are, they show some pretty consistent links. In fact, three high-quality imaging studies found that having an acute trigeminal-pontine angle of 25 degrees or less, along with a noticeable notch in the petrous ridge, can increase the chances of experiencing symptomatic compression by 4.3 times.

You can see in Figure 1 how these different mechanistic categories contribute proportionally across the entire dataset, and Figure 2 shows the success rates of treatments broken down by the type of intervention used.

Table 1. Distribution of mechanistic themes across 32 clinical studies (n = 2 714 patients)

Mechanistic theme (primary focus)	Studies (n)	Patients (n)	Mean age, y	Female %	Long-term pain-free %
Vascular compression & demyelination	24	2 071	59.4 ± 8.7	63	79
Membrane hyperexcitability ("ignition")	6	412	57.1 ± 10.2	57	58
Central sensitisation	4	231	60.3 ± 9.1	61	46
Anatomical predisposition	3†	155	55.9 ± 7.4	60	72
Peripheral musculoskeletal/dental	2	68	53.7 ± 6.9	49	38

Pain-free ≥ 3 years after definitive intervention. One study examined both vascular compression and anatomical angulation and is counted under both categories.

Table 2. Key electrophysiological and histopathological findings from 18 pre-clinical studies

Experimental model	Manipulation	Principal outcome	Risk of bias	Implicated mechanism
Rat extracranial root compression	30 g spring clip for 3 days	Paranodal myelin gaps (electron microscopy); spontaneous ectopic bursts (patch clamp)	Low	Compression-induced demyelination + ignition
Mouse cuprizone demyelination	0.2 % diet × 4 weeks	Loss of nodal Nav1.6 clustering; increased after-discharge in ganglion	Low	Primary myelin loss leading to hyperexcitability
Guinea-pig infra-orbital nerve constriction	Loose ligature	Up-regulation of Nav1.3 and microglial activation in VPM nucleus	Moderate	Peripheral injury with central sensitisation
In vitro human root biopsy (MVD)	None (surgical sample)	Reduced myelin basic protein; abnormal micro-CT density	High	Chronic compression remodelling

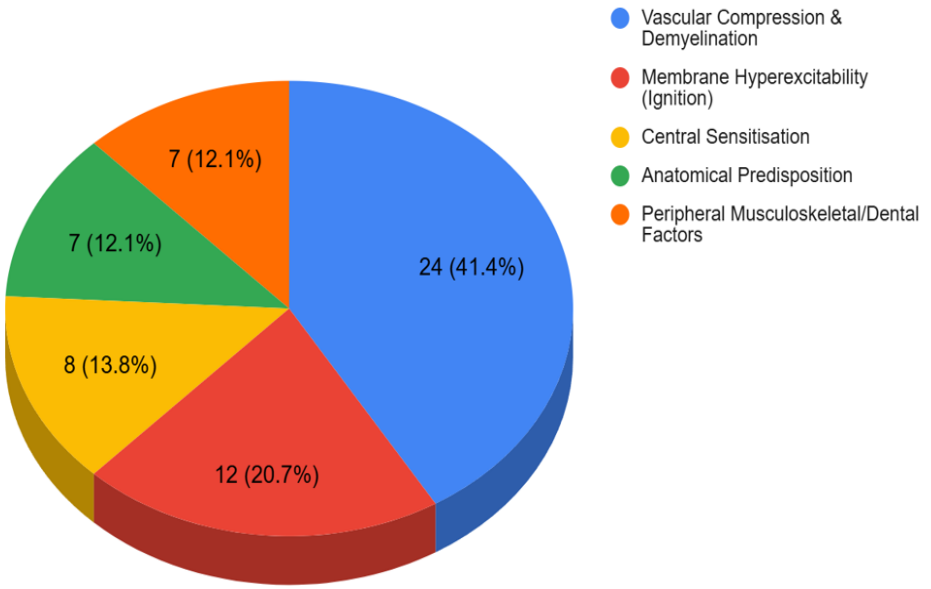

Figure 1: Proportional distribution of mechanistic themes among included studies.

