Facultad de Medicina

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Tratamiento de la neuralgia del trigémino refractaria en un hospital de tercer nivel

Treatment of refractory trigeminal neuralgia in a third level hospital

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Santander, Mayo 2024

Index

1. Resumen

Introducción: La neuralgia del trigémino es una enfermedad caracterizada por un dolor orofacial unilateral similar a una descarga eléctrica de corta duración siguiendo una o más de las ramas del nervio trigémino. Es una enfermedad muy refractaria a tratamiento médico necesitando en ocasiones distintos fármacos orales y, en ocasiones, terapias avanzadas para controlar el dolor.

Objetivos: Evaluar las características demográficas, clínicas de la enfermedad, pruebas de imagen realizadas, clasificación y tratamientos actualmente existentes evaluando su eficacia y tolerabilidad a los mismos.

Métodos: Se llevó a cabo la recogida de datos en una cohorte de 41 pacientes con neuralgia del trigémino refractaria en seguimiento por la Unidad de Cefaleas del servicio de Neurología del Hospital Universitario Marqués de Valdecilla. Se obtuvieron datos de sus antecedentes médicos, características clínicas y pruebas de imagen realizadas. Se analizaron las líneas de tratamiento preventivo oral recibidas por cada paciente, dosis de inicio y mantenimiento ideales de cada fármaco, efectos adversos y datos de eficacia o refractariedad. Finalmente, se han analizado las terapias avanzadas realizadas en cada paciente de acuerdo con las características de su enfermedad y la eficacia de las mismas.

Resultados: De los 41 pacientes del estudio, 54% eran mujeres y 46% hombres. Los antecedentes personales más frecuentes de la muestra fueron la HTA, el tabaco y la migraña. La edad media de inicio de los síntomas fue 54,3±15,3 años, sin diferencias entre sexos. La mayoría de los diagnósticos fueron realizados por un neurólogo. En relación a las características de la enfermedad, un 63,4% de los pacientes presentaban dolor en el lado derecho y un 36,6% en el lado izquierdo. V2 fue la rama más afectada (34,1%), seguido por V3 (31,7%) y V2+V3 (12,2%), siendo V1 la rama menos afectada (7,3%). La prueba de imagen más realizada para la caracterización de la neuralgia fue la RMN en un 87,8% de los pacientes (ampliada a angioRMN en un 94,4% de ellos). En las pruebas de imagen encontramos un contacto vascular en el 46,3% de los pacientes (NT Clásica), no encontramos ningún hallazgo en el 31,7% (NT Idiopática) y patologías secundarias en el 7,3% de los pacientes (NT Secundaria). El fármaco oral de primera línea más usado ha sido la carbamazepina en un 75,6% de los pacientes, siendo sus principales efectos adversos inestabilidad (77,4%), somnolencia (51,6%) y confusión (12,9%). En cuanto a las terapias avanzadas, la cirugía descompresiva ha sido la que ha logrado una mayor eficacia en nuestros pacientes, un 57,1% de los pacientes sometidos a la intervención refirieron una mejoría completa del dolor con una reducción estadísticamente significativa en los fármacos orales usados a los 3 meses del procedimiento.

Conclusiones: Las características demográficas y clínicas de los pacientes estudiados son similares a los descritos en la literatura. La NT está infradiagnosticada fuera del servicio de Neurología. El fármaco más utilizado en el tratamiento es la carbamazepina aunque conviene individualizar en cada paciente debido a sus efectos secundarios. La terapia avanzada más efectiva es la cirugía descompresiva en aquellos casos en los que se ha encontrado un contacto vascular (NT Clásica).

Palabras clave: neuralgia del trigémino (NT), resonancia magnética (RMN), tratamiento farmacológico, idiopática, carbamazepina, cirugía descompresiva.

2. Abstract

Introduction: Trigeminal neuralgia is a disease characterized by unilateral orofacial pain similar to an electric shock of short duration with an abrupt beginning and end following one or more of the divisions of the trigeminal nerve. It is a disease that is very refractory to medical treatment, sometimes requiring several lines of different oral drugs and advanced therapies for pain management.

Objectives: To evaluate demographic and clinical characteristics of the disease, imaging tests performed, classification and currently existing treatments, assessing their efficacy and tolerability.

Methods: Data collection was carried out in a cohort of 41 patients with refractory trigeminal neuralgia under follow-up by the Headache and neuralgia unit of the Neurology Department of the Marqués de Valdecilla University Hospital. Data were obtained on their medical history, clinical characteristics of the pathology, neuroimaging tests, and findings of interest found in these imaging tests. The lines of oral preventive treatment received by each patient, ideal starting and maintenance doses of each drug, main adverse effects of the drugs and efficacy or refractoriness data were analyzed. Finally, the advanced therapies performed in each patient according to the characteristics of their disease and their efficacy data were analyzed.

Results: Of the 41 patients in the study, 54% were women and 46% men. The most frequent personal antecedents in the sample were HBP, smoking and migraine. The mean age of symptom onset was 54.3±15.3 years, with no difference between sexes. Most of the diagnoses were made by a neurologist. In terms of disease characteristics, 63.4% of patients had right-sided pain and 36.6% left-sided. Furthermore, V2 was the most affected branch (34.1%), followed by V3 (31.7%) and V2+V3 (12.2%), with V1 being the least affected branch (7.3%). The imaging test most frequently used to characterize neuralgia was MRI in 87.8% of patients (extended to MRI angiography in 94.4% of patients). We found a vascular contact in 46.3% of the patients (Classical TN), no findings in 31.7% (Idiopathic TN) and secondary pathologies causing the disease in 7.3% of the patients (Secondary TN). The most used first-line oral drug was carbamazepine in 75.6% of patients, with gait instability (77.4%), somnolence (51.6%) and confusion (12.9%) being the main adverse effects. In terms of advanced therapies, decompressive surgery has achieved the greatest efficacy in our patients, with 57.1% of the patients who underwent the procedure reporting a complete improvement of the disease and a statistically significant difference in the oral drugs used before and 3 months after the procedure.

Conclusions: The demographic and clinical characteristics of the patients studied are similar to those described in the literature. TN is underdiagnosed outside the Neurology department. Carbamazepine is the most used drug in the treatment of TN, although with various side effects. The most effective advanced therapy is decompressive surgery in cases where vascular contact has been observed (classic TN).

Keywords: trigeminal neuralgia (TN), magnetic resonance imaging (MRI), oral preventive treatment, idiopathic, carbamazepine, decompressive surgery.

3. Introduction

3.1. Definition

Trigeminal neuralgia (TGN), also called Tic Doloreux, Fothergill's disease, Prosopalgia or Suicide disease, is defined by the International Association for the Study of Pain (IASP) as ''unilateral painful orofacial condition characterized by brief duration of electric shock-like sensation with an abrupt onset and termination, and limited to one or more sensory divisions of the trigeminal nerve''. Typically, these sudden attacks of pain are intermittent, severe, sharp, lasting from a few seconds to minutes with pain-free intervals between attacks. There is very rare variant with constant pain.

Pain can appear spontaneously or due to a `trigger` factor that triggers it due to mechanical stimuli or movements such as mastication. TGN most frequently affects the maxillary (V2) and mandibular (V3) branches of the nerve. The pain is usually unilateral (although there are cases of bilateral pain especially in the secondary forms) and usually affects the right side more frequently than the left[(1)].

3.2. Anatomy

The trigeminal nerve, the largest among the cranial nerves, functions as a sensory-motor nerve, offering sensory and motor innervation to the face. It facilitates facial sensation through its three primary segments (opthalmic, maxilary and mandibular branches) and controls the muscles of mastication via the mandibular branch.

In the brainstem, the trigeminal nerve houses both motor and sensory nuclei. The sensory aspect is divided into three nuclei: the principal sensory nucleus, spinal nucleus and mesencephalic nucleus. Positioned on the lateral surface of the pontine tegmentum, the motor nucleus, serving as the principal sensory nucleus, is situated on the posterolateral surface of the pontine tegmentum, lateral to the motor nucleus.

The mesencephalic nucleus is an upward extension of the pontine nucleus within the midbrain, positioned near the superior cerebellar peduncle. Additionally, the spinal nucleus extends caudally from the pontine nucleus, descending from the lower pons to the spinal cord (C2-C4 level) and connecting with the cervical grey matter in the dorsal horns.

Originating from the anterolateral surface of the midpons, the trigeminal nerve comprises sensory and motor roots with the sensory part located posterolaterally. The nerve traverses the prepontine cistern and enters Meckel`s cave through an opening in the dura mater called 'porus trigeminal'. The point where the roots emerge from the brain stem is known as root entry zone (RET). The RET is of grear importance because it is the area where compression of the trigeminal nerve by vascular loops occurs most frequently[(1)].

Within Meckel`s cave, the Gasser or semilunar ganglion (sensory branch) divides into three subdivisions: ophthalmic (V1), maxillary (V2) and mandibular (V3) nerves. The

motor root passes directly beneath the ganglion in Meckel`s cave. Both the ophthalmic (V1) and maxillary (V2) divisions cross the cavernous sinus on its lateral wall, below the abducens nerve[2].

Starting from Gasser's ganglion, which is located on the dorsal surface of the petrous portion of the temporal bone[3], the distribution branches head forwards in search of various orifices at the base of the skull through which they reach their distribution territory. But before passing through these orifices, the 3 sensory branches are connected to the external wall of the cavernous sinus, passing through the thickness of the dura mater, especially V1 and V2.

