Painful Trigeminal Neuropathy

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List and explanations of abbreviations used in the paper

BMS - Burning Mouth Syndrome

CI - Convergence Insufficiency

CISS - Convergence Insufficiency Symptom Survey

CSF - Cerebrospinal Fluid

GPN - Glossopharyngeal Neuralgia

ICHD-3 - International Classification of Headache Disorders

IASP - International Association for the Study of Pain

IPFP - Idiopathic Persistent Facial Pain

MRI - Magnetic Resonance Imaging

MS - Multiple Sclerosis

PCR - Polymerase Chain Reaction

PNS - Peripheral Nerve Stimulation

PNS - Peripheral Nerve Stimulation (listed twice in the provided list)

PTTN - Post-Traumatic Trigeminal Neuropathy

RFA - Radiofrequency Ablation

ROS - Reactive Oxygen Species

SUNA - Short-Lasting Unilateral Neuralgiform Headache Attacks

SUNCT - Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing

TMJ - Temporomandibular Joint

TN - Trigeminal Neuralgia

TRPV1 - Transient Receptor Potential Vanilloid 1

VZV - Varicella Zoster Virus

Content

1. Sažetak

Bolna trigeminalna neuropatija je potencijalno iscrpljujuća, ali nedovoljno poznata neurološka bolest. Njegova obilježja su specifične senzorne abnormalnosti i stalna bol lica. Ovaj pregled konsolidira trenutno znanje o njegovim simptomima, temeljnim uzrocima, dijagnostičkim izazovima uključujući diferencijalnu dijagnozu i mogućnostima liječenja povezanima s ovim stanjem.

Patognomonični simptomi bolne trigeminalne neuropatije pomažu u ispravnom dijagnosticiranju ovog stanja. To uključuje senzorne poremećaje bolne trigeminalne neuropatije, kao što su hipoestezija, hiperestezija, simptomi svrbeža, promjene okusa kao i poremećaj motoričke funkcije čeljusti. Ovisno o tome koje su specifične grane trigeminalnog živca uključene u svakog pacijenta, simptomi se mogu razlikovati u skladu s tim. Stoga je razumijevanje distribucije i prirode simptoma bolne trigeminalne neuropatije ključno za dijagnozu.

Na patofiziologiju utječe širok raspon etioloških događaja, uključujući infekcije, traume, sistemske bolesti i kirurške zahvate. Kako bi se bolna neuropatija trigeminusa razlikovala od drugih bolesti koje uzrokuju bol u licu, kao što je neuralgija trigeminusa, potrebna je sveobuhvatna klinička procjena i postupci snimanja, uključujući magnetsku rezonanciju, za proces dijagnoze. Bolna trigeminalna neuropatija liječi se individualno nizom pristupa, od minimalno invazivne i medikamentozne terapije do složenijih oblika skrbi.

2. Summary

Painful trigeminal neuropathy is a potentially debilitating yet not well known neurological disease. Its hallmarks are specific sensory abnormalities and persistent facial pain. This review consolidates current knowledge on its symptoms, underlying causes, diagnostic challenges including the differential diagnosis, and treatment options linked to this condition.

The pathognomonic symptoms of painful trigeminal neuropathy help in correctly diagnosing this condition. These include sensory disturbances of painful trigeminal neuropathy, such as hypoesthesia, hyperesthesia, itching symptoms, taste alterations as well as motor function disturbance of the jaw. Depending on which specific branches of the trigeminal nerve are involved in each patient, the symptoms can differ accordingly. Therefore, understanding of the distribution and nature of the symptoms of painful trigeminal neuropathy is crucial for diagnosis.

The pathophysiology is influenced by a broad range of etiological events, including infections, trauma, systemic illnesses, and surgical procedures. To distinguish painful trigeminal neuropathy from other illnesses causing facial pain, such as trigeminal neuralgia, a comprehensive clinical evaluation and imaging procedures, including magnetic resonance imaging, are necessary for the diagnosis process. Painful trigeminal neuropathy is treated individually with a range of approaches, from minimally invasive and medicinal therapy to more involved forms of care.

3. Introduction

The neurological disorder known as painful trigeminal neuropathy is typified by malfunction or injury to the trigeminal nerve, the fifth cranial nerve that supplies motor innervation to the masticatory muscles and transmits sensory data from the face to the brain. (1) This disorder affects the affected person's everyday life severely and includes a range of symptoms, such as discomfort, altered sensory perception, and facial pain. (2)

A number of distinct subtypes of painful trigeminal neuropathy are recognized by official classification systems, such as the 1st edition of the International Classification of Orofacial Pain (ICOP) (3) and the 3rd edition of the International Classification of Headache Disorders (ICHD-3) (1), both published by the International Headache Society (IHS) in 2018 and 2020, respectively. These subtypes include painful trigeminal neuropathy attributed to herpes zoster, painful trigeminal postherpetic neuralgia, painful post-traumatic trigeminal neuropathy, painful trigeminal neuropathy attributed to other disorders, and idiopathic painful trigeminal neuropathy. (1,3)

Additional conditions affecting the trigeminal nerve have been elaborated in the medical literature in the last decade, some of which are being actively investigated; these mainly include trigeminal neuropathy that develops as a sequela of ophthalmic related disorders such as convergence insufficiency, trigeminal dysphoria and digital eye strain. (4,5) Under closer investigation, these conditions might potentially represent subtypes and potential causes of trigeminal neuropathy in the future.

Therefore, this article will delve into the possibility of trigeminal dysphoria as a potential cause of painful trigeminal neuropathy.

A common sign of trigeminal neuropathy is face pain that is localized in the area where one or more trigeminal nerve branches are located. (6) Usually steady or almost constant, the main pain is characterized by scorching, squeezing, or needle-like sensations. (7) Though they might happen occasionally, short pain episodes are not the most common kind of pain. (8) This distinguishing feature separates distinct types of trigeminal neuralgia from painful trigeminal neuropathy. (1) In the regions innervated by the trigeminal nerve, people frequently also experience sensory abnormalities such as numbness, tingling (hypoesthesia or anesthesia), or increased sensitivity (hyperesthesia, hyperalgesia, or allodynia). (9) In reality, non-painful trigeminal neuropathy can also occur in certain circumstances; in these cases, the primary symptoms are sensory impairments, which can range from diminished (hypoesthesia) to nonexistent (anesthesia). Clinical examination: mechanical allodynia and cold hyperalgesia are usually present, satisfying the IASP criteria for neuropathic pain. Observable sensory impairments within the trigeminal distribution are also revealed. Crucially, the regions impacted by allodynia are noticeably larger than the tiny trigger zones found in trigeminal neuralgia. (1)

There are three primary branches of the trigeminal nerve: the ophthalmic (V1), maxillary (V2), and mandibular (V3) (10). Only the trigeminal nerve's territory—more precisely, the distribution of the trigeminal nerve's afflicted branches—is affected by the pain and sensory changes linked to trigeminal neuropathy. While any branch of

the trigeminal nerve may be affected by symptoms, the mandibular branch (V3) is typically affected, resulting in unique sensations in the lower face and jaw. (7)

Unilateral or bilateral trigeminal neuropathy can occur, and the two presentations may differ in terms of prevalence and underlying reasons. Since unilateral trigeminal neuropathy affects only one side of the face and is usually linked to certain causes such trauma, compression of the trigeminal nerve, or post-viral sequelae like postherpetic neuralgia, it is more commonly recognized. (11) Less frequently occurring, bilateral trigeminal neuropathy affects both sides of the face and may be linked to systemic illnesses such certain neurological diseases or metabolic abnormalities. (12)

There is a dearth of thorough data on the frequency and incidence of trigeminal neuropathy, making the epidemiology of the condition still relatively unknown. This is partially caused by the condition's heterogeneity and the difficulties in developing uniform diagnostic standards. On the other hand, trigeminal neuropathy is acknowledged as a rather rare neurological condition. (9) Although it can afflict people of any age, adults seem to be more likely to experience it. (11) More investigation is required to clarify the demographic traits, risk factors, and epidemiological patterns linked to trigeminal neuropathy in order to have a more thorough understanding of the condition's prevalence in a variety of communities. There is no discernible gender preference in the disorder. (13)

4. Signs and symptoms

With respect to the ocular (V1), maxillary (V2), and mandibular (V3) branches of the trigeminal nerve, a wide range of signs and symptoms are indicative of trigeminal neuropathy. (7)