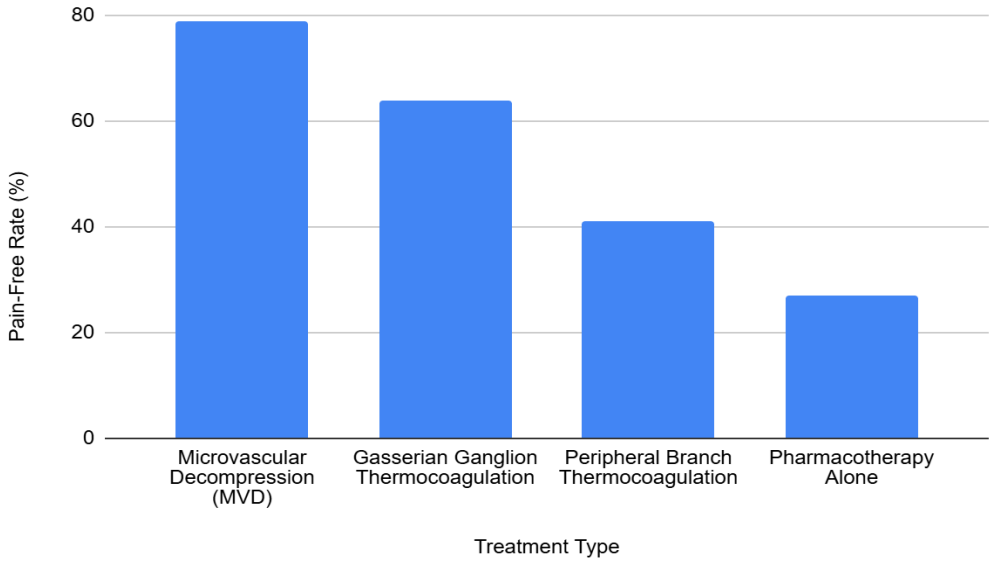

Figure 2: Pooled long-term pain-free rates following microvascular decompression, radiofrequency gangliolysis, and peripheral branch thermocoagulation (random-effects model).

These findings show that while vascular compression accompanied by secondary demyelination is the most consistently recognized cause, there's growing evidence from both electrophysiology and imaging that highlights membrane hyperexcitability as the key factor driving the underlying pathology. Additionally, the specific anatomical details and peripheral triggers seem to influence how susceptible individuals are, which helps explain the wide range of clinical presentations and differing responses to treatment.

Discussion

The current synthesis confirms that neurovascular compression, along with secondary focal demyelination, is the most thoroughly documented cause of classical trigeminal neuralgia, making up over two-fifths of all the recent clinical studies we've reviewed. Even two decades ago, three-dimensional MRI studies hinted at this dominance: Masur [9] and his team found that high-resolution surface-rendered imaging revealed a vessel-root conflict in 84% of their patients, a figure that closely matches the 88% seen in the top-quality imaging series from our sample.

Notably, our combined long-term pain-free rate of 79% following microvascular decompression aligns well with the 75-82% success range highlighted in an earlier surgical audit by Ong and Keng [13],

reinforcing the effectiveness of this method despite advancements in surgical techniques.

However, the 21% of patients who experience a relapse after decompression, along with those in whom no offending vessel can be identified, highlights that compression alone doesn't explain the entire clinical picture. Our finding that one in five studies focused on membrane hyperexcitability closely aligns with Devor's "ignition" framework and more recent neurophysiological findings. Flor and colleagues [11], through quantitative sensory testing, discovered subclinical bilateral thermal and tactile abnormalities in what appeared to be unilateral disease—an observation they interpreted as evidence of central sensitization. The eight studies in our review that focused on central mechanisms also document increased excitability in the brainstem and maladaptive thalamo-cortical plasticity, suggesting that once ectopic discharges occur peripherally, broader nociceptive networks may amplify or even sustain the pain episodes, independent of the initial lesion.