After crossing this sector, V1 (ophthalmic branch) reaches the superior orbital fissure (or sphenoid fissure) and passes through it to reach the orbit where it is distributed. Its territory of distribution encompasses the sensitivity of the eyeball and conjunctiva, eyelids, frontal region, nasal skin, naso-sinus mucosa and vegetative innervation of the lacrimal glands.

In the case of V2 (maxillary branch), it seeks the foramen rotundum in the middle fossa of the skull base reaching the pterygopalatine region where it provides multiple collateral branches. The main trunk of this branch continues into the floor of the orbit to emerge into the face through the infraorbital foramen and distribute to the skin of the mid-facial territory as well as part of the oral cavity.

Finally, V3 (mandibular branch), which travels with the motor nerve root, crosses the base of the skull through the foramen ovale, reaching the deep masticatory space. There it gives rise to multiple nerve branches, sensory to the lower third of the face and part of the oral cavity, as well as the temporomandibular joint (mandibular branch), while the motor branches are in charge of the masticatory muscles[4].

Figure 1. Origin and course of trigeminal nerve. Girija Prasad Rath. Handbook of trigeminal neuralgia. Singapore Springer; 2019.

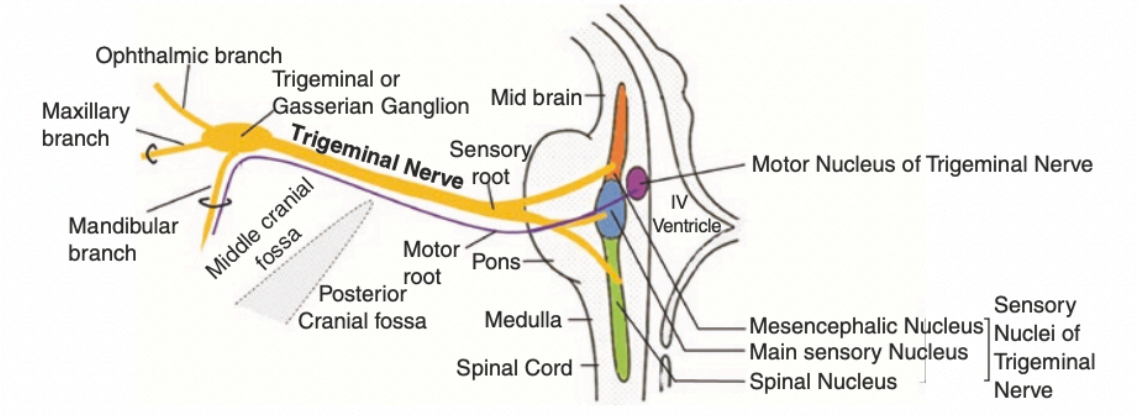
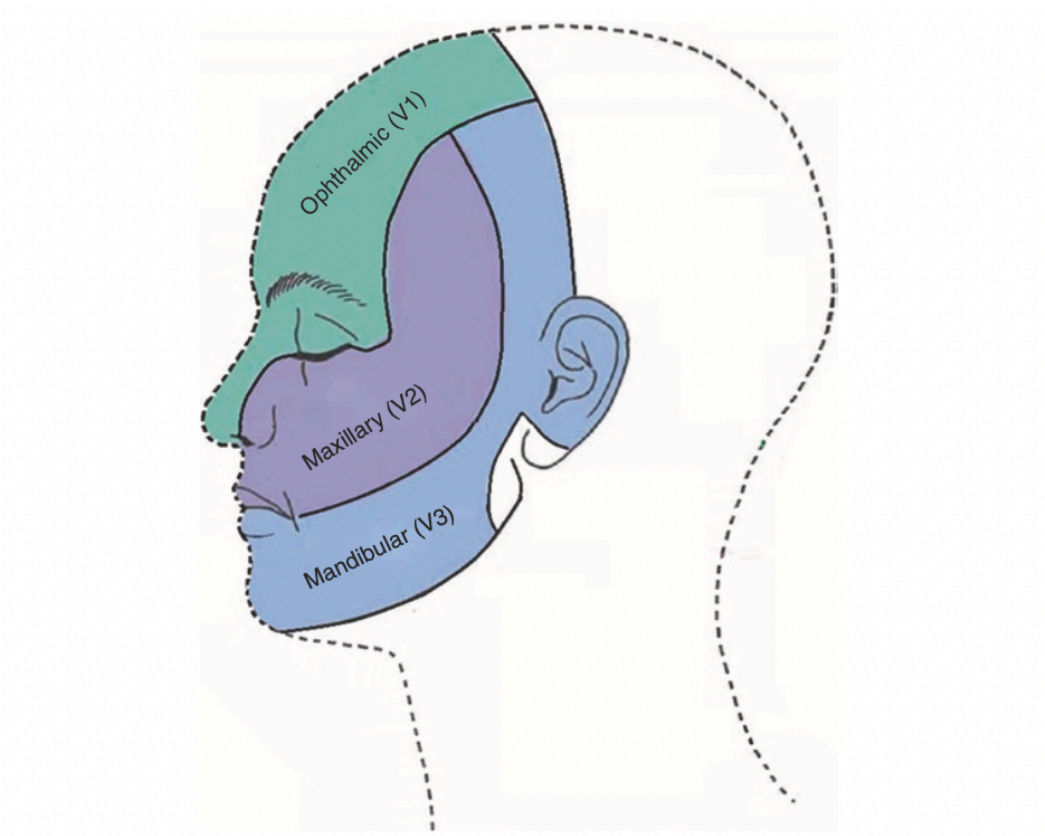


Figure 2. Sensory distribution of three primary divisions of the trigeminal nerve. Girija Prasad Rath. Handbook of trigeminal neuralgia. Singapore Springer; 2019.



3.3. Epidemiology

There are few epidemiological studies about trigeminal neuralgia and most of them have a small number of patients and TGN is frequently misdiagnosed and underdiagnosed. TGN world prevalence is estimated to be 0.16%-0.3%[(5)]. The incidence is variably between studies with a range from 4.3 to 27 new cases per 100.000 people per year. The incidence is higher in women than men and increases with age. The male-to-female prevalence ratio ranges from 1 to 1.5 to 1 to 1.7[(6)]. The average age of onset of classical TGN is 53 years and 43 years in secondary TGN[(7)].
In Spain, according to data from the Spanish Society of Neurology (SEN), trigeminal neuralgia affects more than 30,000 people and around 2,000 new cases are diagnosed each year in our country. In recent years there has been an increase in incidence and prevalence due to the progressive ageing of the population. From the sixth decade of life onwards it constitutes 90% of the cranial neuralgias that occur in older people [(8)].

This disease has a significant impact on the quality of life of patients, primarily due to the intensity of pain. The electric pains experienced by these patients lead to diagnostic delays and a continuous fear of sudden attacks. Trigeminal neuralgia patients suffer from depression and anxiety three times more than the general population. The disease is accompanied by impaired performance in daily activities, social isolation, sleep

disturbances, asthenia and anorexia. Psychiatric comorbidity is closely related to the intensity of pain and the duration of the disease[9].

Furthermore, trigeminal neuralgia has a considerable economic impact as many patients affected by the disease are of working age, leading to over 50% of patients experiencing work limitations[10].

3.4. Etiology

It is important to know the etiology of TGN in order to choose proper management and elimination of contributing factors. Although there are many patients who have no identifiable cause of the disease and it remains idiopathic[1].

In the 1934 it was proposed that in at least 30% of TGN patients the pain was caused by the compression of the trigeminal nerve by a blood vessel. Nowadays, it is agreed that the most common cause of TGN is compression and morphological changes of the nerve usually located in the cerebellopontine cistern[11]. There are other causes of TGN, some of them caused by secondary diseases, nerve compression by tumors, among other factors.

There are also hereditary forms of TGN that constitute less than 4-5% overall TGN, however patients with bilateral form have a higher hereditary predisposition than those with unilateral presentation. Familial forms are rare, occurring in approximately 1-2% of patients. There are cases in families where the predominant inheritance pattern is autosomal dominant with a phenomenon of genetic anticipation[12]. Although there is not full evidence, it appears that people with hypertension and migraine have a higher risk of developing TGN[1].

3.4.1. Direct trauma or compression of the trigeminal nerve

The most common is compression of the trigeminal nerve at the root entry zone (REZ) to the pons. This compression is often caused by a vascular loop, arteriovenous malformation, tumors such as meningiomas, schwannomas, tuberculomas, aneurysms, or arachnoid cysts. Tumors account for 2% of trigeminal neuralgia cases, with vascular loop compression being the most frequent cause (80-90% of cases). The arteries most commonly implicated are the superior cerebellar artery, anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), or vertebral artery. It's important to note that not everyone with vascular compression develops trigeminal neuralgia; the presence of a vascular loop does not explain symptoms in all cases. However, in trigeminal neuralgia cases, a majority of patients exhibit vascular nerve compression. Due to the nerve fiber arrangement, compression of medial fibers leads to symptoms along the V2 pathway, while lateral or caudal fiber compression causes symptoms in V3, and cranial fiber involvement results in V1 symptoms.

