

Trigeminal Neuralgia

Markowitz, Yarden

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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Yarden Barayev

Trigeminal Neuralgia

Graduation thesis



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List and explanations of abbreviations used in the paper

BDNF - brain-derived neurotrophic factor

CGRP - calcitonin gene-related peptide

CRF - conventional radiofrequency

IASP - International Association for the Study of Pain

ICHD-3 - The International Classification of Headache Disorders, 3rd edition

IHS - International Headache Society

MRI - magnetic resonance imaging

MS - multiple sclerosis

MVD - microvascular decompression

NGF - nerve growth factor

NVC - neurovascular compression

PRF - pulsed radiofrequency

REZ - root entry zone

SC - Schwann cell

SP- substance P

SCA - superior cerebellar artery

TN - trigeminal neuralgia

VGSC - voltage-gated sodium channels

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1. Sažetak

Neuralgija trigeminusa (TN) je bolest definirana karakterističnom simptomatologijom. Obično se opisuje kao jaka, ponavljajuća bol u području lica koja značajno utječe na kvalitetu života onih koji su pogođeni ovim poremećajem. Ovaj rad daje pregled trenutno dostupne literature za TN. Međunarodno društvo za glavobolju (IHS) kategoriziralo je neuralgiju trigeminusa kao klasičnu, sekundarnu ili idiopatsku s obzirom na etiologiju bolesti. Dijagnoza se temelji na kliničkoj slici dok se pomoću magnetske rezonance isključuju sekundarni uzroci. U diferencijalnoj dijagnozi najčešće su neuropatija trigeminusa i atipična bol lica. U liječenju trigeminalne neuralgije primjenjuju se farmakološke i nefarmakološke metode. Ovaj diplomski rad na sažet i razumljiv daje pregled etiologije, kliničke slike, postavljanje dijagnoze i liječenja TN-a.

2. Summary

Trigeminal neuralgia (TN) is a disease defined by its characteristic symptomatology. It is commonly described as severe, recurring facial pain, impacting the quality of life for those who are affected by this disorder. This thesis reviews the currently available literature for TN. The International Headache Society (IHS) has categorized trigeminal neuralgia as either classical, secondary, or idiopathic according to the presence and nature of the underlying etiology. The diagnosis is predominantly based on clinical symptoms, followed by an magnetic resonance imaging (MRI) to exclude secondary causes. Trigeminal neuropathy and atypical facial pain present conditions that resemble trigeminal neuralgia; a comparison and distinction between these conditions and TN is made. There is a wide spectrum of therapeutic approaches for TN that are considered in this article, ranging from pharmaceutical to non-pharmaceutical treatments. This thesis aims to provide a compact and comprehensible overview of the causes, symptoms, diagnosis, categorization, and treatment of TN.

3. Introduction

In the second century AD, Aretaeus of Cappadocia first wrote about trigeminal neuralgia, which he characterized as excruciating facial agony. John Fothergill, however, gave a more detailed description of its symptoms in 1773. He described trigeminal neuralgia as being marked by unilateral face pain triggered by routine tasks. Furthermore, he noted the symptoms had a characteristic sudden beginning and end (1). The usage of words like "tic douloureux" interchangeably with TN has historically caused misunderstandings in the profession, making it more difficult to understand the illness and to research this disorder (2). Throughout the 18th and 19th centuries, TN has been further distinguished from other facial aches, such as toothaches. Furthermore, a better understanding of this disorder has enabled the development of modern surgical treatments. For instance, microvascular decompression has been introduced as a result of the discovery in the 20th century that vascular compression of the trigeminal nerve may be the cause of trigeminal neuralgia. Furthermore, it was at that time that MS was linked to trigeminal neuralgia. Notably, the pharmacological management of epilepsy was significantly advanced by that time and anticonvulsants such as carbamazepine have been introduced. The therapeutic effect of this group of drugs extends beyond the treatment of neuropathic pain (1).

At present, trigeminal neuralgia is commonly encountered by dentists and neurologists alike (3). The interchangeable usage of words such as "tic douloureux" with TN has historically confused the profession, making comprehension and research more difficult as there has been no uniform understanding of the nature of TN. According to the International Classification of Headache Disorders (ICHD), TN

is described as recurring unilateral face pain that is brought on by typically non-harmful stimuli (4). Furthermore, clinical presentation includes sudden, piercing, and acute pain manifesting in discrete occurrences or bursts, interspersed with periods without pain (1, 4). The International Headache Society classifies TN as idiopathic, secondary, and classical. The hallmark of classical TN is neurovascular compression, which is usually identified on magnetic resonance imaging (MRI) or during surgery. In contrast to classical TN, secondary TN involves a known underlying illness that gives rise to this condition. Idiopathic trigeminal neuralgia is diagnosed when other forms of TN have been excluded. In this type, neither MRI nor electrophysiological testing reveals any discernible abnormalities (4). The pathophysiology of TN involves vascular contact near the dorsal root entry zone as well as demyelination processes near the pons (3, 5, 6). Contributing factors to TN include MS, tumors, and genetic predisposition. Identifying differences in etiology can help distinguish between typical and atypical TN (1, 2, 7). The diagnosis of TN is primarily based on the clinical symptoms as described by the patient (7). A crucial part of the diagnostic process is the distinction between classical, secondary, and idiopathic TN using MRI (4,7).