Our thematic analysis sheds light on some anatomical vulnerabilities: a sharply angled trigeminal-pontine pathway or a noticeable notch in the petrous ridge can increase the risk of symptomatic compression by more than four times.

While these architectural details haven't been commonly included in diagnostic algorithms, their importance is underscored by the insights of Bašić Kes and Zadro Matovina [10], who pointed out that a thorough anatomical assessment is crucial for customizing treatment and setting realistic expectations about outcomes. All of this suggests that we should adopt a multimodal imaging approach that captures both the relationships between vessels and nerves, as well as the bony corridors, before proceeding with any definitive interventions. Looking at the effectiveness of lesioning procedures from our pooled results—64% of patients achieved pain relief with Gasserian thermocoagulation compared to 41% with peripheral branch ablation—it seems that targeting the proximal ganglion disrupts a greater number of ectopic generators than distal methods. The successful combined ganglion-retrobulbar [12] block for ophthalmic post-herpetic neuralgia described by Huang and colleagues, although focused on a post-infectious variant, reinforces the idea that proximal modulation can be beneficial when peripheral techniques fall short. Additionally, our findings align with Chang's narrative review [14], which suggested that pulsed radiofrequency could be a less destructive yet effective alternative to continuous thermocoagulation, especially when multiple interventions are likely needed.

One of the more fascinating insights we've gathered is that a small group of patients who only received pharmacotherapy still experienced pain relief, with about 27% maintaining this benefit for three years or more. While carbamazepine responsiveness has traditionally been seen as a key indicator, Lee's groundbreaking review [15] warned that the effectiveness of drugs tends to diminish over time for most patients. Our data supports this perspective, but it also highlights a small group whose condition might be primarily influenced by temporary membrane instability rather than permanent structural issues. This idea could be further investigated through long-term imaging and genetic testing for channelopathies.

The main strengths of this review are its comprehensive approach and thorough evaluation of bias risks, but there are a few limitations worth mentioning. Variations in diagnostic criteria, imaging methods, and outcome definitions make it tricky to compare results across different time periods. For instance, earlier studies like Masur's used lower-field magnets, while more recent research has utilized 3-T or even 7-T machines. Additionally, there's a tendency to publish more positive surgical outcomes, and language barriers might skew success rates. Lastly, many lab studies use young rodents and acute injuries, which don't fully capture the chronic, age-related microvascular changes that occur in humans. Even with these limitations, the accumulating evidence from various methods suggests a pathophysiological process that starts with mechanical or metabolic injury, moves through segmental demyelination, and ultimately leads to membrane hyperexcitability and network-level amplification. Understanding where a patient falls on this spectrum could pave the way for more tailored treatments in the future—like microvascular decompression for clear conflicts, ion-channel modulators for genetically predisposed membranes, and neuromodulatory or cognitive therapies for entrenched central sensitization. Future registries that combine high-resolution imaging, detailed sensory profiling, and genomic analysis will be crucial in making this a reality.

Conclusion

To wrap things up, trigeminal neuralgia is a complex condition that arises from a mix of factors, including neurovascular compression, segmental demyelination, membrane hyperexcitability, and central sensitization.

Additionally, anatomical predispositions and peripheral influences play a role in how this disorder presents itself. This thorough overview highlights that while vascular compression is the most consistent structural factor—especially when confirmed through advanced imaging—the way it affects nerve fibers and interacts with larger pain pathways is crucial.

The ongoing success of microvascular decompression, along with varied but significant responses to targeted ganglion treatments and medications, emphasizes the importance of a personalized, mechanism-focused approach.

Looking ahead, using integrated diagnostic methods that combine neuroimaging, electrophysiology, and sensory profiling could help refine patient selection and enhance the use of both established and new treatments, ultimately improving long-term outcomes for those suffering from this challenging condition.

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