3.4.2. Causes related to systemic diseases.

Multiple sclerosis (MS) may be associated with sensory alterations like painless paresthesias or facial pain, possibly due to trigeminal neuralgia. Secondary involvement of the trigeminal nerve in MS is less common than perceived, occurring in 0.9-4.5% of MS patients[1]. Conversely, 1.7-15% of trigeminal neuralgia patients also receive a diagnosis of multiple sclerosis[13]. In these patients, magnetic resonance imaging reveals multiple sclerosis plaques along the nerve and demyelinating lesions in the root entry zone at the pons level[14]. Characteristics of these patients include a higher prevalence in women than men, an earlier onset, typically between 40-50 years, and a tendency for right-sided facial involvement, although it is common for pain to be bilateral in multiple sclerosis; 18% of patients with trigeminal neuralgia and multiple sclerosis report experiencing episodes of bilateral pain. It's essential to note that in 37% of patients with secondary trigeminal neuralgia, there are clinical impairments in discriminatory sensory functions, which strongly suggest the presence of secondary TN. Although an earlier age, bilateral nature and sensory deficits of the trigeminal nerve raise suspicion of trigeminal neuralgia associated with multiple sclerosis, the absence of these clinical features does not rule out secondary TN due to MS.

Other systemic diseases such as vascular disorders, rheumatoid arthritis, diabetes mellitus, are believed to be risk factors for trigeminal neuralgia development[1]. Studies suggest an increased risk in patients with hypertension or atherosclerosis, potentially due to functional and morphological changes altering nerve vascular supply, contributing to neuralgia[15].

3.4.3. Diverse causes

Trigeminal neuralgia can arise postoperatively following surgeries unrelated to the trigeminal nerve. This secondary effect might result from changes in pressure and cerebrospinal fluid flow, leading to contact between the trigeminal nerve and vascular structures, causing neuralgic pain[16]. The occurrence depends on individual patient susceptibility. Allergy has also been proposed as a cause, given observations of elevated serum histamine levels, degranulated mast cells, and immune complex collections around the nerve. Other potential causes include narrowing of bony channels at the nerve exit, temporomandibular joint pathology, elevated vertex of the petrous pyramid of the temporal bone, acute bony angle of the petrous crest, and shortening of the trigeminal nerve cistern, all contributing factors to trigeminal neuralgia[17].

3.5. Pathophysiology

The symptoms of trigeminal neuralgia have been proposed to result from the demyelination of the nerve leading to ephaptic transmission of impulses[18]. This is explained as follows: the injury to the sensory root can occur at the entry point to the pons (extra-axial) or within the fascicle (intra-axial). Various alterations in the trigeminal nerve secondary to compression by vascular structures, focal demyelination at the entry

root to the pons, axonal atrophy, damage to Schwann cells, and myelin are observed[9]. Various pathophysiological hypotheses will be explained below.

In Classical TN, there is compression of the trigeminal nerve at the root entry zone (REZ) or by a vascular loop. In this entry zone of the root into the pons, the transition from peripheral myelination by Schwann cells to central myelination by oligodendrocytes occurs, making this nerve zone more susceptible to compression and demyelination injuries[19]. In most cases, this compression is secondary to an arterial vessel or the superior cerebellar artery; less commonly, venous compression occurs[20]. This compression-induced injury can lead to the formation of focal areas of axonal demyelination, where spontaneous action potentials may occur, traveling bidirectionally along the nerve. Similarly, a single action potential can evoke sustained posterior discharges of more action potentials in these areas.

Another hypothesis is that nerve injury can cause abnormal coupling between primary afferents, creating atypical neuronal communication leading to ephaptic transmission. Nerve root or ganglion damage results in the formation of a group of hyperexcitable primary sensory neurons linked to each other, discharging action potentials spontaneously or evoked by other connected neurons. These potentials propagate rapidly through ephaptic mechanisms to excite an entire population of adjacent sensory neurons, clinically giving rise to a sudden burst of pain.

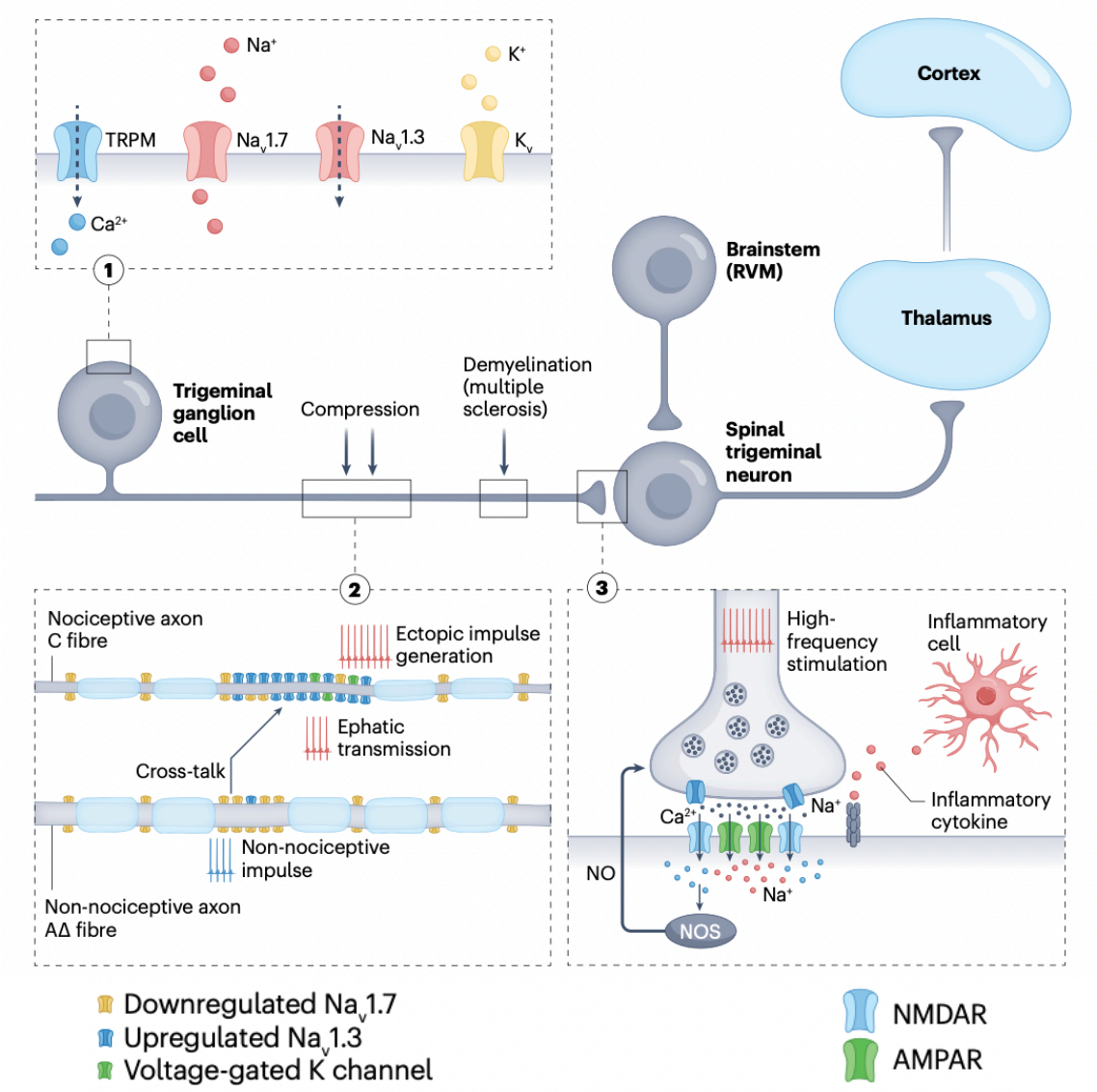
This cross-ephaptic communication may explain the trigger zone mechanism observed in trigeminal neuralgia. A harmless cutaneous stimulus can activate these hyperexcitable neurons and ephaptic communication, triggering spontaneous action potentials and sudden pain attacks[21]. This trigger zone phenomenon is related to interactions between low-threshold, large-diameter, fast-conducting sensory afferents (A-beta fibers) and smaller-caliber fibers carrying nociception (A-delta and C fibers).

The characteristic refractory period after the TN attack can be explained by the suppressive effect of A-fiber stimulation on C-fiber responses and C-fiber stimulation o A-fibers through central inhibitory mechanisms. By contrast, ephaptic cross-communication and ectopic impulse generation cannot explain the presence of concomitant continuous pain. It has been hypothesized that in these patients there may be a centrally mediated facilitation of nociceptive processing or a reduced descending inhibitory mechanism.

On the other hand, in idiopathic trigeminal neuralgia (where no abnormalities are found in imaging tests, indicating no compression or identifiable local or systemic disorders), multiple theories have been proposed, with the involvement of sodium ion channels standing out[20]. There is accumulating evidence that voltage-gated sodium channels (VGSCs) play a crucial role in the generation of ectopic activity in trigeminal afferents[22].

Some studies have shown that dysfunctional NaV 1.1, 1.3, 1.6, 1.7 and 1.8 channels may play a role in triggering trigeminal neuralgia[23]. Mutations in the NaV 1.7 channel are suggested to cause congenital insensitivity to pain or chronic neuropathic pain syndromes, while co-expression with NaV 1.8 sustains the initial action potential. Also some studies suggest that a Met136Val mutation in SCN8A (gene coding for sodium channel Nav 1.6) increases the excitability of the trigeminal ganglion, and thereby reduces the threshold for action potentials in TG neurons. By contrast there is an upregulation of Nav 1.3 and Nav 1.1[24], and a downregulation of Nav 1.7[21] (Figure 3). Increased attention has been drawn to gain of function mutations of voltage gated sodium channels (NaV) because sodium channel blockers as carbamazepine are the most effective drugs to relieve trigeminal neuralgia pain[23] which is why some researchers believe that there are trigeminal neuralgias with calcium channel mutations that would explain the good response of some patients to gabapentin, which works as a calcium channel blocker[21].