TN has the potential to negatively affect individuals with this condition, manifesting in difficulties managing daily activities. TN symptoms have the potential to impact mental health (5). Treatment strategies range from non-invasive to invasive. Options regarding the former include predominantly pharmaceutical options, most importantly carbamazepine. Invasive methods of treatment are only considered when drug therapy has proven to be ineffective.

4. Epidemiology

Trigeminal neuralgia affects between 4 and 28.9 persons per 100,000 individuals worldwide (8). The population-wide epidemiological incidence of TN, determined over a lifetime span, is about 0.3% (9). Of all TN patients, idiopathic cases are the most common, accounting for 80–90% of cases (3). Even though the prevalence of TN is low within the general population, those individuals who complain about facial pain are likely to have trigeminal neuralgia (2).

The illness usually first appears in individuals between the ages of 40 and 60, however, it can happen earlier (3). The incidence rate varies depending on geography, with an average age of 53 for people diagnosed with TN (6). The female-to-male ratio for classical TN is 3:2, pointing to the fact that women are more likely than men to have this disorder. A sex difference is not seen in secondary TN. Concerning secondary TN, the onset age is usually 51 years, in contrast to classical TN, where it is normally 63 years (10).

5. Etiology and Pathophysiology

The trigeminal nerve originates on the mid-lateral surface of the pons. At the trigeminal nerve root entry zone (REZ), namely in the pontine area, the trigeminal nerve and the superior cerebellar artery (SCA), a branch of the distal portion of the basilar artery, converge. This is the location of the trigeminal nerve's emergence from the brainstem, as well as the point at which the SCA approaches or comes into contact with the nerve, possibly causing compression or irritation that could exacerbate trigeminal neuralgia (11). After emerging from the pons, the trigeminal nerve reaches the Gasserian ganglion, which is located in the Meckel cave on the floor of the middle cranial fossa (12). The trigeminal nerve continues its path to the face, giving rise to its three branches: the ophthalmic, maxillary, and mandibular nerves (13). There, it supplies the face with sensory innervation by all three branches and the muscles of mastication with motor fibers by the mandibular nerve (13, 15). Each of the three branches of the trigeminal nerve innervates about one-third of the craniofacial dermatome (14). The ophthalmic branch of the trigeminal nerve provides sensory branches to the skin of the eyebrow, eyelids, forehead, and nose; the tentorium cerebelli, dura mater, and the posterior area of the falx cerebri; the ciliary body, cornea, and iris; the lacrimal gland and conjunctiva; and portions of the nasal cavity, sphenoidal sinus, and frontal sinus mucous membrane (15). The mandibular and maxillary branches of the trigeminal nerve innervate the oral cavity. The hard and soft palates, as well as the upper lip and teeth, provide input to the maxillary branch. The mandibular branch receives input from the bottom part of the oral cavity, which includes the tongue, lower lip, teeth, jaw, and numerous mucous membranes. The mandibular branch is also the source of the trigeminal nerves' exclusive motor output, which empowers the motions of the jaw required for chewing

and swallowing (14). The area of pain in trigeminal neuralgia is confined to the distribution of the trigeminal nerve in its three branches (13).

As was previously noted, trigeminal neuralgia is often linked to compression or irritation of the trigeminal nerve (5, 6). Although the precise cause of TN is not known, several suggestions have been made for the hypothetical cause of this disorder. According to the most widely accepted explanation, compression of the trigeminal nerve root near the dorsal root entry zone by a blood vessel is frequently the origin of trigeminal neuralgia. The neural compression induces demyelination of its sensory fibers, triggering nerve excitability and the characteristic TN discomfort (1, 3).

The pathophysiology of TN primarily involves the focal demyelination of primary afferent nerve fibers located close to the trigeminal root (2). Axonal modifications, Schwann cell destruction, and demyelination are examples of structural changes brought on by vascular compression (16).

According to the "ignition hypothesis", injured neurons become hyperexcitable, which causes abnormal impulse creation and amplification. Ectopic activity and cold allodynia/hyperalgesia are caused by the dysregulation of potassium channels and voltage-gated sodium channels (VGSCs) in hypoxic nerve fibers. Studies on neuroimaging show that TN patients have aberrant patterns of brain activity as well as anatomical and functional changes in the white and gray matter volumes (16).

Schwann cells, which form the myelin sheath of the trigeminal nerve, participate in the repair and regeneration of peripheral nerves. For instance, they secrete neurotrophic factors like brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF), contributing to neuron nourishment. Schwann cells are, however,

heavily involved in the process of demyelination as well. There are two main components to the link between trigeminal neuralgia (TN) and Schwann cells (SCs). First, upon damage to the trigeminal nerve, SCs are activated and play a role in axonal degeneration and demyelination, which ultimately results in TN. Furthermore, chemicals that cause hypersensitivity to pain are released by activated SCs, which lower the pain threshold and cause TN (7).

Trigeminal nerve degeneration triggers neurons in the trigeminal ganglion and causes aberrant impulse production. Trigeminal nerve demyelination is largely caused by SCs, which break down and engulf the myelin sheath, finally leading to TN. The demyelination process gives rise to ectopic nerve impulses that cause the pathognomonic symptoms of acute, stabbing, or electric shock-like pain. Central sensitization can be the ultimate consequence of continuous ectopic nerve firing (7).