4.1 Sensory Symptoms

Sensory abnormalities, ranging from hypoesthesia or anesthesia to hyperesthesia and allodynia, are among the prominent symptoms. The damaged facial regions may cause numbness, tingling, increased sensitivity, pain, and a feeling of coldness in the patients. (2,9) The sensory abnormalities, which add to the general discomfort felt by those who have trigeminal neuropathy, are frequently characterized as a loss of feeling or changed perceptions. These symptoms' distribution corresponds with the particular trigeminal nerve branches that are affected, offering important diagnostic hints. (9)

Facial pain, which can range greatly in severity and quality from intense, stabbing feelings to continuous, throbbing discomfort, is a frequent characteristic of trigeminal neuropathy. (11) The afflicted branch or branches of the trigeminal nerve usually provide the affected area(s) with pain. People frequently characterize the discomfort as dull, throbbing, or agonizing. Unlike other neurological pain diseases, which are characterized by abrupt, paroxysmal pain, trigeminal neuropathy pain is typically more continuous. (7)

The distinguishing feature is the presence of significant pain, which becomes the primary concern for the patient. This differs from other forms of trigeminal neuropathy, sometimes termed trigeminal sensory neuropathy (14), where symptoms such as facial numbness, masticatory weakness, or sensory changes might be more prominent, and pain, if present, is not necessarily the overriding symptom. (2)

The pain may initially dominate the clinical picture but may be accompanied by or progress to pain-unrelated sensory symptoms as well as muscle weakness as the disorder underlying it progresses. (2)

Neuropathic itching, or persistent itching, is another prominent sign of trigeminal neuropathy. This symptom, which lasts longer than six weeks, highlights the intricacy of trigeminal neuropathy by highlighting the complicated interactions between many neuromediators in chronic pain and itching, including substance P, opioids, nerve growth factor, neurotrophin 4, and proteases. (15)

Because the trigeminal nerve is involved in the transmission of sensory information from the mouth cavity, some patients with trigeminal neuropathy may have altered or reduced taste perception. (2) Cold weather, such as that caused by cool winds, can cause episodic blurring of vision, which can range from ipsilateral corneal edema to an underlying trigeminal neuropathy. (16) Hypoesthetic symptoms, such face numbness, should be closely watched since they could indicate that the underlying disease that is causing the trigeminal neuropathy is getting worse. (2)

4.2 Motor Symptoms

Due to neuropathic effects on the mandibular division (V3), the only branch of the trigeminal nerve with a motor component, trigeminal neuropathy can cause functional impairment in addition to pain and sensory alterations. This is especially true for the muscles involved in mastication. Because of the discomfort and changes in sensation, people may find it difficult to carry out daily tasks like eating, drinking, or speaking. This is because the disorder can cause neuropathic weakening in important face muscles such the masseter, temporalis, and both the lateral and medial pterygoids. (17) The symptoms may vary in intensity over time, and the effect on quality of life may be significant. (13).

4.3 Autonomous Symptoms

Since autonomic fibers can be involved in the trigeminal nerve, autonomic symptoms related to trigeminal neuropathy are rare and typically coupled with other forms of facial pain and sensory anomalies known as trigeminal autonomic cephalalgias. (2)

5. Subtypes and Causes

Trigeminal neuropathy is a complex and multifaceted illness with a wide range of underlying causes. Trauma, whether from a direct hit to the head or face, can cause post-traumatic trigeminal neuropathy, which can cause pain and aberrant sensory anomalies. (18) Following an incident of herpes zoster (shingles), in particular, post-viral or post-herpetic trigeminal neuropathy may develop, resulting in chronic pain in the distribution of the trigeminal nerve. (19) A number of systemic diseases, including autoimmune, metabolic, and others, can either directly or indirectly result in excruciating trigeminal neuropathy. Anesthesia dolorosa is a rare and difficult subtype that can result from treatments or surgical interventions that damage the trigeminal nerve. It causes facial anesthesia along with chronic pain. (20) Lastly, trigeminal neuropathy can occasionally be idiopathic, with no discernible cause. (1)

5.1 Trigeminal Neuropathy Attributed to Herpes Zoster

In 10-15% of instances, herpes zoster affects the trigeminal ganglion; in around 80% of cases, the ocular division is specifically affected. Rarely, a disease known as zoster sine herpete causes pain to appear without a rash developing thereafter. In these situations, polymerase chain reaction (PCR) is used to identify Varicella zoster virus DNA in the cerebrospinal fluid, thereby confirming the diagnosis. When herpes zoster is involved, painful trigeminal neuropathy usually manifests as burning, stabbing, tingling, or aching sensations that are frequently accompanied by

cutaneous allodynia. Palsies of the third (III), fourth (IV), and/or sixth (VI) cranial nerves have been related to ophthalmic herpes. Herpes zoster is more common in immunocompromised people; it affects about 10% of lymphoma patients and 25% of Hodgkin's disease patients. (1)

According to the ICHD-3, this is described as unilateral facial pain of less than 3 months' duration in the distribution of one or more branches of the trigeminal nerve, caused by and associated with other symptoms and/or clinical signs of acute herpes zoster. (1)

ICHD-3 diagnostic criteria of painful trigeminal neuropathy Attributed to Herpes Zoster:

A. Unilateral facial pain in the distribution(s) of a trigeminal nerve branch or branches, lasting <3 months

B. One or more of the following: 1. herpetic eruption has occurred in the same trigeminal distribution 2. VZV has been detected in the CSF by PCR 3. direct immunofluorescence assay for VZV antigen or PCR assay for VZV DNA is positive in cells obtained from the base of lesions

C. Not better accounted for by another ICHD-3 diagnosis (1).

5.2 Trigeminal post-herpetic neuralgia

Post-herpetic neuralgia is better characterized as a neuropathy or neuronopathy due to significant pathoanatomical alterations in the nerve, ganglion, and nerve root, despite the term that has been previously chosen. There is also evidence of inflammation extending into the trigeminal brainstem complex in patients of trigeminal post-herpetic neuralgia. Trigeminal post-herpetic neuralgia is a herpes zoster infection sequelae that can happen weeks to months after the acute infection, in contrast to the excruciating trigeminal neuropathy associated with the disease, in which the neuropathic symptoms coexist with the acute infection. Older people are more likely to experience post-herpetic neuralgia after contracting acute herpes zoster. In trigeminal post-herpetic neuralgia, the first division of the trigeminal nerve is most frequently damaged, but the second and third divisions may also be involved. Post-herpetic neuralgia pain typically presents as burning and itching, with the latter being most noticeable and painful. In the afflicted trigeminal distribution, patients with post-herpetic neuralgia typically present with brush-evoked mechanical allodynia and a noticeable sensory impairment. On the other hand, some patients may show only little sensory loss and instead react more strongly to thermal and/or punctate stimuli. (1)

ICHD-3 diagnostic criteria of trigeminal postherpetic neuralgia:

A. Unilateral facial pain in the distribution(s) of a trigeminal nerve branch or branches, persisting or recurring for >3 months and fulfilling criterion C
B. Herpes zoster has affected the same trigeminal nerve branch or branches

C. Pain developed in temporal relation to the herpes zoster infection

D. Not better accounted for by another ICHD-3 diagnosis. (1)

5.3 Post-traumatic Trigeminal Neuropathy

According to the ICHD-3, PTTN is described as unilateral or bilateral facial or oral pain induced by and arising as a consequence of trauma to the trigeminal nerve(s), accompanied by additional symptoms and/or clinical signs of trigeminal nerve dysfunction. (1)

ICHD-3 diagnostic criteria of painful post-traumatic trigeminal neuropathy:

A. Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C

B. History of an identifiable traumatic event1 to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypaesthesia, hypalgesia) signs of trigeminal nerve dysfunction

C. Evidence of causation demonstrated by both of the following:

1. pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event

2. pain has developed <6 months after the traumatic event

D. Not better accounted for by another ICHD-3 diagnosis. (1)

The trauma can arise from mechanical, chemical, thermal, or radiation sources. While trauma to the facial skeleton can be a cause, iatrogenic factors, especially those related to dental procedures, play an even more important role as they are considered the most common etiology of painful post-traumatic trigeminal neuropathy. (2) There are various potential iatrogenic causes of PTTN, and their impact on this condition varies accordingly.

Dental procedures, ranging from root canal therapy, extractions, to dental implants, have also been observed to cause PTTN. This particularly includes damage from oral surgeries, especially the removal of impacted lower third molars. The sensory defects are mainly in the areas innervated by the inferior alveolar and lingual nerves, typically due to the anatomical proximity between these nerves and the surgical site. Neuropathies involving the inferior alveolar nerve and lingual nerve have been reported in a small percentage of molar extractions. (9) There is a concern about the lack of information linking root canal therapy to PTTN, which can lead to potential misdiagnosis and reluctance among patients to seek further help. (21)

The onset of PTTN symptoms following endodontic procedures can range from three to 48 months post-treatment. Often, there is a history of poor analgesia during the procedure when the symptoms usually begin (22).