Figure 3. Proposed molecular mechanisms of TN[39].



3.6. Types of trigeminal neuralgia – Classification

Table 2. Classification of trigeminal neuralgia according to ICHD III:

Classical trigeminal neuralgia
• Classical trigeminal neuralgia, purely paroxysmal • Classical trigeminal neuralgia with concomitant continuous pain
Secondary trigeminal neuralgia
• Trigeminal neuralgia attributed to multiple sclerosis • Trigeminal neuralgia attributed to space-occupying lesion • Trigeminal neuralgia attributed to other cause
Idiopathic trigeminal neuralgia
• Idiopathic trigeminal neuralgia, purely paroxysmal • Idiopathic trigeminal neuralgia with concomitant continuous pain

The International Classification of Headache Disorders in its third edition (ICHD-3) classifies pain attributable to a lesion or disease of the trigeminal nerve into Trigeminal Neuralgia (TN) and Painful Trigeminal Neuropathy. In this case, we will focus on Trigeminal Neuralgia, which can be further subdivided into three main types based on the etiology of the pain: classical, idiopathic, and secondary[9].

3.6.1. Classical trigeminal neuralgia

The category of classical trigeminal neuralgia refers to cases where the condition is likely caused by compression of the nerve root by a tortuous blood vessel. Compression of this vessel occurs in the sensory portion of the trigeminal nerve, near the root entry zone (REZ) in the brainstem. Typically, the compression is caused by a branch of the basilar artery, with the superior cerebellar artery being responsible in 58-75% of patients. Venous compressions are less common (10%). It's important to note that a simple contact between the nerve and a vascular structure does not seem to be sufficient to explain the disorder. For trigeminal neuralgia to be due to neurovascular compression, the vessel must induce alterations in the trigeminal root, such as distortion or atrophy. The most characteristic finding in surgery is a tortuous artery or arterial loop impinging on the medial aspect of the trigeminal root at its entry zone into the brainstem, causing lateral displacement, distortion, flattening, or atrophy of the trigeminal root[19]. This contributes to a better surgical candidate selection, as those with only vascular contact do not experience improvement after decompression surgery. Patients with atrophic

alterations in the nerve root due to vascular compression by an arterial loop are good candidates for microvascular decompression surgery.

3.6.2. Secondary trigeminal neuralgia

Secondary TN manifests as recurrent crises of unilateral facial pain that meet TN criteria, with documented underlying disease causing and explaining the neuralgia. Approximately 15% of trigeminal neuralgias are secondary. Clinical features suggestive of a secondary form include onset before the age of 50 (appearing at a younger age than classical or idiopathic forms), bilateral involvement, involvement of the first trigeminal branch, and signs and symptoms of sensory dysfunction in addition to pain[9]. The main causes of secondary trigeminal neuralgia are multiple sclerosis (MS) or tumor compression, mainly in the cerebellopontine angle. In adults, the most common cause of secondary TN is extra-axial compression, mostly by tumors. Conversely, in young patients, it is typically intra-axial due to multiple sclerosis. Tumors account for 3 to 9.4% of all TN patients, compressing the nerve root. Tumors are located along the nerve's course (meningioma, neurinoma, meningeal carcinomatosis, epidermoid tumors) or in the posterior fossa (meningioma and neurinoma). Interestingly, trigeminal neuromas (very rare tumors) have not been associated with trigeminal neuralgia. Compression of the trigeminal nerve by tumors eventually leads to focal demyelination of the nerve root, triggering the same generation of high-frequency discharges in denuded axons as seen in vascular nerve compression. MS is also a common cause (2-11% of all cases). The risk of TN is 20 times higher in this disease, affecting 2-5% of patients. In the case of TN related to multiple sclerosis, it is attributed to a demyelinating plaque in the trigeminal nerve fascicle as it passes through the ventral pons[19]. 3.6% of secondary TN is due to cranial bone disease (osteomyelitis, Paget's disease, osteomas), arteriovenous malformation, dural fistula, pontine infarction, tuberculoma, cholesteatoma, arachnoiditis, hydrocephalus, lipoma, etc.

3.6.3. Idiopathic trigeminal neuralgia

Pain in the trigeminal nerve territory without being able to identify any cause for the pain. In these cases, neither neuroimaging nor neurophysiological tests find any cause or disease that can explain the pain[1]. They account for approximately 10% of cases.

3.6.4. Other classifications

It's also important to note that according to ICHD-III, both classical and idiopathic trigeminal neuralgia are further subdivided into trigeminal neuralgia with continuous or nearly continuous pain between attacks (referred to in other classifications based on symptoms as Atypical Trigeminal Neuralgia or TN type 2 according to the Burchiel classification)[11] and purely paroxysmal trigeminal neuralgia, characterized by pain-free intervals between paroxysmal attacks[25] (Typical or TN type 1).

Table 3. Comparision of TN Classifications[26].

Classifications	ICHD-3	Typical vs. Atypical TN by Ramussen	Burchiel Classifications
Characteristic	This classification of TN is the most universally accepted among clinicians and academics.	This is the first classification that subclassify TN based on its attack characteristics in 1990	The classification by Burchiel categorized seven types of TN based on the pain characteristic or its associated eliciting event in order to provide a framework to better diagnose and treat different types of TN.
Subclassifications	• Classical TN • Secondary TN • Idiopathic TN *Classical and Idiopathic TN are also sub-categorized as ''purely paroxysmal'' or ''with concomitant continuous pain''.	• Typical TN: sharp, electrical and paroxysmal pain, mostly located in V2 and V3. • Atypical TN: pain describeb as dull, constant, and located in all 3 divisions.	• TN type I: sharp, electrical shock-like, episodic pain due to neurovascular compression of TN. • TN type II: constant pain >50% of the time. • TN due to an injury. • Trigeminal deafferentation pain (post-surgical). • TN secondary to multiple sclerosis. • Infection related postherpetic TN • Atypical somatoform facial pain
Comments	Most recent classification of TN. Helps treatment modalities (medical vs. surgical)	Classification too broad to guide specific treatment based on symptons alone.	This classification guides differencial diagnosis by using objective and reproducible criteria.

3.7. Clinical features

The pain of trigeminal neuralgia is based on three main characteristics: pain restricted to the territory of one or more divisions of the trigeminal nerve, paroxysms of pain that are sudden, intense, and very brief (lasting 10-15 seconds[26] to minutes, but more frequently seconds), and described as a "shock" or "electric sensation"[20]. Between 91-99% of patients report these paroxysmal pain attacks, indicating that this trait is pathognomonic of trigeminal neuralgia[19]. The pain starts and ends abruptly. The frequency of pain attacks varies among patients, ranging from a few attacks to hundreds[20]. These pain episodes are followed by a refractory period during which the episode cannot be repeated; the duration of this pain-free refractory period varies among patients[26]. The pain associated with the attack may be accompanied by involuntary contraction of the face, which is why trigeminal neuralgia is also known as "Tic Douloureux"[27]. It is important to note that 14-50% of patients[23] may experience concomitant less intense, continuous, or nearly continuous dull, pulsating pain in the same area where the intermittent pain attack occurs[20].

These pain attacks are typically unilateral, more frequently affecting the right side (57%) than the left side (43%)[5] of the face, although there are cases where the nerves are affected bilaterally (bilateral involvement should raise suspicion of secondary causes). The most affected branches are the maxillary branch (V2) and the mandibular branch (V3), with the ophthalmic branch (V1) rarely affected (Figure 4). When V3 is affected, patients may complain of weakness while chewing and deviation of the jaw when opening the mouth, or they may present with serous otitis media (due to dysfunction of the Eustachian tube from malfunctioning of the tensor veli palatini muscle). Additionally, although rare, if V1 is affected, the corneal reflex may be absent (nasociliary nerve) with an increased risk of corneal injury and ulceration[27].

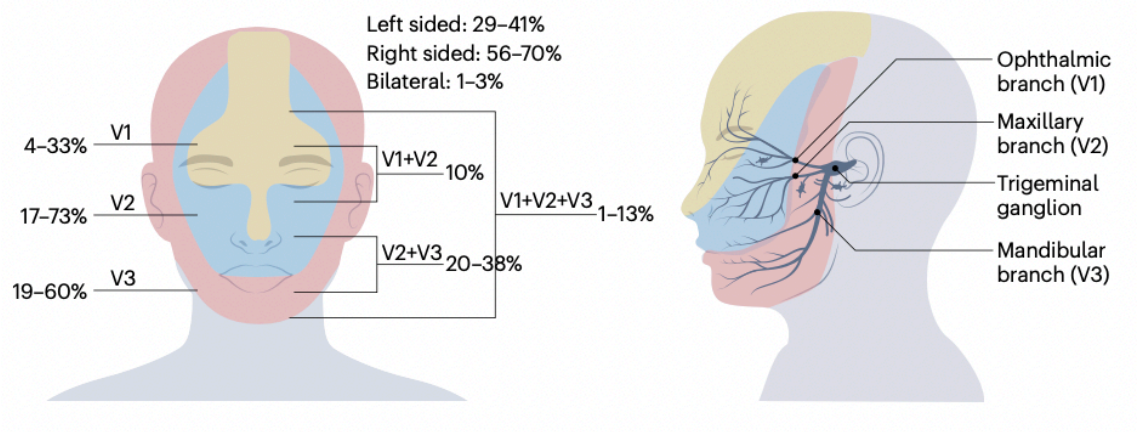
Pain crises are triggered by trigger phenomena; excitation of the cutaneous and mucosal territory (more unusual) in the area where the neuralgia is located produces pain crises. These areas are called trigger zones and are usually within the painful territory. Stimulation such as touch, facial expressions, chewing, and speaking are most effective in triggering pain, while thermal sensations, painful stimuli, and pressure in the area are usually ineffective[5].