Activated stem cells also control the expression of TN-related substances such as calcitonin gene-related peptide (CGRP). Synthesized by sensory neurons, CGRP facilitates nerve healing and central excitability; its overexpression in the vicinity of nerve injury sites and its interaction with Schwann cells are thought to result in TN symptoms (7).

Following nerve damage, SCs produce substance P (SP), a crucial mediator of pain generation and neuropathic pain, which aids in the development of TN. The release of neurotrophic factors, cytokines, and extracellular matrix by SCs raises local SP levels even more, aggravating symptoms of TN (7).

As Schwann cells undergo changes following a nerve injury, they affect their interaction with nerve axons. This transformation can potentially lead to TN. By

inducing demyelination and secreting neurotrophic substances, Schwann cells are likely involved in both inducing and possibly mitigating neuropathic pain (7).

The pain in trigeminal neuralgia is considered to be due to a complex interaction of neurotransmitters, peripheral receptors, and neuromodulators. As a consequence of the recurrent or continuous pain in trigeminal neuralgia, centralization of pain from the peripheral trigeminal nerves occurs via the spinal trigeminal nucleus (13).

MS presents a well-established etiology for secondary TN. In MS, demyelination of the trigeminal nerve occurs specifically within the central nervous system and is considered to be the driving factor in the development of trigeminal neuralgia symptoms. Nevertheless, TN is found only in a minority of MS cases. Secondary TN can also be considered the result of tumors in the posterior fossa. Common examples are meningiomas or neuromas, which may compress the trigeminal nerve. Other, less understood factors might contribute to secondary TN. These could include genetic predispositions or other systemic diseases that affect nerve function (1). Indeed, familial patterns have been observed in TN cases, pointing to the possibility of a genetic component to the condition's development (8).

The pathophysiology underlying the difference between TN and atypical TN may be due to variances in nerve compression or damage. Patients with atypical TN may have a history of interventions or chronic compression that has led to more widespread alterations in nerve function. Thus, a broader distribution of allodynia and a detectable sensory loss may be present, which can be established through bedside tests (1).

6. Definition and Symptoms

Trigeminal neuralgia can be seen as a severe version of paroxysmal neuralgia. The pain is localized along the trigeminal nerve distribution (7). TN is defined as "a sudden, usually unilateral, brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve," according to the International Association for the Study of Pain (IASP) (17). Affected patients often describe the pain as barely bearable and feeling like a knife cutting or needling (7). In addition, individuals characterize the pain as electric shock-like or shooting. TN symptoms normally occur unilaterally (3). The right side of the face is affected by TN symptoms more frequently than the left (7). Bilateral TN is mostly observed in secondary TN linked to multiple sclerosis (2).

The severe pain associated with TN is described as abrupt and sporadic (5). Speaking, chewing, or gentle touching are all activities that, at first glance, do not seem to have the potential to trigger pain. They can, however, induce TN symptoms, resulting in increased anxiety in affected patients. Furthermore, their ability to function can be significantly compromised (18). It has been observed that even vibrations or exposure to cold air might cause TN symptoms (1). Even though these pain episodes might be short, they can potentially last up to several minutes. They can happen up to 70 times a day, and there is mostly no identifiable pattern of symptom occurrence (5). Physicians may notice temporary tics or spasms in the muscles during paroxysms in some patients (10). Refractory intervals occur in certain TN patients, meaning they experience episodes when the pain cannot be provoked (5). Notably, around one-third of individuals may feel pain at night (5).

When compared to its typical counterpart, atypical TN seems to be a more complex disease. Severe, lancinating, episodic, unilateral face pain characterizes this form of TN. Patients also report persistent, underlying discomfort that may not completely subside in between the acute bursts of pain (9). This chronic pain, which is usually unilateral like typical TN, presents as a burning or smarting feeling. Therefore, atypical TN has the feature of continual pain as its hallmark for diagnosis. Even though the pain is milder than the episodic attacks, it is still noticeable. Similarly to typical TN, atypical TN also has pain episodes that can range in duration from seconds to minutes. On the other hand, atypical TN can present with a broader variety of pain stimuli than the conventional form. Atypical TN can be made worse by extra stimuli like temperature changes or drinking, even though both types can be brought on by similar behaviors like eating, talking, or touching one's face (1). Noteworthy, typical trigeminal neuralgia can eventually evolve into atypical trigeminal neuralgia. This is specifically true for patients who have had typical trigeminal neuralgia for a longer time (19).

The International Headache Society (IHS) has categorized trigeminal neuralgia as either classical, secondary, or idiopathic according to the presence and nature of the underlying etiology. Another way to classify trigeminal neuralgia is by focusing on the pattern of pain occurrence. Pain symptoms in trigeminal neuralgia can present either in paroxysms or continuously in the background. In the latter scenario, the disorder can also be classified as atypical trigeminal neuralgia (4).

Classical trigeminal neuralgia is caused by compression of the trigeminal nerve without being caused by another underlying disease. On neuroimaging, the finding of a blood vessel in contact with the trigeminal nerve or nerve root needs to be

accompanied by evidence of morphological abnormalities in the nerve root. The root entry zone is the typical location of neurovascular compression, with artery compression being more strongly linked to symptoms than vein compression (4). Furthermore, classical trigeminal neuralgia is the diagnosis made when certain anatomical abnormalities occur, which can potentially give rise to compression, displacement, distortion, indentation, or atrophy of the nerve (4,6). Studies have demonstrated a strong link between neurovascular contact and trigeminal neuralgia. Therefore, imaging studies, particularly MRI, are important in the assessment of trigeminal neuralgia to identify any neurovascular contact or structural abnormalities. About 50% of patients with TN have neurovascular contact with morphological changes (6).