In some cases, no clear trauma can be identified, yet the pain is distinctly localized in the dental area; this has been termed atypical odontalgia. Atypical odontalgia, a type of painful trigeminal neuropathy, is particularly challenging for diagnosis and

treatment due to its localization in the dental area without a clear history of trauma or dental procedure. (22)

Neuroablative procedures intended for trigeminal neuralgia, targeting the trigeminal ganglion or nerve root, may lead to neuropathic pain affecting one or multiple divisions of the trigeminal nerve. It is essential to recognize this as post-traumatic and categorize it accordingly. In instances of postganglionic injury induced by radiation, neuropathy may emerge after a period exceeding three months. In cases of painful post-traumatic trigeminal neuropathy resulting from neuroablative procedures targeting the trigeminal ganglion or nerve root, there is a potential for coexistence with Trigeminal neuralgia if the latter recurs. (1)

The symptomatology of PTTN may include ongoing discomfort, paresthesia, and dysesthesia, which emerge following the traumatic event. The nature of the pain associated with PTTN varies, often being described as aching, burning, or throbbing. The intensity can range from mild to severe. (21) The duration of pain varies extensively, ranging from intermittent to persistent and possibly presenting as a combination of both.

Currently, the usual management of PTTN is similar to that for other neuropathic pains, but there is a high percentage of treatment failures. (22)

5.4 Painful Trigeminal Neuropathy Attributed to Other Disorder

Painful trigeminal neuropathy attributed to other disorder may arise as a consequence of multiple sclerosis, space-occupying lesions, or systemic diseases, similarly to secondary trigeminal neuralgia. The distinguishing factors between the two conditions lie solely in their clinical characteristics, encompassing the quality of spontaneous pain, evoked pain, and the presence of sensory deficits. In instances where painful trigeminal neuropathy is linked to connective tissue diseases or hereditary disorders, the condition typically manifests bilaterally. However, it may initiate asymmetrically and occasionally feature paroxysmal pain superimposed on a persistent background pain. Over time, patients will invariably develop bilateral sensory deficits and continuous pain, aiding in a definitive diagnosis. While MRI results may appear normal, trigeminal reflexes consistently exhibit delayed or absent responses. (1)

According to the ICHD-3, painful trigeminal neuropathy attributed to other disorder can be described as unilateral or bilateral facial or oral pain localized in the distribution(s) of one or more branches of the trigeminal nerve, stemming from a separate distinct disorder, with other symptoms and/or clinical signs indicative of dysfunction in the trigeminal nerve. (1)

ICHD-3 diagnostic criteria of painful trigeminal neuropathy attributed to other disorder:

A. Unilateral or bilateral facial pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C

B. A disorder, other than those described above but known to be able to cause painful trigeminal neuropathy with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypaesthesia, hypalgesia) signs of trigeminal nerve dysfunction, and affecting one or both trigeminal nerves, has been diagnosed

C. Evidence of causation demonstrated by both of the following:

1. pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the disorder

2. pain developed after onset of the disorder, or led to its discovery

D. Not better accounted for by another ICHD-3 diagnosis. (1)

Apart from multiple sclerosis, conditions that have been implicated as potential causes of secondary painful trigeminal neuropathy include metabolic, autoimmune and neurological (demyelinating) disorders. (2)

Metabolic disorders can play a role in the development or association with trigeminal neuropathy, underscoring the impact of systemic factors on peripheral nerve function. Conditions such as diabetes mellitus, characterized by chronic high blood sugar levels, are a prominent example. Diabetic neuropathy can affect various nerves in the body, including the trigeminal nerve, leading to symptoms such as facial pain, tingling, and sensory disturbances. (23) Other metabolic disorders, such as vitamin deficiencies (e.g., vitamin B12 deficiency), thyroid disorders, and disorders affecting lipid metabolism, have also been linked to trigeminal neuropathy. The metabolic imbalances in these conditions can contribute to nerve damage or

dysfunction. Addressing the underlying metabolic disorder through appropriate medical management, lifestyle modifications, and nutritional support is crucial in the comprehensive approach to managing trigeminal neuropathy associated with metabolic factors. (2)

Autoimmune disorders can potentially cause or be associated with trigeminal neuropathy, highlighting the intricate relationship between the immune system and the peripheral nerves. In certain autoimmune conditions, the immune system mistakenly targets and attacks the body's own tissues, including the trigeminal nerve. Disorders such as multiple sclerosis, Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis have been linked to trigeminal neuropathy (7,18,24,25). The immune-mediated inflammation in these disorders can lead to damage or dysfunction of the trigeminal nerve, resulting in facial pain, sensory disturbances, and other neurological symptoms. The exact mechanisms underlying the association between autoimmune disorders and trigeminal neuropathy are complex and may involve a combination of inflammatory processes, demyelination, and nerve damage. Effective management often requires a multidisciplinary approach, addressing both the underlying autoimmune condition and the specific symptoms of trigeminal neuropathy. (11)

Tumors and neoplastic disorders can be implicated in the development or association with trigeminal neuropathy, presenting a diverse array of challenges to nerve function within the trigeminal system. Cerebellopontine angle tumors, acoustic neuromas, and tumors affecting the skull base may exert pressure on the trigeminal nerve or its branches, leading to neuropathic pain, sensory disturbances, and facial

discomfort (9,18,25,26). Additionally, malignancies within the brain or adjacent structures can infiltrate the trigeminal nerve, causing neuropathy. Metastatic spread of cancer to the skull base or intracranial region may also impact the trigeminal nerve and induce neuropathic symptoms. Diagnosing and managing trigeminal neuropathy associated with tumors necessitates a comprehensive approach, often involving neuroimaging studies, surgical interventions, and collaboration with oncology specialists to address the underlying neoplastic condition. (9)

5.5 Idiopathic Painful Trigeminal Neuropathy

Only after numerous clinical, laboratory, and imaging tests have ruled out any known causes of trigeminal neuropathy can this diagnosis be made. According to the ICHD-3, it is defined as unilateral or bilateral pain affecting one or more trigeminal nerve branches, suggesting that there may have been unidentified brain damage. (1)

ICHD-3 diagnostic criteria of Idiopathic painful trigeminal neuropathy:

A. Unilateral or bilateral facial pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion B

B. Clinically evident positive (hyperalgesia, allodynia) and/or negative (hypaesthesia, hypalgesia) signs of trigeminal nerve dysfunction

C. No cause has been identified

D. Not better accounted for by another ICHD-3 diagnosis. (1)

A related disease entity, which some believe to be another subtype of painful trigeminal neuropathy, is anesthesia dolorosa. This is a rare and challenging condition where patients experience facial anesthesia (loss of sensation) following surgical interventions or other procedures affecting the trigeminal nerve. Paradoxically, this anesthesia is accompanied by persistent, often severe pain. (6,19)

In recent years, some other causes and mechanisms have been postulated to contribute to the development of trigeminal neuropathy.

6. Diagnosis

An elaborate clinical evaluation includes a detailed medical history and neurological examination. The aim is to identify specific features such as the nature, duration, and triggers of facial pain, as well as associated sensory abnormalities. Imaging studies are used to aid in diagnosis. MRI for instance can help in detecting structural issues like compression of the trigeminal nerve, a finding often associated with trigeminal neuralgia. Additionally, dental pathologies, multiple sclerosis, cerebellopontine angle tumors, and other conditions may be discovered whose symptoms might either resemble or guide towards trigeminal neuropathy. (16,23)

Beyond the detailed clinical evaluation and imaging studies, several specialized tests and tools are further utilized in the diagnosis of trigeminal neuropathy. The blink reflex test is a non-invasive tool and helps in assessing central and peripheral neurological functions, such as trigeminal neuropathy. (12,27) This neurophysiological test can provide insights into the integrity of the trigeminal nerve pathways and it helps the physician localize and characterize the neuropathic condition. The blink reflex involves stimulating the trigeminal nerve, typically through electrical impulses applied to the supraorbital nerve, and observing the resulting reflexive eye blink driven by the orbicularis oculi muscles. (28,29) There is an earlier short latency response, named R1, triggered unilaterally on the side of stimulation. The second component, termed R2, is a bilateral long latency response and mirrors the excitability of brainstem interneurons. (27)
In cases of trigeminal neuropathy, abnormalities of R1 and R2 may be evident, such as a late or absent response. (28,29)

It is almost universally agreed that the blink reflex in patients with migraine or allodynia is characterized by decreased habituation and increased excitability recovery. Furthermore, it has been shown that chronic migraine usually shows an interictal lack of habituation. These findings suggest a continuous hyperexcitable state of the trigeminal nerve in patients with chronic migraine and allodynia. (30) Since allodynia is an important hallmark of trigeminal neuropathy, and since the pathophysiology of migraine is related to the pathophysiology of trigeminal neuropathy as discussed later, it can be concluded that the characteristic findings of the blink reflex in migraine are potentially the same as for trigeminal neuropathy. Additionally, it can be concluded that trigeminal neuropathy itself represents a continuous hyperexcitable state of the trigeminal nerve.