During crises, some patients may experience vasomotor phenomena and autonomic symptoms: vasodilation and congestion of ocular and nasal mucosa. The painful attack is followed, in some cases, by facial flushing, tearing, and rhinorrhea. This phenomenon is due to vasodilatory stimulation or inhibition of the vasoconstrictor system. Other authors believe that facial flushing may result from stimulation of the greater superficial petrosal nerve, which is close to the Gasser ganglion. The autonomic symptoms presented by some patients can complicate the diagnosis of TN with SUNCT.

It is important to consider the psychological consequences for patients with this condition. They live with fear of sudden pain attacks that can lead to sleep deprivation (more commonly difficulty falling asleep, as attacks are less likely to occur in the middle

of the night), irritability, severe anticipatory anxiety, depression, and even dehydration and malnutrition due to fear of triggering an attack through chewing[27].

Figure 4. Localization of pain in TN[39].



3.8. Diagnosis

Trigeminal neuralgia is a clinical diagnosis, as the diagnostic criteria are based on the patient's history and require a detailed anamnesis, followed by a comprehensive clinical examination[23]. Patients with a characteristic clinical history and normal neurological examination, except for pain, may be treated without the need for further tests. However, modern treatments for trigeminal neuralgia (TN) include pre-treatment imaging tests to exclude secondary causes of TN.

3.8.1. Semiology and Examination

Typically, physical and neurological examinations are normal in patients with trigeminal neuralgia. Any abnormal neurological findings should raise suspicion of secondary trigeminal neuralgia. During the physical examination, it is important to identify trigger points that, when stimulated, can trigger paroxysmal pain attacks. Evoking these painful episodes allows us to gather information about the location of the pain, measure its duration, and check for the characteristic refractory period[23]. Additionally, this approach allows us to assess the presence of accompanying autonomic signs (conjunctival injection, tearing, rhinorrhea), which are less pronounced and briefer than those seen in short-duration trigeminal autonomic cephalalgias such as SUNCT and SUNA; a differential diagnosis with these conditions is necessary[11].

Furthermore, physical examination helps differentiate trigeminal neuralgia from post-traumatic and postherpetic trigeminal pain neuropathies, where deficit signs like hypoesthesia and irritative signs like dysesthesia can be identified. In cases of herpetic trigeminal neuropathies, remnants of skin lesions may be observed[23]. The presence of any sensory abnormalities outside the trigeminal nerve territory, loss of corneal reflex, or facial muscle weakness justifies additional complementary tests to search for other causes[1]. It is important to distinguish between TN and neuralgia of its terminal branches

by precisely delineating the painful area and outlining the extent of sensory alterations[9].

3.8.2. Complementary Tests

When clinically diagnosing a patient with TN, imaging tests are recommended to exclude secondary causes such as tumor compression or ms[28]. Routine cranial imaging is estimated to identify non-vascular structural causes of TN in up to 15% of patients, especially those diagnosed with TN below the age of 40[18,29]. The European Academy of Neurology (EAN) recommends MRI as the first-choice imaging test for studying TN. Additionally, according to the European Federation of Neurological Societies (EFNS) and the American Academy of Neurology (AAN), neurophysiological recording of trigeminal reflexes is a reliable and useful test for neurophysiological diagnosis of TN. However, this diagnostic modality is not very common and is supplanted by advanced neuroimaging tools[1].

3.8.2.1. MRI

Brain MRI should be performed in the initial evaluation of all patients with signs and symptoms of trigeminal neuralgia[1]. Standard 3-T or 1.5-T MRI can reliably exclude secondary intracranial causes of TN (multiple sclerosis, space-occupying lesions, tumors)[20]. However, to evaluate distortion, displacement, or atrophy of the trigeminal nerve by a blood vessel (and diagnose Classic TN), application of FIESTA, DRIVE, or CISS imaging protocols, including T2 + 3D sequences, angioMRI with TOF sequences, and T1 with gadolinium and 3D reconstructions, is necessary[9]. Findings from imaging tests should always be interpreted in conjunction with clinical findings to decide treatment strategies[1].

3.8.2.2. CT Scan

It is used in selected cases where MRI is contraindicated or unavailable. If performing a CT scan, a contrast-enhanced cranial CT should be done to rule out tumors[20]. However, it should be noted that computed tomography has limited utility in the study of TN[9].

3.8.2.3. Trigeminal reflex test

In the absence of imaging tests, guidelines recommend evaluating trigeminal reflexes to differentiate between secondary and primary TN. The combined diagnostic accuracy of trigeminal reflexes to differentiate primary from secondary TN is excellent (sensitivity of 94% and specificity of 88%)[20]. It involves electrical stimulation of the trigeminal nerve divisions and measuring the response with a standard electromyographic device. Trigeminal reflex tests can be useful to detect anomalies in trigeminal nerve divisions that may not seem affected clinically. In patients with facial pain secondary to symptomatic trigeminal neuralgia, postherpetic neuralgia, vascular malformations, benign tumors of the CPA, or MS, objective dysfunction is obtained with the trigeminal reflex test[1].

3.8.2.4. Evoked potentials

Their use is not recommended as they have a sensitivity of only 84% and specificity of 52% to detect and differentiate the two main types of trigeminal neuralgia (Classic and Secondary)[30].

3.8.3. Diagnostic criteria for each type of trigeminal neuralgia according to ICHD-3:

3.8.3.1. Trigeminal neuralgia diagnostic criteria

Table 4. Trigeminal neuralgia diagnostic criteria according to ICHD-3.

Recurrent paroxisms of unilateral facial pain in the distribution (s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
A. Pain has all the following characteristics 1. Lasting from a fraction of a second to 2 minutes. 2. Severe intensity 3. Electric shock-like, shooting, stabbing or sharp in quality.
B. Precipatated by innocuous stimuli within the affected trigeminal distribution.
C. Not better accounted for by another ICHD-3 diagnosis.

1.8.3.2. Classical trigeminal neuralgia

Table 5. Classical trigeminal neuralgia diagnostic criteria according to ICHD-3:

Trigeminal neuralgia developing without apparent cause other than neurovascular compression. **Diagnostic criteria:**
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 in the trigeminal nerve root.

1.8.3.3. Secondary trigeminal neuralgia

Table 6. Secondary trigeminal neuralgia diagnostic criteria according to ICHD-3:

Trigeminal neuralgia caused by an underlying disease. Clinical examination shows sensory changes in a significant proportion of these patients. **Diagnostic criteria:**
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 explaining, the neuralgia.
C. Not better accounted for by another ICHD-3 diagnosis.

1.8.3.4. Idiopathic trigeminal neuralgia

Table 7. Idiopathic trigeminal neuralgia diagnostic criteria according to ICHD-3:

Trigeminal neuralgia with neither electrophysiological test nor MRI showing significant abnormalities. **Diagnostic criteria**
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.
C. Not better accounted for another ICHD-3 diagnosis.

1.9. Treatment

3.9.1. Acute treatment for severe exacerbations

Because of multiple acute exacerbations of trigeminal neuralgia, these patients may present at the hospital dehydrated and even malnourished due to the fact that chewing and mouth movements often trigger acute pain attacks.
First and foremost, we must keep the patient in an observation area for fluid therapy administration to reverse dehydration. Regarding pharmacological treatments in the

acute phase of the attack, there are no randomized controlled trials on acute medical treatment[23]. Both lidocaine (intravenous or injected into the pain-triggering area) and intravenous fosphenytoin have been able to reduce symptoms. We administer phenytoin as an IV bolus of 15-20 mg/kg at a rate not exceeding 2 mg/kg/min or 150 mg/min. In the case of lidocaine, a continuous infusion of 5 mg/kg over one hour will be performed. Due to the frequent side effects of lidocaine administration such as cardiac depression, arterial hypotension, and arrhythmias, continuous cardiac monitoring is necessary during its administration. Therefore, we will proceed with the administration of this medication in the hospitalization ward or in the high-resolution hospital unit. Local injections of lidocaine in the painful area can provide short-term pain relief[30]. Additionally, it is important to note that based on clinical experience, opioids are not effective at safe doses and should be avoided in cases of acute trigeminal neuralgia exacerbations[23].

3.9.2. Long-term treatment

- Pharmacological long-term treatment
- Ablative/destructive techniques
- Microvascular decompression

Pharmacological treatment is the initial treatment in most patients with trigeminal neuralgia. Many of the drugs used have not been evaluated in placebo-controlled clinical trials, nor are there direct comparisons between them, which greatly limits conclusions. Below is a table of the main pharmacological treatments along with their starting dose and usual dose range:

Table 8. First-line treatments[9].

Drug	Initial Dose	Maintenance Dose
Carbamazepine (CBZ)	100-200 mg/12h	1600 mg/24h
Oxcarbazepine (OXC)	150 mg/12h	1800-2400 mg/24h
Lamotrigine	25 mg/24h	600 mg/24h
Baclofen	5-10mg/8h	105 mg/24h
Gabapentin	100 mg/8h	3600 mg/24h
Pregabalin	75 mg/12h	600 mg/24h

If a drug fails or the response is inadequate, combinations can be used, although there is no evidence-based data for the use and recommendation of these combinations. Summary of the main drugs used:

• Carbamazepine: It is the only drug with Class I efficacy (Grade A recommendation) [9]. It is the only drug evaluated in a large number of patients and in randomized controlled trials. It reduces the intensity and number of pain attacks in 70% of patients[31]. The maintenance dose ranges from 400-1200 mg/day. 5% of patients experience side effects that require discontinuation, mainly dizziness, diplopia, gastrointestinal discomfort, and hyponatremia.