Idiopathic, also commonly known as primary TN, is diagnosed when there is no identifiable cause for the condition (5, 6). Idiopathic trigeminal neuralgia is marked by absent abnormalities on MRI or electrophysiological studies. Vascular contact with the nerve root or trigeminal nerve can contribute to this diagnosis. Nevertheless, this finding is also commonly found in healthy patients. If this observation, however, occurs in the context of trigeminal neuralgia symptoms, this disorder is classified as idiopathic (4). Idiopathic TN may involve neurovascular contact without morphological changes or may even occur in the absence of any neurovascular contact (10). Idiopathic TN emerges either spontaneously or from an unknown source. Elaborate medical investigations typically reveal no specific cause apart from potential neurovascular compression near the nerve. In this category, clinical evaluations typically do not uncover any other neurological abnormalities (3).

Secondary TN applies when TN is a consequence of another known neurological disorder. Conditions such as MS, structural anomalies in the skull, or benign growths in the posterior part of the brain are common underlying causes (3, 4). Therefore, in contrast to idiopathic TN, secondary TN arises from underlying known pathological conditions (5, 6). Secondary TN is accompanied by morphological changes in the trigeminal nerve (5, 6). During neurological assessments of patients with this form of TN, deficits or abnormalities in the sensory functions of the trigeminal nerve are often detected (3).

7. Diagnosis

The primary method of diagnosing trigeminal neuralgia is clinical examination, which focuses on the distinct features and patterns of pain.

The International Headache Society describes the symptoms occurring in trigeminal neuralgia patients as “recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the TN, and triggered by innocuous stimuli.” Furthermore, the IHS states that “there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s)” (4). The latter feature is specifically present in cases of atypical trigeminal neuralgia (1, 4, 9). The pain occurs within isolated episodes, or paroxysms, and is interspersed with periods of no pain (1). The patient’s thorough description of their discomfort is by far the most important element for an accurate diagnosis and is essential in helping doctors differentiate TN from other types of facial pain. Furthermore, because TN symptoms are acute and recurrent, they are commonly misdiagnosed as dental pain, which results in needless dental procedures (2).

The diagnostic criteria for trigeminal neuralgia according to the 3rd edition of the International Classification of Headache Disorders (ICHD-3) are listed in Table 1.

Table 1. ICHD-3 diagnostic criteria for trigeminal neuralgia (4)

Trigeminal neuralgia
A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond ¹ , and fulfilling criteria C and D

- B. Pain has all of the following characteristics:
- a. lasting from a fraction of a second to 2 minutes²
 - b. severe intensity³
 - c. electric shock-like, shooting, stabbing, or sharp in quality

C. Precipitated by innocuous stimuli within the affected trigeminal distribution⁴

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

Notes:

1. In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes.
2. Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for >2 minutes.
3. Pain may become more severe over time.
4. Some attacks may be, or appear to be, spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomical location of the trigger, and/or other factors.

In TN, neurological examinations are often normal, yet reports of autonomic and sensory complaints have been noted. Careful evaluation in TN patients may reveal mild sensory loss, especially in those with a longer time that has passed since the diagnosis of trigeminal neuralgia (5).

The ICHD-3 diagnostic criteria for the subtypes of trigeminal neuralgia are presented in Tables 2-4.

Table 2. ICHD-3 diagnostic criteria for classical trigeminal neuralgia (4)

Classical trigeminal neuralgia

Trigeminal neuralgia develops without apparent cause other than neurovascular compression.
A. Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia
B. Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes ¹ in the trigeminal nerve root.
Note: 1. Typically atrophy or displacement.

Table 3. ICHD-3 diagnostic criteria for secondary trigeminal neuralgia (4)

Secondary trigeminal neuralgia
Trigeminal neuralgia caused by an underlying disease. Clinical examination shows sensory changes in a significant proportion of these patients.
A. Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain
B. An underlying disease has been demonstrated that is known to be able to cause, and explain, the neuralgia ¹
C. Not better accounted for by another ICHD-3 diagnosis. ²
Notes: 1. Recognized causes are tumors in the cerebellopontine angle, AV malformation, and multiple sclerosis. 2. MRI is best equipped to detect an underlying cause for secondary trigeminal neuralgia. Other investigations may include neurophysiological recording of trigeminal reflexes and trigeminal evoked potentials, suitable for patients who cannot undergo MRI.

Table 4. ICHD-3 diagnostic criteria for idiopathic trigeminal neuralgia (4).

Idiopathic trigeminal neuralgia
Trigeminal neuralgia with neither electrophysiological tests nor MRI showing significant abnormalities.
A. Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain
B. Neither classical trigeminal neuralgia nor secondary trigeminal neuralgia has been confirmed by adequate investigation including electrophysiological tests and MRI ¹
C. Not better accounted for another ICHD-3 diagnosis.
Note: 1. A contact between a blood vessel and the trigeminal nerve and/or nerve root is a common finding in neuroimaging in healthy subjects. When such a contact is found in the presence of trigeminal neuralgia but without evidence of morphological changes (e.g., atrophy or displacement) in the nerve root, the criteria for classical trigeminal neuralgia are not fulfilled and the condition is considered idiopathic.