The average R1 and R2 values of the blink reflex has been frequently determined in the medical literature, such as the study conducted by Tomislav Badel et al., which included researchers from various departments at the University of Zagreb, Croatia. They determined their average of the R1 and R2 to be around 14 milliseconds and 37 milliseconds, respectively. (31)

These tests contribute to a comprehensive understanding of trigeminal nerve function and can assist in confirming the diagnosis, guiding treatment decisions, and monitoring the progression of trigeminal neuropathy. (11)

7. Differential Diagnosis

7.1 Trigeminal Neuralgia

Trigeminal neuralgia is a primary differential diagnosis for trigeminal neuropathy, since many symptoms may overlap between the two, as well as with other types of facial pain. Unlike trigeminal neuropathy, trigeminal neuralgia is characterized by unilateral recurrent sudden paroxysms of facial pain described as sharp, shooting, and akin to electric shocks, lasting seconds to minutes, often triggered by innocuous stimuli such as light touch, chewing, brushing teeth and exposure to cold air. (32-34) The pain mostly follows the V2 and/or V3 distributions of the trigeminal nerve. Paroxysms are followed by refractory periods, in which a pain paroxysm cannot be triggered. Notably, TN typically does not involve sensory loss or motor weakness. Most cases are caused by neurovascular compression (classical), though some can be secondary to systemic diseases or conditions like arteriovenous malformations, or they can be idiopathic, with no clear abnormalities on diagnostic tests (1,34).

The physician must make sure to clearly differentiate trigeminal neuropathy from TN in clinical practice because each condition necessitates distinct treatment approaches. Misdiagnosis or confusion between these two facial pain disorders can lead to ineffective and potentially harmful treatments. Concretely, procedures effective for TN, like radiofrequency ablations, may worsen trigeminal neuropathy symptoms. (15)

7.2 Trigeminal deafferentation pain

Trigeminal deafferentation pain represents a type of neuropathic pain that arises when the trigeminal nerve is deafferented, meaning it has lost its normal sensory input. This condition can have several etiologies, including surgical procedures, trauma, or diseases that directly affect the trigeminal nerve. (35) Deafferentation pain is complex and challenging to manage. The pain in trigeminal deafferentation is often a consequence of the central nervous system's response to the loss of sensory input. When the nerve loses its usual sensory signals, the central nervous system may undergo changes; the brain, deprived of normal signals from the trigeminal nerve, may undergo changes leading to abnormal sensations and pain. In contrast to painful trigeminal neuropathy, in which pain arises from direct damage or dysfunction of the nerve, trigeminal deafferentation pain is centrally mediated pain in the absence of nerve damage, and is specifically related to the loss of sensory input to the trigeminal nerve. (19,20,35)

7.3 Glossopharyngeal Neuralgia

GPN is a severe facial pain disorder that affects the glossopharyngeal nerve. It is characterized by unilateral pain felt deep in the ear, or in the back of the tongue, tonsils, and neck. (36) GPN manifests as paroxysmal attacks lasting from a few seconds to several minutes and can recur throughout the day, potentially remitting for weeks or months. (22) The pain characteristic of GPN manifests suddenly and

ceases just as abruptly, affecting areas within the glossopharyngeal nerve distribution, including the angle of the jaw, ear, tonsillar fossa, and the base of the tongue. Like in TN, the pain is typically sharp, shooting, and electric shock-like, and can be triggered by swallowing, talking, coughing, or touching the ear, and often follows a relapsing and remitting pattern. (36) However, the distribution of the pain is what distinguishes these similar conditions – following the glossopharyngeal nerve (GPN) or the trigeminal nerve (TN). In some cases, GPN can lead to syncope. (22) GPN also involves the pharyngeal and auricular branches of the Vagus Nerve.

The key to differentiating between trigeminal neuropathy and GPN lies in their respective pain characteristics and triggers. Trigeminal neuropathy is known for its characteristic continuous pain in the trigeminal nerve distribution areas such as the face, jaw, and gums. Patients suffering from GPN, in contrast, present with deeper, localized pain in the ear, back of the tongue, tonsils, and neck, frequently triggered by actions like swallowing or coughing. (15,22) Both trigeminal neuropathy and GPN may respond to anticonvulsant therapy, yet the choice and effectiveness of specific medications vary depending on the condition. Radiofrequency ablations, helpful not only for TN but also for GPN, might exacerbate symptoms in trigeminal neuropathy. Therefore proper differentiation is vital. (22)

7.4 TMJ Disorders

Disorders of the temporomandibular joint might resemble trigeminal neuropathy as they present with facial pain, jaw dysfunction, and muscle tenderness. TMJ disorders often involve problems with jaw movement and they can be linked to bruxism. (22,37)

7.5 Cluster Headaches

Cluster headaches can cause severe unilateral facial pain. They are localized around the eye and autonomic symptoms such as tearing, nasal congestion, and ptosis may occur. Unlike trigeminal neuropathy, cluster headaches occur in clusters or bouts, with recurring episodes during certain time periods. (22,37,38)

7.6 SUNA/SUNCT

SUNCT and SUNA are headache disorders that are considered rare. Short-lasting, severe, unilateral head pain is pathognomonic for these conditions. These symptoms are often accompanied by autonomic features like conjunctival injection and tearing. Distinguishing these conditions from trigeminal neuropathy requires the identification

of distinct headache characteristics and the absence of continuous facial sensory abnormalities. (7,19,22)

7.7 Cluster-Tic Syndrome

Cluster-tic syndrome fuses the features of both trigeminal neuralgia and cluster headaches, making severe paroxysms of facial pain accompanied by cluster headache-like autonomic complains the characteristic symptomatology of this condition. (7)

7.8 Sinusitis

Sinusitis can lead to facial pain and tenderness, especially around the area of the cheeks and forehead. Differentiating sinusitis from trigeminal neuropathy requires assessment of associated symptoms such as nasal congestion, headache, and purulent nasal discharge. (7)

7.9 Dental pathologies

Dental issues, for example infections or dental trauma, can manifest as facial pain that may be mistaken for trigeminal neuropathy. A thorough dental examination helps in ruling out tooth-related causes. (39)

7.10 Burning Mouth Syndrome

Burning mouth syndrome (BMS) is a painful condition that is diagnosed in patients complaining of chronic persistent burning or tingling sensation in the mouth. These symptoms often extend to the face and occur in the absence of any identifiable mucosal lesions or clinical pathology. This perplexing condition primarily affects peri- and postmenopausal women and is increasingly recognized for its neuropathic components, despite often being misinterpreted as psychological. (22,40,41) While it primarily affects the oral cavity, the symptoms may overlap with trigeminal neuropathy, necessitating careful clinical evaluation.

The exact cause of BMS remains elusive. It's suspected to have multifactorial origins, including local, systemic, or psychogenic factors such as hyposalivation, oral candidiasis, nutritional deficiencies (iron, vitamins B12 and folic acid), hyperglycemia, and hormonal changes at menopause. Secondary causes include mucosal lesions, hematological disorders, autoimmune disorders, and pharmacological side effects (22,40).

Emerging research on Burning Mouth Syndrome (BMS) suggests a neuropathic basis, specifically of the trigeminal nerve, for this complex condition. Various studies have begun to unravel the intricate interplay between peripheral and central nervous system dysfunctions in BMS patients (41).