• Oxcarbazepine: Comparative studies with carbamazepine show similar efficacy and better tolerance, although similar side effects (sedation, dizziness, cognitive disorders, hyponatremia, rash)[9]. It also has fewer interactions. Oxcarbazepine is a Class IV drug, Grade C recommendation[22]. The maintenance dose ranges from 600-1200 mg/day.

• Eslicarbazepine: Its efficacy has been demonstrated in postherpetic neuralgia and polyneuropathies. Although there are no placebo-controlled clinical trials or other drugs in TN, it is a drug to be considered and is commonly used as an alternative to carbamazepine and oxcarbazepine. Also Class IV, Grade C recommendation.

• Gabapentin: There is not enough evidence, although some therapeutic benefit has been demonstrated with this drug in short series or in isolated patients. Gabapentin may be useful in elderly patients and in TN secondary to MS because these patient groups have lower tolerance to first-line and second-line drugs affecting the central nervous system.

• Pregabalin: It has demonstrated efficacy in postherpetic neuralgia and diabetic neuropathy, fibromyalgia, and neoplastic neuropathic pain. Similar efficacy to gabapentin but worse tolerability[9].

• Baclofen: There is only one randomized trial in a small series of patients. It starts with doses of 5 to 10 mg per day and is escalated to a maintenance dose of 50 to 80 mg per day divided into 3 or 4 daily doses[28]. It has also shown effectiveness when associated with carbamazepine or phenytoin. Its greatest utility would be in cases of TN and multiple sclerosis. Long-term efficacy decreases, being ineffective in 22% of cases at 18 months.

• Lamotrigine**:** It has been shown to have an additional effect in patients with insufficient relief with carbamazepine or phenytoin, at maintenance doses of between 200 - 400 mg/day[24].

• OnabotulinumtoxinA (Botox): Botulinum toxin type A can reduce the transmission of ephaptic impulses and desensitize trigger points. The current recommendation is to use it in patients with pharmacoresistant TN, at doses of 25 – 75 U (2.5-5U per point), separating about 15 mm each point in the map of the painful area which may include the oral mucosa (Class II, Grade B recommendation)[32]. In the largest trial, 84 patients

were randomized into three arms to receive placebo, doses of 25U, or doses of 75 U. No significant differences were found based on the doses. The proportion of patients experiencing a greater than 50% reduction in pain scale was 70% for the group treated with 25U and 86% for the group receiving 75U[33]. Adverse reactions have generally been mild and transient. Adverse reactions described include facial asymmetry, facial dysesthesia, chewing weakness, and inflammation at injection sites[34].

Additionally, a series of uncontrolled observations and routine clinical practice suggest that phenytoin, clonazepam, sodium valproate, lidocaine, amitriptyline, clomipramine, topiramate, levetiracetam, and lacosamide are also effective in the treatment of TN. Their use should be individualized in each case[9].

In any case, the drug with the highest level of certainty and first choice in TN is carbamazepine. In fact, it is the only drug approved for this specific indication in its technical data sheet.

1.9.3. Invasive treatments

There is no evidence supporting their use at the onset of symptoms, and currently, the European Academy of Neurology recommends that medical treatment must be used at the correct doses and with adequate monitoring of the response before proposing an invasive procedure. In general, these treatments are based on interrupting nerve impulses at some point along the trigeminal pathway (peripheral nerve, ganglion, root, and mesencephalon). In clinical practice, we act on the ganglion or root. The techniques are different, some, such as vascular decompression, are non-destructive while others cause lesions in the ganglion or root (radiofrequency or balloon compression). Gammaknife is the only technique that is destructive but non-invasive as it is based on radiation in a specific area.

Surgical treatment is only indicated when pharmacological treatment has failed, that is when the maximum tolerated doses for the patient have been reached with at least one therapeutic trial of a first-line drug (carbamazepine/ozcarbazepine). However, it has not been defined when is the optimal time to switch to surgical techniques, nor how many drugs have to be tried beforehand, alone or in combination, to consider medical treatment failure.

In these cases, a multidisciplinary approach is proposed. In case of medical treatment inefficacy, evaluation by Neurosurgery and Pain Management Unit will be considered once relevant complementary studies are completed.

In patients with classic TN, microvascular decompression is the technique of first choice with an efficacy of 62-89% of pain-free patients. The most frequent complications are cranial nerve paralysis (4%), hearing loss (1-8%), and facial hypoesthesia (3%). This is the technique of choice in those patients with confirmed vascular compression by MRI and who tolerate major surgery (proper operability of the patient in addition to resectability).

When MRI does not show vascular contact, ablative treatments such as percutaneous balloon compression, gamma knife, and radiofrequency thermocoagulation will be the first option.

In cases where MRI shows an underlying secondary lesion (tumor of the pontocerebellar angle, meningiomas, cholesteatomas...), treatment will be specific to it.

Below is a brief description of the main characteristics of these techniques:

3.9.3.1. Ablative/Destructive Techniques

Their objective is to selectively destroy nociceptive fibers. Within these ablative techniques, we have those carried out through percutaneous surgery and others such as stereotactic surgery or neuromodulation. The main percutaneous surgery techniques are:

• Thermocoagulation of the Gasserian ganglion: an electrode needle is introduced through the foramen ovale to apply thermal radiofrequency to the ganglion. It can be done with the patient awake to locate the branch to treat or with the patient sedated with neurophysiological study. This technique is not recommended in the V1 branch due to the possibility of causing a sensory deficit affecting the cornea.

• Percutaneous balloon compression of the Gasserian ganglion (Mullan technique): introduction through the foramen ovale of a 15G needle with a Fogarty balloon catheter under fluoroscopy and general anesthesia. The balloon is inflated in the Meckel's cave and compression is maintained for 60 to 120 seconds and then deflated. Note that balloon inflation can cause adverse effects such as bradycardia and hypertensive crisis/emergency.

• Percutaneous retrogasserian glycerol rhizotomy: consists of injecting 0.2-0.5 cc of 99.99% anhydrous glycerol into the Gasserian ganglion through the foramen ovale with local anesthesia and after performing contrast cisternography. The problem with this technique is that it has a high initial failure rate and a high probability of recurrence. This technique can be performed in V1 TN and bilateral TN due to MS[9].

1.9.3.2. Others

• Stereotactic radiosurgery (Gamma knife): It is a non-invasive technique in which multiple fine beams of gamma radiation are convergently directed onto the trigeminal root or onto an adjacent vascular or tumoral anomaly. The main problem with this technique is that while other techniques provide immediate pain relief, with gamma knife, patients usually take 6 to 8 weeks to feel pain relief. It has also been seen in published studies that 34% of patients do not show pain relief in the first year after the intervention[19].

• Neuromodulation: motor cortical stimulation and thalamic stimulation (little use of these techniques).

These techniques are minimally invasive, require only local anesthesia and sedation. They can cause sensory loss in up to 50% of patients, with paresthesias or painful anesthesia being much less frequent. Likewise, pain recurrence occurs in up to 50% of patients after 5 years of treatment.

There are no randomized controlled clinical studies comparing the described ablative techniques in the treatment of TN. Thermocoagulation is the technique that offered the highest rates of complete pain relief, compared to glycerol rhizolysis and stereotactic surgery, although it also presents the highest number of postoperative complications. There is not enough data to compare its effectiveness with microcompression balloon.

1.9.3.3. Microvascular Decompression

Microvascular decompression involves performing a suboccipital craniotomy to find and resolve the triggering cause of trigeminal nerve compression. This technique shows good results in pain relief, often immediate, and satisfactory long-term results are obtained, generally preserving trigeminal function intact. There are observational studies where long-term efficacy of this technique with a favorable response at 10-20 years of follow-up is evidenced in 60-70% of cases. The most frequent complication (<5%) is hearing loss. Despite the absence of prospective comparative studies, findings from retrospective studies show better results for microvascular decompression compared to ablative techniques[35].

2. Hypothesis

The current literature on trigeminal neuralgia provides information on the clinical characteristics of the disease and existing treatments for it. The aim of this study is to describe the clinical characteristics of patients with trigeminal neuralgia and brain imaging studies in a third level hospital such as the Marqués de Valdecilla University Hospital, and to bring the disease closer to other services outside the field of neurology in order to increase its diagnosis, especially in the Emergency Department and Primary care.
We want to provide information on the main treatments available for the management of the disease. In the case of oral preventive treatments, it's important to make known the main lines of preventive oral treatment with their respective starting and maintenance doses as well as the side effects of the drugs and their refractoriness rates. Also to present the advanced therapies available in our hospital and describe their main indications and efficacy rates for the correct management of the disease.

3. Objectives

Main objective:

To evaluate the clinical features, currently applied types of treatment, and brain imaging studies in patients with refractory TN in a third level Hospital in Spain.

Secondary objectives:

- To describe the demographic characteristics and clinical features which most frequently appear in patients with refractory TN.

- To evaluate the clinical efficacy and tolerability of treatments in a cohort of patients with TN by collecting and analyzing clinical data from patients from the neurology service of the Marqués de Valdecilla University Hospital (HUMV).