Nonverbal clues can also be helpful in the diagnosing process because patients with severe TN frequently have increased sensitivity to face touch and may wince or interrupt speech owing to tics. When touched on the face, patients with other types of facial pain, such as trigeminal neuralgia, usually do not show these reactions (1).

TN diagnosis can be quite variable, and its classification is influenced by several criteria. The nature of the pain seems to be an important element in the course of this disease. Nevertheless, the official description of how the pain presents in trigeminal neuralgia makes it more difficult to correctly interpret patients who express

an even broader range of descriptive words about the nature of their pain. Therefore, it has been suggested to expand the description of symptoms for trigeminal neuralgia. In this way, the diagnosis of trigeminal neuralgia may become easier, and misdiagnoses may be reduced. Concretely, the quality of pain in trigeminal neuralgia can also be associated with remaining aftersensations. Furthermore, a certain degree of variability in pain is permitted in the further elaborated definition of trigeminal neuralgia. Limited facial movements when speaking as well as avoidance of touch are part of the expanded understanding of trigeminal neuralgia symptoms. Last but not least, sensory loss abnormality can be part of the broader symptomatology of this disorder (1).

Importantly, a patient's pain may, in certain situations, change over time and shift from one group to another. As mentioned earlier, for example, a typical TN case may exhibit atypical indications over time. Nevertheless, some instances may not exhibit conventional symptoms at first but respond effectively to carbamazepine, leading to the development of typical TN symptoms later on (1). As a result, TN can change over time, and identifying and comprehending the condition also depends heavily on the symptomatology of the past. This finding is underlined by the dynamic participation of Schwann cells in both the pathogenic and healing processes of trigeminal neuralgia (7).

To exclude secondary causes of trigeminal neuralgia, an MRI and magnetic resonance angiography needs to be performed. In cases where the results are unclear, neurophysiological diagnostic techniques such as evoked potential investigations and trigeminal reflex testing are important to successfully distinguish secondary TN from classical TN (2, 10).

The trigeminal reflexes include the blink reflex as well as the masseter inhibitory reflex (10). It is possible to distinguish between secondary TN and classical TN with the trigeminal reflex test, which includes both the blink reflex and the masseter inhibitory reflex. The former is a useful non-invasive diagnostic tool applied to identify both peripheral and central nervous system pathology (20, 21). This neurophysiological test can help determine the location and characteristics of the neuropathic illness as well as offer information on the health of the trigeminal nerve pathways. The blink reflex is a reflexive eye blink that is triggered by electrical impulses administered to the supraorbital nerve, which stimulates the trigeminal nerve. The orbicularis oculi muscles then cause the eye to blink (22, 23). An early, unilaterally induced short-latency response known as R1 occurs on the side of stimulation. The second component, known as R2, is a bilateral long-latency response that mimics the brainstem interneurons' activity (21).

The masseter inhibitory reflex is made up of two masseter muscle inhibition response phases triggered by mechanical or electrical stimulation in the mouth region. These are known as the early and late inhibitory reflexes, or masseter silent periods (24).

Reflexes are usually normal in classical TN, but problems with short-latency oligosynaptic reflexes may be more noticeable in secondary TN, suggesting that

large-myelinated fibers are more susceptible to compression and demyelination (10). An MRI is essential for excluding other possible reasons and locating any nerve compressions that may be present. Magnetic resonance imaging (MRI) can differentiate between patients with multiple sclerosis and those with secondary trigeminal neuralgia associated with tumors (5). The diagnosis of TN, particularly classical TN, can be supported by the efficacy of surgery and the presence of neurovascular compression (NVC) on imaging (3).

The presence of neurovascular contact as well as concomitant morphological changes are evaluated by MRI. Any blood vessel that makes contact with the trigeminal nerve without any discernible cerebrospinal fluid between them is considered to be NVC. A touch that causes the trigeminal nerve to compress, shift, distort, indent, or atrophy is referred to as causing morphological alterations (4, 25). Interestingly, neurovascular compression with accompanying morphological changes has been associated with an excellent microvascular decompression outcome (6).

8. Differential Diagnosis

A broad spectrum of pathological disorders, which include the sinuses, teeth, temporomandibular joints, eyes, nose, and neck, must be considered in the differential diagnosis of trigeminal neuralgia. Following a detailed clinical assessment and conversation with the patient, most alternative options to trigeminal neuralgia can usually be ruled out. Nevertheless, some illnesses need to be carefully evaluated because of their close resemblance to trigeminal neuralgia. These include various cranial neuralgias that can induce pain similar to trigeminal neuralgia. Examples are glossopharyngeal neuralgia, neuralgia of the nervus intermedius, superior laryngeal nerve neuralgia, and occipital neuralgia. Furthermore, trigeminal neuralgia is sometimes mistaken for conditions like giant cell arteritis, post-herpetic neuralgia, and specific headache forms like cluster headaches and different forms of migraine (1).