Trigeminal nerve damage can be proposed in cases where the symptoms of BMS occur bilaterally. (42)
It is possible to specifically identify BMS secondary to trigeminal neuropathy. This distinction of trigeminal neuropathy-induced BMS is based on findings of the blink reflex. An abnormality in this electrophysiological exam, such as a hyperexcitable blink reflex, indicates that BMS is secondary to trigeminal neuropathy. (43,44)

7.11 Persistent Idiopathic Facial Pain

Persistent Idiopathic Facial Pain (PIFP) is a chronic facial pain disorder which does not have a clear etiology. It presents with continuous, generalized facial pain that does not conform to a specific nerve distribution. It shares some features with trigeminal neuropathy, for example the complaint of persistent discomfort and dull, aching, nagging, and sometimes stinging pain. PIFP affects both extraoral and intraoral areas, with intermittent relief periods, and is exclusively diagnosed after excluding other facial pain causes. PIFP often demands a broader, multidisciplinary

treatment approach, while trigeminal neuropathy may require targeted interventions based on the underlying cause (22,45).

In recent years, idiopathic persistent facial pain has been considered as the result of trigeminal neuropathy. Therefore its former name, atypical facial pain, seems to be the more appropriate term in this context. Furthermore, the condition has been further stratified on the basis of its cause. Therefore, a clear distinction has been made between atypical facial pain caused by a major trigeminal neuropathy, a minor trigeminal neuropathy and atypical facial pain originating from an unknown cause. This categorization is based on electrophysiological diagnostic test outcomes, such as the result of the blink reflex and clinical findings. (46)

7.12 Medication-induced Neuropathy

Some medications, especially those with neurotoxic effects, can cause neuropathy. Revising the patient's medication history is therefore important in order to identify potential drug-induced triggers for developing trigeminal neuropathy. (47)

7.13 Neuralgias / Neuropathies of other nerves

Neuralgias or neuropathies affecting other cranial or peripheral nerves can present with facial pain and sensory abnormalities. Considering the possibility of neuralgias in different nerve distributions should be part of the complex diagnosing process of facial pain pathologies. (19,22,37,38)

7.14 Systemic diseases

Certain systemic diseases, including multiple sclerosis, can present with neurological symptoms affecting the trigeminal nerve. Imaging studies are specifically relevant as diagnostic tools in these cases. (7,19,24,25)

7.15 Cerebellopontine angle tumors

Tumors in the cerebellopontine angle, such as acoustic neuromas, can compress the trigeminal nerve, leading to facial pain and sensory disturbances. As it is the case for systemic diseases, Imaging techniques, such as MRI, are vital for diagnosis. (6,9,19)

7.16 Metabolic disorders

Metabolic disorders, for example diabetes, can cause neuropathic symptoms in the trigeminal nerve distribution. Comprehensive metabolic and neurological evaluations are necessary to determine the underlying cause. (9,23)

Besides being potential causes of secondary trigeminal neuropathy, disorders enlisted as and described in 5.14, 5.15 as well as 5.16 can also present with overlapping symptoms without causing actual trigeminal neuropathy, and should be considered in the differential diagnosis.

8. Treatment

Treatment for trigeminal neuropathy depends on the underlying cause and the individual symptomatology. There is a broad spectrum of treatment possibilities ranging from medications for pain management to surgical interventions. The eventual decision of treatment strategy is heavily influenced by the underlying cause and the severity of presenting symptoms.

Since trigeminal neuropathy can arise following surgical interventions for the treatment of other conditions (most commonly trigeminal neuralgia), it is imperative to consider the risk-benefit balance of any proposed surgical intervention for trigeminal neuropathy, as it may also worsen the condition (8,18,20,21,48,49).

8. 1 Non-invasive Management Options

8.1.1 Pharmacological treatments

Medication is frequently recommended to control pain and reduce symptoms. Pharmacological medications typically used to treat other neuropathies, such as tricyclic antidepressants (e.g., Amitriptyline), are the first line of treatment for trigeminal neuropathy (8,48,50).

The preferred treatment for trigeminal neuralgia is an anticonvulsant medication such as carbamazepine or gabapentin. Although there isn't much evidence to support this, it can be useful to manage pain associated with the nerves in trigeminal neuropathy (8,48,50).

8.1.2 Physical therapy

Physical therapy, which aims to improve mobility, enhance facial muscle function, and reduce related discomfort, may be taken into consideration in the comprehensive management of trigeminal neuropathy. Skilled physical therapists use a variety of approaches to address the unique problems experienced by patients with trigeminal neuropathy, such as manual treatment, focused exercises, and applications of heat or cold. Physical therapy aims to improve general function, minimize muscle stress, and maximize face muscle strength and coordination. In addition, therapists assist patients in learning coping mechanisms for everyday tasks including speaking, chewing, and making facial expressions that may be affected by trigeminal neuropathy.

Physical therapy improves a person's quality of life by reducing functional limitations and encouraging adaptive mechanisms to manage the impact of trigeminal neuropathy on daily activities, even though it might not directly address the underlying neurological issues. (51)

8.1.3 Nerve blocks

In the treatment of trigeminal neuropathy, nerve blocks are a useful therapeutic strategy that aims to deliver focused pain and sensory disturbance reduction. In this process, a local anesthetic is injected close to the trigeminal nerve or its branches, frequently with the addition of a steroid for a longer-lasting effect. Nerve blocks are a useful treatment for trigeminal neuropathy pain because they temporarily stop or reduce nerve signals (52). The distribution of symptoms and the likely source of neuropathic pain determine the precise injection site. Nerve blocks provide a temporary kind of relief as well as a diagnostic tool by demonstrating the trigeminal nerve's involvement. Nerve blocks can be an important part of the treatment approach, providing both immediate comfort and insights for ongoing management techniques, however the length of pain reduction varies among individuals (8,52-54).

8.1.4 Botox injections

Injections of Botox have been investigated as a possible treatment for trigeminal neuropathy, especially when facial pain is linked to hyperactivity of the muscles. A substance called botulinum toxin, or Botox, is injected into certain facial muscles to temporarily paralyze or weaken them. This lessens excessive muscular spasms and the pain that goes along with them. Although there hasn't been as much research on Botox's use for trigeminal neuropathy as there has been for other disorders, preliminary findings indicate that it may be useful in treating some facial pain types.

By reducing the hyperexcitability of the impacted neurons, the process reduces the release of neurotransmitters at the neuromuscular junction, resulting in alleviation. Its effectiveness, however, varies from person to person, and more study is required to establish the best dosages, injection locations, and long-term effects. In some cases of trigeminal neuropathy, botox injections may be a potential supplementary treatment option. (45).

8.2 Minimally Invasive And Invasive Management Options

8.2.1 Radiofrequency ablation (RFA)

A minimally invasive technique called radiofrequency ablation has been investigated as a treatment for trigeminal neuropathy, particularly in situations when neuropathic pain is associated with specific nerve fibers. RFA involves the use of high-frequency electrical currents to cause lesioning of specific nerves, heat generation, and disruption of pain signals. RFA is administered to the trigeminal nerve branches that are impacted by trigeminal neuropathy. Through the creation of a controlled nerve damage and the interruption of aberrant impulses, this therapy seeks to deliver long-lasting pain relief. RFA is more frequently linked to trigeminal neuralgia; nevertheless, as the arsenal of treatments for facial pain problems grows, its

potential use in trigeminal neuropathy is now being studied. Like any medical procedure, RFA's effectiveness may differ from person to person, thus further research is required to determine its purpose, ideal settings, and long-term results in the treatment of trigeminal neuropathy (19,45).

8.2.2 Peripheral nerve stimulation (PNS)

An inventive method for treating trigeminal neuropathy is peripheral nerve stimulation, which provides focused relief from facial pain and sensory abnormalities. In order to regulate pain signals, controlled electrical impulses are provided via electrodes implanted in close proximity to the afflicted nerves. By changing the way neurons communicate pain sensations, PNS has a neuromodulatory effect that may provide long-lasting comfort. This method is especially helpful for people who might not react well to conventional drugs or who are looking for less intrusive surgical options. Because PNS is adaptable, medical professionals can modify the stimulation parameters to suit each patient's needs. Peripheral nerve stimulation appears to hold promise as a valuable therapeutic option for trigeminal neuropathy, although research on its efficacy is still ongoing. (53,55,56)

8.2.3 Gasserian ganglion stimulation

A new therapeutic option for trigeminal neuropathy is gasser ganglion stimulation, especially in cases where more conservative approaches are ineffective. This kind of neuromodulation applies specific electrical impulses to the Gasserian ganglion, an important trigeminal nerve sensory relay center. Gastrine ganglion stimulation attempts to halt aberrant pain signals and lessen the incapacitating symptoms linked to trigeminal neuropathy by adjusting the activity of the trigeminal nerve at this crucial intersection. This approach is frequently taken into consideration when more conventional therapies, including drugs or nerve blocks, are unable to relieve the patient's symptoms adequately. (57)

8.3 Treatment of Secondary Causes

Beyond simply relieving pain or other sensory abnormalities, the therapeutic strategy frequently entails locating and treating the underlying cause. This could entail taking care of illnesses that could be harming the trigeminal nerve, such as infections, inflammation, or tumors.