- To analyze the radiological features of the neuroimaging test and their indication in TN patients.

- Review the existing scientific literature on trigeminal neuralgia treatments and advanced therapies.

- To evaluate the clinical evolution of patients that received advanced therapies over time.

4. Methodology

Patients of the Outpatient clinic in the Headache Unit of the Hospital Universitario Marqués de Valdecilla with refractory TN were included.

Our study was based on an exhaustive search through the Headache and neuralgias database of the Neurology Department of the Marqués de Valdecilla University Hospital (Santander, Cantabria). Accordingly, cases of TN refractory to several treatments evaluated in the outpatient clinics in January 2024 were selected. The inclusion criteria applied were:

[1] Patients aged 18 years or older.
[2] TN diagnosis according to 2010 criteria of The International Headache Society third edition (7).
[3] Data available in the clinical record.
[4] Patients who have received at least two medical treatment options at the appropriate doses and for the minimum necessary time without any improvement of pain.

On the other hand, patients with other headaches or neuralgias different from TN were excluded. A retrospective collection of data of patients that full-field these criteria were carried out from outpatients in the Neurology Department of the Marqués de Valdecilla University Hospital by two neurologist specialist in Headache and neuralgias.

The individual study of each patient required the systematic evaluation of different variables in a wide range of fields such as demography, clinical, laboratory determinations, radiology and other complementary studies.

Several demographic variables were systematically assessed for each patient including gender, age at the time of the study, cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus and obesity (considered as the detection of a BMI (body mass index) greater than or equal than 30); exposure to smoking, personal history of autoimmune diseases, and another relevant personal history. In addition, family history of interest for our study was compiled, such as the family history of other neurological diseases.

Likewise, the clinical variables included in our study concerning the TN include: age at onset of symptoms, branch of the trigeminal nerve where pain is located, lateralization of pain, triggers of pain (such as chewing, speaking, washing the face, touching, brushing the teeth, opening the mouth, swallowing, shaving, cold exposure, stress).

Regarding diagnosis, the time from the onset of each patient`s symptoms to the diagnosis of the disease was studied in months, as well as the place where the diagnosis was made (considering the Neurology Department by a neurologist, General Practioner in the Primary Care, Emergency Department, dentist and Pain Unit as the most frequent).

As a consequence of the study, there was a need to study radiological variables, obtained by reviewing the CT, MRI scans and angiographies performed on the patients during the

diagnosis or follow up. It was verified that the MRI scans in all cases were performed under the usual conditions of clinical practice, including at least axial and sagittal planes in T1-weighted, T2-weighted, FLAIR and T1-weighted sequences after the administration of gadolinium. We have collected the imaging tests that have been carried out on our patients as well as the findings in these tests in order to categorize the type of trigeminal neuralgia in each patient. For this purpose, we have recorded a qualitative variable depending on the finding of a vascular contact, secondary lesions causing the disease (such as multiple sclerosis or herpes) and no findings of interest.

Regarding treatment, we have collected information on oral preventive treatment and advanced therapies. In case of oral preventive treatment, up to six lines of treatment have been analyzed. In each line of treatment, we have analyzed the drug taken by the patient, maximum daily dose, side effects derived from taking the drug, maintenance of that treatment nowadays and concomitance with other drugs.

In the case of advanced therapies, we have analyzed if the patients have undergone any of these therapies and, if so, to which ones they have been subjected as well as the total percentage of patients in the sample requiring advanced therapies as an indicator of refractoriness to oral preventive treatment. In the case of botulin toxin, we have analyzed the minimum and maximum dose of OnanbotulinumtoxinA administered to each patient, adverse effects of the treatment and maintenance of the treatment at present. In the case of other advanced therapies: decompressive surgery, rhizotomy and gamma knife we have analyzed the time from the onset of symptoms in years to the procedure and the existence of absence of immediate complications (recorded as a dichotomous qualitative variable the existence or not of immediate complications). Finally, it was considered essential to assess the clinical evolution of patients over time after receiving treatment. For this purpose we studied pain improvement reported by the patient (recorded as a qualitative variable: complete improvement, partial improvement or no improvement), as well as the number of oral preventive drugs taken by the patient before the advanced therapy and at 3 months after advanced therapies as indicators of the effectiveness of the treatments.

Statistical analysis

All data extracted from the database were analyzed statistically. Incomplete data due to lack of reference in the clinical history were excluded. A descriptive analysis of the variables studied was performed. It was considered statistically significant if $p<0,05$. The SPSS software was used to perform the statistical analysis.

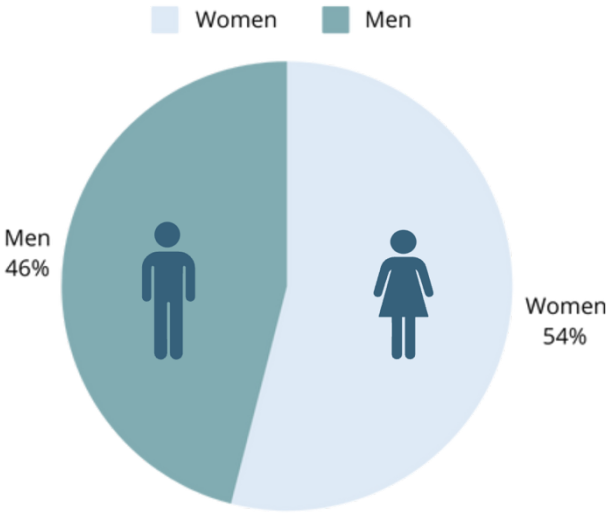
5. Results

Among the patients attended in the Headache Unit of the Hospital Universitario Marqués de Valdecilla, 41 patients with refractory NT recruited by the specialist fulfilled all inclusion criteria and were included in our study.

7.1. Demographic data

The total number of patients analyzed was 41. Of the 41 patients included, 19 patients (46.3%) were men and 22 patients (53.7%) were women (Figure 5). The mean age of the patients at the moment of the study was 67.9 years with a mean deviation of 15.3 years, which is a normal variable; with a range of ages from 29 to 93 years.

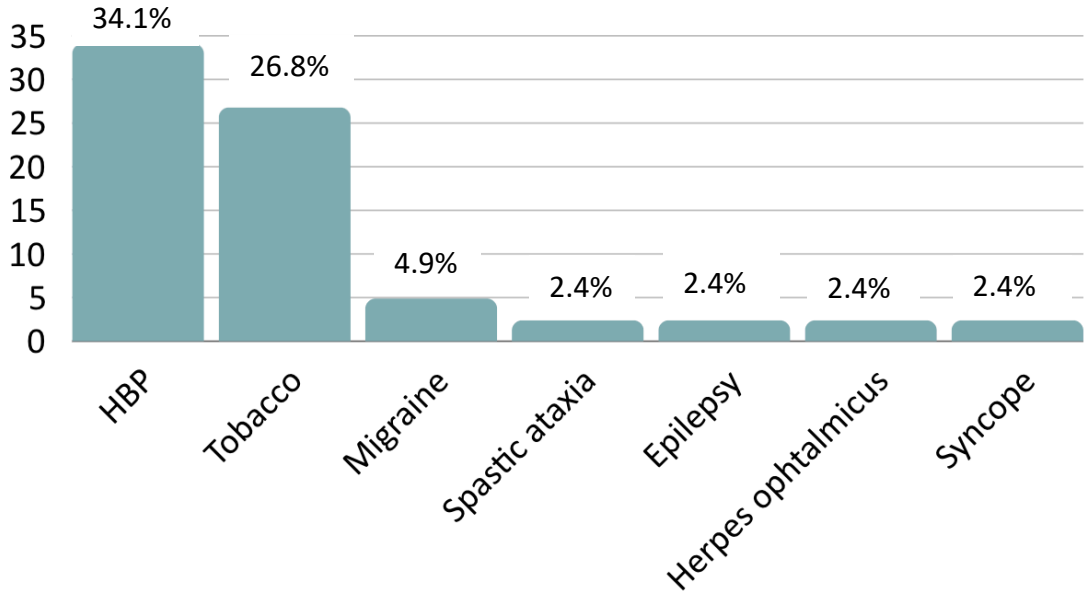
Figure 5. Gender distribution of the sample



7.2. Medical history

Of the total sample available, 25 patients had a medical history of interest (Figure 6). Regarding cardiovascular risk factors, the most prevalent personal history of interest among the patients in the sample was high blood pressure (HBP), presented in 14 patients (34.1%). Accordingly, no patients with diabetes mellitus were reported in the investigation. Exposition to tobacco as a toxic habit was present in 11 patients (26.8%). Less prevalent in order of relevance were migraine in 2 patients (4.9%). Besides, another relevant medical history from the patients' medical records was collected and there were 1 patient with spastic ataxia (2.4%), epilepsy (2.4%), herpes ophthalmicus (2.4%) and syncope (2.4%).