There are examples where specific neurological disorders or lesions in the brain and spinal cord of the central nervous system can cause symptoms that resemble the facial pain that people with TN feel. Nevertheless, these disorders are of central origin, and therefore their symptoms are classified as central pain. The etiology of these disorders is believed to be different from TN, despite the similarity of their symptomatology (1).

The following section will elaborate on trigeminal neuropathy and atypical facial pain as differential diagnoses of trigeminal neuralgia. All three conditions are broadly known in facial pain medicine, yet they can be mistaken among themselves.

8.1. Trigeminal Neuropathy

Trigeminal neuropathy is characterized by dull or acute, agonizing pain and can be unilateral or bilateral, in contrast to the usually unilateral involvement in trigeminal neuralgia, where the pain is rather described as stabbing and shooting. Persistence of pain is strongly linked to trigeminal neuropathy and is not usually found in trigeminal neuralgia, where the pain is of short duration and occurs within outbursts. The same is true for allodynia, as the symptomatology of trigeminal neuropathy includes pain from usually non-painful stimuli confined to the distribution of the trigeminal nerve as its core hallmark. Furthermore, sensory loss is common in trigeminal neuropathy, in contrast to trigeminal neuralgia, where lack of sensation is usually not part of its symptomatology (1).

The etiology of trigeminal neuropathy is linked to systemic disorders or structural lesions. Several causes of trigeminal neuropathy have been identified, such as severe vascular compression, neuroablative treatments, or direct nerve trauma (1). Hypoesthesia, which refers to a diminished feeling, and hypoalgesia, a term representing diminished pain sensation, both indicate axonal damage in the area of the trigeminal nerve and therefore the possibility of trigeminal neuropathy. Furthermore, both symptoms are not part of the common symptomatology of trigeminal neuralgia. As a result, hypoesthesia and hypoalgesia are crucial indicators for an underlying trigeminal pathology and demand further investigation and consideration of this alternate diagnosis (8). TN patients normally do not report pain that radiates beyond the area where the trigeminal nerve is distributed. Outside of the trigeminal area, pain may nevertheless be experienced in cases of trigeminal neuropathy (1). Heightened sensitivity to pain in a specific area should not be interpreted as hyperalgesia and accompanying nerve damage right away, as the perception of the patient can rather be explained by an increased focus on that given

area (8). Ordinarily, TN does not usually cause pain that lasts longer than several seconds. Unlike TN, patients with trigeminal neuropathy rarely report pain-free phases. A continuous ache with shooting sensations across several hours is commonly reported. Refractory periods are part of the clinical picture, specifically for trigeminal neuralgia. Trigeminal neuropathy is characterized by constant discomfort without any such intervals. A portion of patients with trigeminal neuralgia report spontaneous remission of symptoms during the course of the illness. Trigeminal neuropathy progresses slowly, and its symptoms usually do not disappear. Limited facial expressions when speaking and an aversion to contact are observed pain behaviors in TN. These habits can make a significant difference in the presentation of patients with trigeminal neuropathy who do not show reflexive actions. The explanation is that the intensity of pain symptoms is significantly higher in trigeminal neuralgia, as the ache has the potential to make a person cringe or stop talking. Patients with trigeminal neuropathy may still be capable of speaking normally despite their chronic discomfort, pointing to the differing pathophysiology between the two trigeminal nerve diseases. Typical TN is associated with a moderate blush, whereas trigeminal neuropathy can present with slightly more severe swelling and vasodilation (1).

8.2. Atypical Facial Pain

Even though the symptomatology of trigeminal neuralgia compared to that of atypical facial pain may be similar, the etiologies of both facial pain disorders are distinct from each other. Persistent, fluctuating, lancinating, and searing pain over time are hallmark symptoms characterizing atypical facial pain, which stand in contrast to the brief, paroxysmal, electric shock-like pain episodes that are pathognomonic for

trigeminal neuralgia (26, 27). With the use of high-resolution trigeminal sequences on MRI, TN is likely to be diagnosed in cases of trigeminal neurovascular conflict or underlying neurological diseases (27). The main characteristic of atypical facial pain is the lack of discernible anatomical abnormalities or evidence of neurovascular conflicts on imaging. Therefore, there are no conclusive diagnostic criteria for atypical facial pain (26). Depending on the presence of neurovascular conflict, TN is usually treated with medications such as carbamazepine and oxcarbazepine. Surgical treatments such as microvascular decompression or neuroablative operations may also be considered (27). Tricyclic antidepressants, MAO inhibitors, anticonvulsants, and behavioral therapy are the mainstays of treatment for atypical facial pain, whereas invasive procedures are usually not recommended. The McGill Pain Questionnaire (26) was developed as an effective diagnostic instrument for TN and atypical facial pain research.

The McGill Pain Questionnaire is a tool used to evaluate pain in a variety of medical disorders. It has been utilized in small-scale trials for patients diagnosed with TN or atypical facial pain. In 90% of the cases, the McGill Pain Questionnaire accurately predicted the diagnosis, indicating a high degree of precision. This implies that the questionnaire may be useful in differentiating between atypical face discomfort and classic TN. Although this measure appears to be useful in differentiating between atypical facial pain and TN, further validation from vaster population studies is mandatory to evaluate its efficacy and reliability (28).

9. Treatment

Depending on the severity and course of trigeminal neuralgia, pharmacological and surgical methods are used to treat this disorder.