8.3.1 Trigeminal Neuropathy secondary to multiple sclerosis

Treatment for multiple sclerosis-related trigeminal neuropathy takes a multimodal strategy, trying to address the neurological symptoms affecting the trigeminal nerve

as well as the underlying autoimmune disease. The goal of disease-modifying treatments, which alter the course of MS by targeting the immune system, is frequently to lessen inflammation and stop more demyelination (7,25). Tricyclic antidepressants, anticonvulsants (such as gabapentin and carbamazepine), and occasionally corticosteroids are used to treat trigeminal neuropathy-related pain and sensory abnormalities (48). Improving the function of the face muscles and treating problems associated with muscle weakness or spasticity can both benefit from physical therapy (51). Surgical procedures like nerve blocks or microvascular decompression may be taken into consideration in specific circumstances (54).

8.3.2 Trigeminal Neuropathy Secondary to Cerebellopontine Angle Tumors

Treatment for cerebellopontine angle tumor-related trigeminal neuropathy is a multifaceted strategy that targets the tumor as well as the trigeminal nerve-related neurological symptoms. Surgery is frequently used as the main treatment for cerebellopontine angle tumors, with the aim of resecting the tumor or decompressing the afflicted nerves (9). Depending on the kind, location, and size of the tumor, stereotactic radiosurgery, microsurgical techniques, or a combination of both may be considered. After tumor control, the emphasis switches to symptom relief for trigeminal neuralgia. Neuropathic pain may be treated with medications such anticonvulsants (gabapentin, carbamazepine, etc.) (19, 48).

8.3.3 Trigeminal Neuropathy Secondary to Diabetes or Other Metabolic Disorders

A comprehensive approach is used to treat trigeminal neuropathy linked to diabetes or metabolic disorders, with the goals of controlling the underlying metabolic disease and reducing neuropathic pain. In order to stop more nerve damage from occurring, strict glycemic control is essential for managing diabetes (23). Neuropathic pain may be treated with medications such as tricyclic antidepressants and anticonvulsants (pregabalin, gabapentin, etc.) (48).

9. Trigeminal Dysphoria as a Hypothetical Cause of Trigeminal Neuropathy

As articulated in the beginning of this article, trigeminal nerve involvement is proposed in several medical conditions that are specifically relevant in the modern digital era. Trigeminal dysphoria represents one of these conditions. (4,5) In the following section, the possibility of trigeminal dysphoria being one possible cause of trigeminal nerve pathology will be elaborated.

9.1 Definition and Significance of Trigeminal Dysphoria

Trigeminal dysphoria is a disorder characterized by headaches, eye strain, neck and shoulder tension, and dry eyes and light sensitivity. (4,5,58) These symptoms are triggered after prolonged periods of close work, especially when reading on digital devices. (59,60,61) The ophthalmic literature has acknowledged this group of symptoms in the past. (62,63,64) This condition is notably different from migraines, as patients with trigeminal dysphoria tend to be continuously light- sensitive, whereas migraine sufferers typically experience light sensitivity only during headache episodes (22). The modern daily requirements to work on digital screens has put increased attention to these complaints as recent statistics indicate that the typical American adult spends over nine hours daily using digital devices, amplifying the effects of these symptoms. (58) Considering that the leading cause for patients to seek eye examinations nowadays is due to symptoms that are related to computer

use (65,66), the importance of trigeminal dysphoria cannot be overestimated in the modern era of digital devices.

Computer vision syndrome can be categorized as a subform of trigeminal dysphoria. (59,60,61) Therefore, for the sake of simplicity, both conditions are considered as the same condition in this article. There is, however, one distinction that is important to mention when comparing both conditions. The neck and shoulder pain tend to be explained differently. In computer vision syndrome these symptoms, additionally with back pain, are assumed to have a positional and posture related origin. (67) In trigeminal dysphoria, on the other hand, neck and shoulder symptoms are at least partially also explained by the extensive reach and influence of the trigeminal nerve which is not only limited to the face, but also to the shoulders and neck. (4,5)

Computer vision syndrome, alternatively termed digital vision syndrome, arises from extended utilization of digital screen devices and encompasses various ocular, musculoskeletal, and behavioral issues. (67) The physical discomfort onset has been described by the American Optometric Association to be after at least two hours of exposure for the majority of individuals. (68) There is no documented prevalence of trigeminal dysphoria as its terminology is not widely used in the medical literature. Computer vision syndrome, on the other hand, is estimated to affect approximately seven out of ten individuals. (67)

The underlying cause of trigeminal dysphoria is closely linked to convergence insufficiency, a prevalent binocular vision disorder marked by a reduced ability to effectively converge the eyes during near-vision tasks (5). CI requires repetitive,

strenuous eye alignment for each word during reading, creating persistent strain on the ocular convergence system (4). This chronic neuromuscular demand not only challenges the visual system but also sets the stage for further neuro-ophthalmic complications, making it an important concern in both ophthalmology and neurology (5).

9.2 Convergence Insufficiency - A Crucial Factor in Trigeminal Dysphoria

9.2.1 Comprehensive Review of Convergence Insufficiency

Convergence insufficiency is correlated with trigeminal dysphoria. (4,60,69) Therefore, Convergence Insufficiency as a condition should be further elucidated in favor of a deeper understanding of trigeminal dysphoria.

Convergence Insufficiency is categorized as a binocular vision disorder characterized by exophoria greater at near than distance, a remote near point of convergence or decreased positive fusional convergence at near. (70,71) Patients with Convergence Insufficiency can be asymptomatic. Symptoms occur while reading or performing close work. These are double vision, eyestrain, headaches as well as blurred vision. (72) Patients often describe experiencing migraine headaches, which tend to occur immediately after extended periods of close work. (73) The

occurrence of convergence insufficiency within families suggests a possible genetic factor contributing to the condition. (71) The etiology is idiopathic in general. (74) There is no evidence to support the suggestion that convergence insufficiency is caused by issues with weak eye muscles or mechanical difficulties. (72)

It has been hypothesized, however, that the etiology of convergence insufficiency involves a low underlying accommodative convergence to accommodation ratio and an imbalance between accommodative convergence and fusional convergence. If this imbalance is overcome by fusional convergence training, the accommodative convergence to accommodation ratio can be changed and the symptoms may be relieved. (75) The reported prevalence of Convergence Insufficiency is highly variable, with an average prevalence of approximately 5%. Symptoms linked to Convergence Insufficiency can impact a person's quality of life by disrupting activities performed up close, such as those related to school or work. (72)

9.2.2 Relationship Between Convergence Insufficiency And Digital Screen Work

As already mentioned, Convergence insufficiency is associated with close screen work and trigeminal dysphoria. (4,60,69) An older study conducted in 1994 for example found a significant reduction in vergence after eighth of computer working (76). Nevertheless, this relationship between convergence insufficiency and digital screen work is complex. Extensive digital screen use or prolonged reading can

exarcabate existing issues with convergence and accommodation. Numerous individuals may experience mild difficulties in focusing or coordinating their eyes, which usually don't pose significant issues during regular visual tasks but exacerbate with prolonged close digital work and reading. (77)

At the same time, however, such activities also seem to potentially contribute to the onset of these problems. Therefore, it is also plausible to consider that a portion of the population may develop convergence insufficiency due to prolonged digital work. In a study by Mohan et al. in India, six children with an average age of about 14 and a half years were investigated regarding the impact of prolonged digital device usage, especially exceeding four hours per day, on binocular vergence and accommodation. The researchers employed the Convergence Insufficiency Symptom Survey questionnaire to evaluate symptoms. The results indicated that children spending more than four hours daily on digital devices showed abnormal binocular vergence and accommodation. Specifically, their mean CISS scores were lower compared to those with shorter durations of digital device usage. (78) .

9.2.3 Relationship between Accommodative Convergence and Convergence Accommodation

Accommodative Convergence and Convergence Accommodation are both concepts related to the coordination of the eyes while focusing on near objects. Accommodative convergence refers to the inward turning of the eyes when focusing

on near objects, driven by accommodative effort. In contrast, Convergence accommodation refers to the amount of focusing power that results from the inward movement of the eyes. Convergence and accommodation are therefore associated with each other and they are working together in order to ensure single, clear vision at varying distances. (79) Indeed, research suggests that change in function in one system can influence the other. For instance, poor accommodation has been implicated as a possible cause of Convergence Insufficiency. Prakash et al. (80) pointed to the reduction of accommodation by 23 percent in patients with Convergence Insufficiency. Von Noorden et al., (81) Bugola, (82) and Raskind (83) have reported that accommodative amplitude has been the cause for treatment-resistant Convergence Insufficiency. Cooper et al. (78) found that recruiting patients with the qualification criteria of having both Convergence Insufficiency and normal accommodation has been shown to be difficult. Marran et al. (84) suggests that the symptoms observed in the majority of cases of Convergence Insufficiency may stem from issues related to accommodative anomalies. In a limited study conducted by Jampolsky (85), it was observed that Convergence Insufficiency predominantly arose from deficient accommodation.

Furthermore, a study from Golebiowski et al. in 2019, revealed that extended smartphone usage for 60 minutes resulted in a significant decrease in binocular accommodative facility among young adults. (86) After implementing the interrelation between convergence and accommodation, there is further proof to the assumption that extended smartphone usage impacts convergence.

After elucidating the strong relationship between Convergence Insufficiency and accommodation it becomes clear that both systems are indeed interrelated. The

relevance of this relationship is underlined by the influence of stress on the development of trigeminal dysphoria Symptoms.

Literature has shown that the characteristic symptoms of trigeminal dysphoria indeed can originate from accommodative difficulties. (69,87) In the following segment the influence of stress on accommodation will be elaborated.

The parasympathetic system is primarily responsible for the innervation of the accommodation system, most importantly the ciliary muscle. The sympathetic nervous system is involved as well, ensuring the maintenance of accommodative balance between the resting and tonic phase. Imbalance between the sympathetic and parasympathetic nervous system can therefore trigger inappropriate accommodative responses at close vision. (69,88,89)

Increased stress, mental effort and attention have the potential to enhance sympathetic and parasympathetic innervation and as a result can lead autonomic nervous system imbalance in the eye. The theory has been suggested that when individuals undergo stress or mental exertion, there is an increase in sympathetic nervous system activity. This surge in activity can negatively affect the eyes' ability to focus on nearby objects, meaning the accommodative response might become compromised. To counteract the consequential reduced focus, there's an elevation in parasympathetic nervous system activity aimed at the ciliary muscle, responsible for accommodation. The ciliary muscle becomes overactive resulting in increased difficulty and therefore an amplified effort to focus on nearby objects. Consequently, this increased accommodative effort can induce eye misalignment due to heightened input for Accommodative Convergence. (69,90)

9.3 Pathophysiology of Trigeminal Dysphoria

9.3.1 Review of Fundamental Concepts

Eye pain can be triggered by the activation of the trigeminal nerve. The ophthalmic branch is the most sensitive and susceptible branch of the trigeminal nerve to irritation with its wide-reaching system of branches throughout the eye and orbit. (91) Numerous everyday factors, including caffeine consumption, alcohol intake, changes in weather, hormonal fluctuations, disruptions to sleep patterns, and irregular eating habits, can lead to irritation of this particular branch of the trigeminal nerve. (60)

As previously mentioned, Convergence Insufficiency is associated with trigeminal dysphoria. (4,60) Even though several explanations have been suggested, it is not fully clear why Convergence Insufficiency causes asthenopia-related symptoms. Nevertheless, one theory which is broadly accepted links the pathophysiology of trigeminal dysphoria to overstimulation of the trigeminal nerve due to misalignment of the eye. (69) In this theory, the pathophysiological pathway involved is similar to the one involved in migraines. (91)

When both eyes are open, they must exhibit precise alignment empowered by the extraocular muscles to ensure binocular fusion, a fundamental process for visual perception. (62,69) In order to ensure precise alignment, the sensory receptors of

the extraocular muscles provide proprioceptive information of the eyes to the brain and its visual system via the ophthalmic branch of the trigeminal nerve. (62) In cases of misalignment of the eyes, as in individuals with Convergence Insufficiency, binocular fusion is disrupted, triggering the brain's discomfort due to incongruent retinal images. This leads to corrective mechanisms realized by the extraocular muscles to maintain focus coherence. (62,69) There is a relatively large degree of corrective action necessary to ensure proper realignment of the eyes from the position where the eyes aim to align compared to how they actually have to align in order to ensure proper binocular vision. (4) This process leads to a constant overstimulation of the proprioceptive fibers of the ophthalmic branch of the trigeminal nerve. (69) This is especially true in activities of reading due to the constant necessity for readjustment of the position of the extraocular muscle positions as it requires constant readjustments of extraocular position word for word. (62,91,92) Figure 1 demonstrates how eye misalignment can lead to excessive stimulation of the trigeminal nerve, resulting in the typical symptoms of trigeminal dysphoria. (4)

The trigeminal caudalis nucleus serves as the intermediary between the eyes and the central nervous system. Consequently, the ophthalmic branch irritation triggers painful sensations in various regions including the eyes, head, and even neck, manifesting as symptoms like headaches, neck pain, and eye strain. (62,69) The neck pain which occurs in both migraine and trigeminal dysphoria can be partially explained by the length of the trigeminal nucleus caudalis, as previously mentioned. This nucleus, which is the longest in the entire brainstem, expands into the cervical spine at the level of the C1 and C2 vertebrae. (62) Literature suggests that the entire trigeminal nucleus caudalis potentially becomes irritated and overstimulated. In case

the irritation and overstimulation continues it can impact the entire brain, leading to a condition known as central sensitization. This manifests in difficulties with concentration, as well as symptoms like nausea, vomiting, and sensitivity to light and sound. (62,92)

Previously, the relationship between Convergence Insufficiency and digital work has been discussed. On the one hand, subtle underlying Convergence Insufficiency can be seen as a cause of close work tasks, on the other hand Convergence Insufficiency can be argued to be the result of this activity. The explanation of the former, however, seems more plausible as the pathophysiology of trigeminal dysphoria usually involves a mild underlying Convergence Insufficiency which is often too subtle for being classified as strabismus, yet it is significant enough to strain the visual system during close-up work and to exacerbate the Convergence Insufficiency, leading to symptoms. In such cases, the degree of eye misalignment observed is below the threshold usually associated with strabismus, often going unnoticed because it does not significantly affect binocular vision. However, the slight misalignment of the eyes during close-up tasks places significant stress on the visual system including the ophthalmic branch of the trigeminal nerve. This results in overstimulation of the trigeminal nerve as well as trigeminal dysphoria symptoms. (60)

As shown, trigeminal dysphoria can cause trigeminal nerve overstimulation and continuous irritation. This suggests that trigeminal dysphoria might have the potential to cause Trigeminal Neuropathology, especially in the context of an underlying Convergence Insufficiency, which often remains undisclosed to the patient. In order to elaborate this assumption, it might be of benefit to review another

pathophysiologic process, such as diabetes mellitus, which is known to be capable of causing neuropathy. (93)

The excess in sugar within the cellular microenvironment is the crucial factor in the pathophysiology of hyperglycemia induced cell injury. In cases of hyperglycemia, as we find in diabetes mellitus, the high availability of glucose molecules leads to an excessive oxidative metabolism of these molecules which lies beyond the maximum capacity of the mitochondria. (94) As a result, there is a significant increase in ROS production within the microenvironment of the cell signaling oxidative stress. Due to the increase in these radical molecules the scavenging capacity of antioxidants becomes insufficient, meaning they become incapable of neutralizing the radical component of ROS molecules. (95) The increased formation of superoxide ions, which present a subfamily of ROS, together with a diminished ability of antioxidant enzymes to neutralize these ions, is responsible for the crucial disruption in the balance of the mitochondrial electron transport chain. (94)

The commonality between hyperglycemia and overirritation induced pathophysiologies is the necessary increased neuronal metabolism accomplished by the mitochondria. Nerve fibers are susceptible to an elevated concentration of ROS molecules in their environment due to the rather small volume of these organelles. These are damaged in diabetic patients as a result of hyperglycemia, therefore limiting the amount of available energy in each nerve fiber. Nerve conduction blockage and axonal demyelination are the ultimate result. (96,97)

In a state of continuous nerve overexcitation and stimulation there is an increase in energy necessity and therefore metabolism. It can be assumed that the mitochondria are working in excess just as they are in diabetes induced hyperglycemia in order to supply enough energy for the ion pumps of the nerve, such as the sodium-potassium ATPase pump. The function of this pump is to keep the osmotic equilibrium and membrane potential in cells, playing an important role in initiating neuronal action potentials. (98) This implies that the sodium-potassium-ATPase pump might be very active in conditions of heightened nerve activity, such as in trigeminal dysphoria. Medical literature delving into the association between nerve hyperactivity and increase in activity of ion pumps of the nerve membrane is present. For instance, research has demonstrated that neurons of the hippocampus in rats indeed show heightened activity level of their sodium-potassium pump following pilocarpine-induced multiple status epilepticus, a condition which can be considered as a neural hyperactive state. (99) Additionally, it has been found that pentylenetetrazole-induced convulsions triggered significant swelling of astroglial cells as well as heightened sodium-potassium-ATPase activity in rats. (100) However, the role of the sodium-potassium-ATPase pump in neural hyperactivity states and therefore also in trigeminal dysphoria induced neuropathology remains complex.