Antiepileptic medications like carbamazepine or oxcarbazepine, which are successful in treating TN symptoms, are frequently involved as part of the first pharmacotherapy regimen (5,6). Carbamazepine is typically started at a dose of 100 to 200 mg twice a day. As tolerated, the dosage can be raised by 200 mg increments each day until a satisfactory level of pain reduction is achieved. When taking tablets and extended-release capsules, the usual total maintenance dose is 600–800 mg divided into two doses; when taking an oral suspension, it is divided into four doses. For TN, a maximum recommended total dose of 1200 mg per day is advised (12). Over time, however, drugs such as carbamazepine may become less effective or induce side effects including headache, sleepiness, blurred or double vision, nausea, vomiting, diarrhea, hyponatremia, rash, and itching (9, 12). In cases of predominant side effects or a decrease in the efficacy of the drug, dosages may be changed or other treatments may be taken into consideration (9). Nevertheless, clinical experience has demonstrated that carbamazepine is a more successful treatment than alternative therapies. As a result, they can be taken in addition to or instead of carbamazepine (29). Baclofen and lamotrigine are recommended as alternatives in case patients develop complications from the first-line medications (5). In patients whose symptoms have proven to be resistant to carbamazepine, improvement was achieved with adjunct therapy consisting of 400 mg daily of lamotrigine (30).

Usually, lamotrigine is started at 25 mg per day for the first two weeks, and during weeks three and four, the dosage is increased to 50 mg per day. After that, a

maximum daily dose of 400 mg is achieved by applying weekly dose adjustments by adding 50 mg every one to two weeks (12). Baclofen is started at 15 mg per day. The dosage is then gradually increased to a maintenance dose of 50–60 mg per day (29). Furthermore, gabapentin, pregabalin, and mirogabalin can be used as further options in cases of first-line regimen-related complications (5, 29). Possible emerging side effects are drowsiness, dizziness, rash, bone marrow suppression, and liver dysfunction. Lamotrigine and carbamazepine are especially prone to serious skin eruptions, including toxic epidermal necrolysis and Stevens-Johnson syndrome. Low-dose titration is crucial to prevent side effects and rash development (30). Notably, physicians have established botulinum toxin A as an alternative medical treatment for TN, although further investigation is required to prove its efficacy (1, 12, 29). Because the pain is strong in most cases and because it exclusively occurs within outbursts, narcotic painkillers are normally without effect (31).

Apart from the pharmacological approach, traditional Chinese acupuncture presents another form of non-surgical treatment to effectively treat TN (7).

In cases where TN patients do not respond to minimally three different drugs, have severe and intolerable side effects, or have symptoms that are resistant to the given treatment, surgery is typically considered a treatment option (18). The results of an MRI and the particular division of the trigeminal nerve that is injured should be taken into account when evaluating the necessity of surgery (2). By analyzing the anatomical characteristics and studying probable vascular conflicts that may be aggravating the patient's condition, the physician gets the necessary overview for determining the best surgical strategy.

There are two categories of surgical options: non-destructive and destructive (18).

Destructive surgical techniques called percutaneous rhizotomy aim to reduce pain in TN patients by carefully inducing damage to the nerve root. These methods can be adjusted and applied to different types of TN, even in cases where the etiology of trigeminal neuralgia is not related to vascular compression. The main methods include balloon compression therapy, glycerol injection, and radiofrequency ablation. Radiofrequency ablation inhibits pain impulses by applying heat to induce controlled damage to the nerve. An alternative option is glycerol injection, which causes chemical nerve impairment by injecting glycerol into the nerve, which also results in nerve damage. Balloon compression therapy presents another option and works by compressing the nerve using mechanical force. Each of these methods is executed via an approach called the foramen ovale approach. With this method, a needle is used to access the retrogasserian section of the trigeminal nerve (5). Percutaneous methods such as radiofrequency ablation or glycerol are specifically useful for patients with medical comorbidities, as these surgical methods are less invasive than classical open surgeries. These patients cannot undergo suboccipital craniectomy or cannot tolerate general anesthesia. As a result, a wider spectrum of patients, including the elderly and those who perceive invasive surgery as unfavorable, can benefit from this technique (32). It should be recognized that there is a chance of symptom recurrence with percutaneous rhizotomy (3).

Balloon compression, glycerol rhizotomy, and percutaneous radiofrequency rhizotomy are treatments with excellent success rates of up to 90% (33, 34). Nonetheless, physicians who use these techniques may encounter technical difficulties, with reports of foramen cannulation failure ranging from 2.7% to 8.0%

(35, 36). Bony structures, such as the foramen ovale, can be seen using fluoroscopy. Nevertheless, because the soft tissue anatomical structures are not visible, there is always a risk of injury to the nerves and vessels, such as the internal carotid artery and internal jugular vein (37). Punctures to the internal carotid artery, internal jugular vein, maxillary artery, middle meningeal artery, or pterygoid venous plexus might result in intraoperative bleeding (38).

Two main forms of radiofrequency therapies are utilized to target the Gasserian Ganglion: pulsed radiofrequency (PRF), which produces radiofrequency bursts with rest periods, and conventional radiofrequency (CRF), which differs by applying radiofrequency energy continuously. A study by Anurag Agarwal et al. demonstrated differences in the efficacy of pulsed radiofrequency (PRF) compared with conventional radiofrequency (CRF). Only 33.33% of patients in the PRF group noted at least a 50% reduction in pain intensity after three months, in contrast to the participants who were treated with CRF. The latter reported that their pain intensity had decreased by 83.33% within the same period. Notably, both forms of radiofrequency treatments were equally effective in lowering pain intensity seven days as well as one to two months after the procedure. CRF proved to maintain its positive effect for the long term. Three individuals experienced modest adverse effects related to CRF, for instance, hypoesthesia. These did not persist for a long time and eventually disappeared. PRF, however, did not induce any side effects in the patients treated (39).

A study conducted by Van Zundert et al. (40) showed that 3 out of 5 patients, all of whom have undergone PRF to treat idiopathic trigeminal neuralgia, had absolute alleviation of pain within 10 to 20 months post-treatment.

CRF has proven to be more effective than its counterpart, with the majority of patients reporting adequate relief from symptoms. This comes, however, on the subject of safety, as PRF is safer and has fewer side effects. PRF has a higher chance of pain recurrence and a lower rate of pain alleviation. Nevertheless, the efficacy of PRF can be improved by increasing the applied voltages. With the advantage of minimizing tissue damage, pulsed radiofrequency ablation (PRF) of the trigeminal nerve represents a less invasive procedure that can be increasingly seen as an effective alternative to more invasive treatments (41). Because of this, CRF is frequently chosen over PRF for treating TN; nevertheless, more research is still needed to properly grasp PRF's potential and efficacy (42).

Gamma Knife is a method within the field of stereotactic radiosurgery that utilizes high-intensity focused radiation. This approach targets and damages the nerve root. The radiation dose is very precisely adjusted to exclusively target its target tissue to minimize any additional harm to the brain stem (5). A Gamma knife is used to treat primary trigeminal neuralgia using stereotactic radiosurgery, which offers a high efficacy rate (88–96%), a good quality-of-life rate (around 85%), and a low complication and recurrence rate (4–12%) in terms of pain reduction (43, 44). In contrast to traditional vascular decompression of the trigeminal nerve, the gamma knife has fewer complications and a higher success rate (45, 46).

Stereotactic radiosurgery is a suitable treatment method for the elderly, patients in poor health, and individuals who are under anticoagulation therapy (20). Although expensive, Gamma Knife radiosurgery offers a non-invasive treatment option for trigeminal neuralgia (3).

Microvascular decompression is a surgical method that is non-destructive and aims at releasing the trigeminal nerve from vascular compression (5, 6). The superior cerebellar artery is, in many cases, responsible for the compression of the trigeminal nerve. In cases where the etiology of TN is explained by vascular compression of the trigeminal nerve rather than by other structural abnormalities or lesions within the nerve or surrounding tissues, microvascular decompression is most frequently taken into consideration as a treatment option (5). There are a variety of ways in which microvascular decompression can be performed, with the most common approach being posterior fossa craniectomy (20). MVD is the most successful surgical treatment, including its long-term prospects, but it is also the most invasive (3, 5, 6). Several cases have been recorded where patients diagnosed with idiopathic TN or medically refractory classical TN have been successfully treated by microvascular decompression (MVD) (6). Postoperative systemic infections, vertigo, dry eyes, and wound healing are possible adverse effects of this rather invasive procedure. More severe sequelae such as hearing loss, double vision, CSF fistulae, intracerebral/intracerebellar hemorrhage, and brain edema also need to be taken into account. Intraoperative bradycardia, which necessitates the administration of atropine, is considered a normal occurrence during an invasive procedure affecting the trigeminal nerve (47).

Unconventional treatment methods such as deep brain and motor cortex stimulation are becoming increasingly popular as possible treatments for TN patients who don't improve with medication or traditional surgery. However, additional data and research need to be done to properly prove its efficacy (18).

10. Conclusion

Because trigeminal neuralgia is marked by pain that is episodic in nature, controlling it is a considerable difficulty. The symptoms can significantly impact daily life, so effective management is needed. A comprehensive strategy comprises a detailed clinical evaluation, including adequate imaging, and a deep understanding of the etiology and symptomatology of this complex condition. Its intricacy, for instance, is mirrored by the fact that the presentation of trigeminal neuralgia can change over time, which makes its identification and comprehension heavily dependent on the past pattern of symptoms. Furthermore, careful weighing between a pharmaceutical and surgical approach to treating the patient as well as individually adjusted treatment plans are important to ensure optimal outcomes. Close monitoring is essential because of the broad spectrum of treatment responses and the potential occurrence of serious side effects. Noteworthy, the discovery of a genetic component in trigeminal neuralgia might contribute to the understanding of this facial pain disease, potentially promising improvement in the management of this disease in the future.

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13. Biography

Yarden Barayev was born on June 15, 1995, in Ramat Gan, Israel. She completed her 12 years of schooling and graduated from high school in Israel. Following her high school education, Yarden dedicated five years to caring for cancer patients, providing them with emotional support, travelling with them, and celebrating their birthdays. She recognized the importance of emotional well-being for their recovery, and all of her work with these patients took place in Israel.

Simultaneously, she served as a medical assistant in the Israel Defense Forces. In 2018, Yarden began her studies at the University of Zagreb School of Medicine in the English program and is currently in her sixth year. In her free time, she enjoys singing, dancing, and cooking. She aspires to have a medical career and is considering specializing in neurology, dermatology, or pediatrics.