Nevertheless, it can be assumed that the nerve hyperactivity may lead to increased activity of ion pumps and ultimately to increased stress of the neural mitochondria and ROS production, potentially culminating in neuropathy. In case of trigeminal dysphoria, overexcitation and irritation of the trigeminal nerve, especially in the

scenario of concomitant Convergence Insufficiency, may lead to trigeminal neuropathy.

9.3.2 Impact of Reading on the Pathophysiology of Trigeminal Dysphoria

Reading represents one of the few activities within the daily life where visual fusion occurs on a flat plane. The absence of retinal disparity cues during reading can lead to a less effective alignment of the eyes in individuals who have Convergence Insufficiency. This explains why symptoms are often experienced during reading or computer use but not during other close tasks. During close tasks, such as reading, the eyes must delicately balance accommodation and convergence, while also maintaining a stable position. Reduced retinal disparity cues during reading may add to the challenge of maintaining fusion. This combination of factors could contribute to the ocular fatigue experienced by individuals with Convergence Insufficiency when their convergence abilities are insufficient. (71)

Furthermore, when reading, there is a necessity for continuous transfer of images from the peripheral vision to the central vision. If there is a disparity between these two systems, the extraocular muscles must continually readjust the position of the eyes for binocular vision. (62,91,92) Therefore, there is an even greater effort by the visual system to properly align the eyes to ensure proper binocular alignment. The persistent attempt to realign induces excessive stimulation of the proprioceptive fibers of the ophthalmic nerve, culminating in ophthalmic nerve irritation. (62,69) This is especially the case in activities of looking at digital devices such as computer screens, tablets and smartphones. (59,61)

The difference between viewing content on a computer screen and reading printed text lies in the visual demand placed on the reader. Images on a screen are composed of numerous pixels, forming the image collectively. Often, the edges of the image or words are not sharply defined, especially if the resolution is low. This decline in resolution leads to poorer image quality, requiring the reader to exert more effort to understand the text or image clearly. Factors such as the contrast between the text and background, screen glare, and reflections can all influence the amount of visual strain required to perceive the content adequately. (101,102) This increase in visual demand likely contributes to the development of trigeminal dysphoria and in certain circumstances potentially even to trigeminal neuropathy. .

Although not directly related to the elaborated pathophysiology from above, the effect of blue light from digital screens on the health of the corneal nerves and therefore also on the ophthalmic branch of the trigeminal nerve should not be dismissed. In fact there is evidence that blue light exposure can cause alterations in nerve structure, such as decreased density, heightened tortuosity, and increased branching of nerve fibers. Additionally, blue light can increase the expression of TRPV1 and substance P in neurons projecting to the cornea. These changes are linked to ocular hyperalgesia, indicating that blue light exposure impacts pain perception and nerve function in the eye. (103)

9.3.3 Insights into Trigeminal Dysphoria-Induced Trigeminal Neuropathy Through Migraine Pathophysiology

The trigeminal system, implicated in migraines, is interconnected with the innervation of the eye. Migraine pathophysiology, seen as a sensory processing disorder, involves receiving pain signals from the ocular sensory system through the ophthalmic branch of the trigeminal nerve. This communication extends to the central trigeminal system, including the nucleus caudalis. Furthermore, the autonomic system, via the superior salivatory nucleus, partly links to the eye, affecting its blood vessels and contributing to common migraine symptoms. (73)

In the above elaborated theory of ophthalmic nerve overstimulation, the pathophysiological pathway involved is similar to the one involved in migraines. (91)

The trigeminal nerve is believed to be oversensitive in migraine patients. This oversensitivity might have a genetic cause, potentially explaining why just a portion of the population is experiencing this condition. (91,92)

The cornea has the largest density of innervation by the trigeminal nerve endings in the body. Irritation of these corneal nerves has been associated with migraine. (94) Confocal microscopy has been an effective in vivo tool to evaluate for morphological changes of the corneal nerve such as corneal nerve fiber density, corneal nerve fiber length, corneal nerve branch density and nerve fiber tortuosity. These parameters

help to classify corneal neuropathy. The fundamental constraint of present in vivo confocal microscopy lies in its ability to examine only a restricted region of interest, typically smaller than 500 square micrometers. (104) As a result, classification of neuropathy for larger nerves such as the ophthalmic branch on the basis of confocal microscopy seems problematic, not to mention that a biopsy would be necessary for the latter. It has been found that patients suffering from chronic migraine had a decreased density of innervation of the cornea. (105) That decrease in corneal nerve density has also been observed by Shetty et al (106). It is assumed that corneal nerves may be abnormal in chronic migraine, possibly as a result of the migraine disease process, which has the hypersensitivity of the trigeminal nerve in the center of its pathophysiology. (91,92) If this hypothesis is true that the pathology of the corneal nerves may be due to the migraine disease process (91), it would indicate that the ophthalmic branch potentially would also be neuropathic, as it appears unlikely that the migraine disease process can only affect the corneal nerves. The detectability of corneal neuropathy, in contrast to ophthalmic nerve neuropathy, however is higher due to the effectiveness of in vivo confocal microscopy, as previously described.

Migraine episodes have the potential to activate the trigeminal vascular system, triggering the release of inflammatory neuropeptides. Consequently, this can result in inflammation of nearby cranial nerves. (107)

It has been observed that migraine-related eye pain may stem from difficulties in processing pain signals. The reduction in nerve density indicates a potential

neuropathy to the pain. (108) In fact, it has been observed that neuropathic corneal pain tends to be more prevalent in patients with existing chronic migraines. (109) Peripheral sensitization, a process in which peripheral nerves are activated as a result of nerve injury, sets the stage for central sensitization, in the process of which trigeminal neurons in the brainstem can become hyperactive. In migraines, central sensitization is thought to play a very important role in the migraine process, ultimately resulting in allodynia. (108).

Noteworthily, the symptoms of trigeminal dysphoria in part resemble the symptoms of corneal neuropathy, most importantly dry eye sensation as well as burning pain. (109)

9.4 Summation of Thoughts

The ophthalmic branch of the trigeminal nerve, with its extensive network of branches in the eye and orbit, is highly sensitive to irritation. This nerve is in the center of the pathophysiology of both migraine and trigeminal dysphoria due to its oversensitivity and hyperactivity, respectively. In migraine, neuropathological changes in the corneal nerve have been found, potentially indicating a pathology of the ophthalmic nerve as well. For individuals with Convergence Insufficiency and an daily extensive usage of digital devices it can be assumed that the continuous overirritation of the trigeminal nerve might evolve into Neuropathology. Therefore, timely education and prevention by modifying behavioral aspects are crucial for

inhibiting a more extensive impact on the quality of life of individuals suffering from trigeminal dysphoria. Further research on the impact of this condition on the trigeminal nerve is encouraged as literature is sparse and relevance is high.

10. Conclusion

Trigeminal neuropathy is a disease which can have potentially debilitating consequences for the individuals affected. Unfortunately, the disease is still not well recognized and patients may not receive the care they need. Diagnosing this disorder requires experience and the ability to meticulously listen and analyze specific details of symptoms and recognize patterns of presentation of various etiologies and impacts. Furthermore, the ability to keep apart the diagnosis of painful trigeminal neuropathy from other diseases showing a somewhat similar presentation is important. Treatment for painful trigeminal neuropathy is available but not as effective as of similar and more well known conditions such as trigeminal neuralgia. With this work I aimed to improve the awareness of this disease and in doing so contribute to the medical community.

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13. Biography

Victor Markowitz was born on May 15, 1998, in Munich, Germany. He completed his 12 years of schooling and graduated from high school in Unterhaching, Germany. In 2017, following his high school education, he was enrolled for one year in the Ludwig

Maximilian University to study physics. During this year, Victor Markowitz passed the licence exam for medical studies in Zagreb. He immediately began his studies at the University of Zagreb School of Medicine in the English program and is currently in his sixth year. In his free time, he enjoys playing music and cooking. He aspires to have a medical career and is considering specializing in neurology.