Figure 6. Medical History



7.3. Diagnostic data

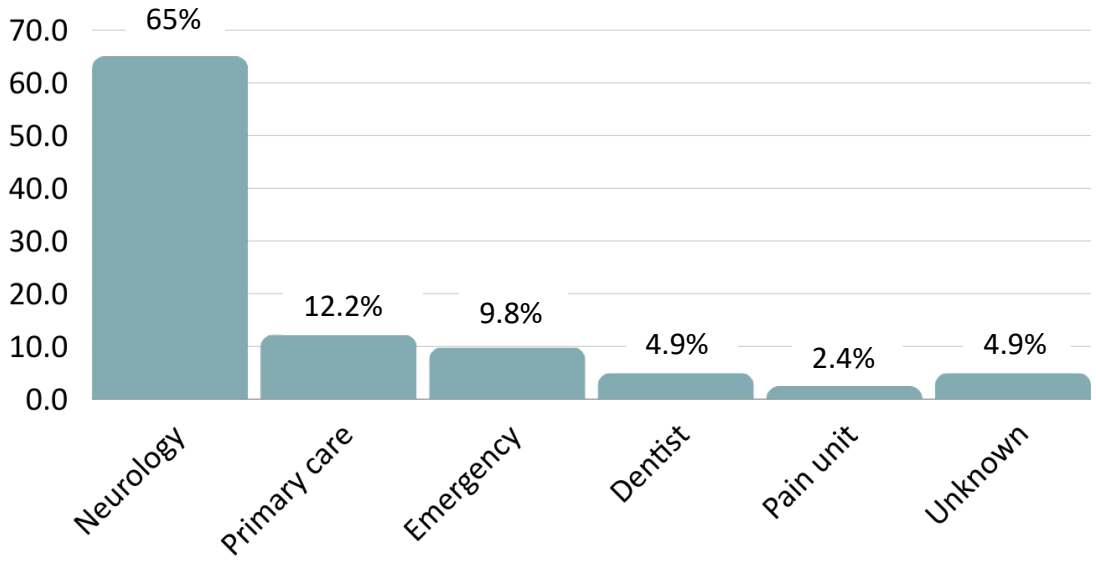
The mean age of the patients at the onset of symptoms was 54.3 years (standard deviation of 15.3 years; range 24-85) and the median age was 54.5 years following a normal distribution.

When studying the age at onset of symptoms in relation to the patient's sex using the independent samples t-test, it was found that trigeminal neuralgia in men began at 51.9 years and in women at 56.7 years (CI of -14.6 to +5.06, with a p=0.33), indicating that there were no significant differences in the age of onset between men and women.

Additionally, the interval between the onset of symptoms and the final diagnosis was available in 38 patients, because the time of diagnosis was missing in 3 of the patients. The median time to diagnosis from the onset of the symptoms was 6 months with an interquartile range of 24 months. The minimum being 0 months in patients diagnosed at the time of the first episode and the maximum being 120 months.

We analyzed who made the diagnosis of TN. Most of the patients were diagnosed in the Neurology Department by a neurologist (27 patients; 65%), followed by a General Practioner in the Primary care (5 patients; 12.2%). Other diagnoses were made in the Emergency Department (4 patients; 9,8%), by the dentist (2 patients; 4.9%) and in the Pain Unit (1 patient; 2.4%). Additionally, there were two patients in the sample who were diagnosed at other centers (4.9%) (Figure 7).

Figure 7. Place of diagnosis (%).



7.4. Follow-up of patients

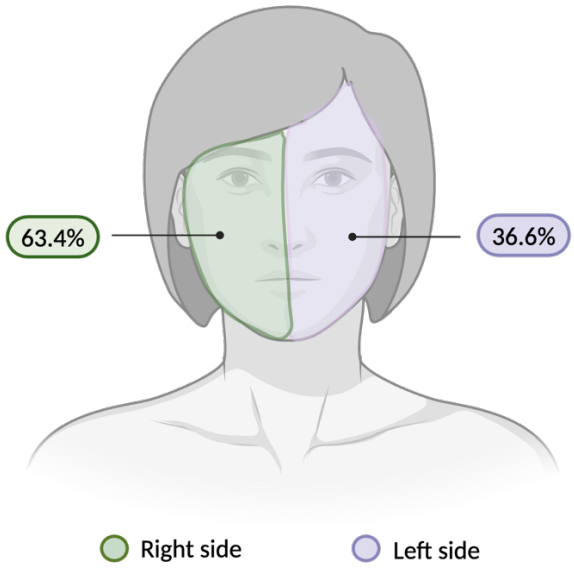
The median follow-up of the patients in the sample was 6.5 years with an interquartile range of 16.25 years.

7.5. Categorization of trigeminal neuralgia

Within the multiple clinical variations that exist within trigeminal neuralgia, depending on the branches of the nerve affected or the lateralization of the pain, the results of this sample have been obtained. Unilateral side involvement was the most common affected region, whereas no patient had a bilateral involvement.

With regard to the laterality of the pain, 26 patients (63.4%) presented pain on the right side of the face, while 15 patients (36.6%) suffered pain on the left side (Figure 8).

Figure 8. Laterization of pain in our patients.



In addition, the branches affected in each patient and the possible combinations between them were studied, obtaining the results shown in the table 9. V2 was the most common trigeminal nerve division (14 patients; 34.1%) involved, followed by V3 (13 patients; 31.7%) and V2+V3 (5 patients; 12.2%). The V1 was the least affected division of the trigeminal nerve (3 patients; 7.3%) (Figure 9) (Table 9).

Figure 9. Trigeminal branches of pain localization in our patients.

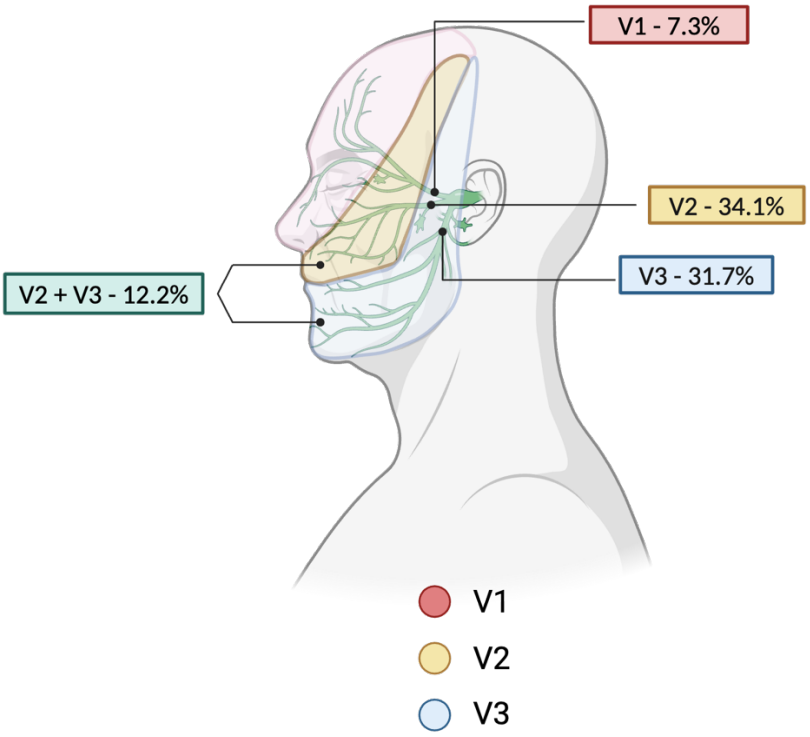


Table 9. Trigeminal branches of pain localization.

Location of pain	N	%
V1	3	7.3
V2	14	34.1
V3	13	31.7
V1+V3	2	4.9
V2+V3	5	12.2
V1+V3	1	2.4
V1+V2+V3	3	7.4

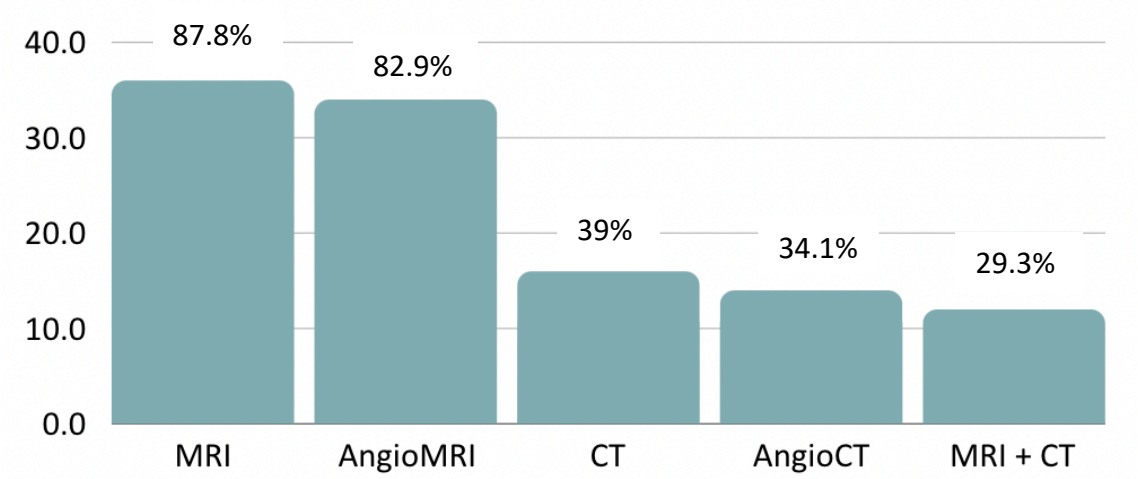
The most common description of pain was an electric shock-like sensation, followed by dull nature pain. Most patients presented more than one triggering activity. The various causative factors of pain reported were chewing, speaking, washing the face, touching, brushing the teeth, opening the mouth, swallowing and shaving.

7.6. Diagnosis

For the diagnosis of this disease, the patient's clinical presentation is fundamental. However, in many cases, complementary imaging tests are necessary to categorize the type of trigeminal neuralgia the patient has and to determine the appropriate therapeutic approach. The most commonly used neuroimaging tests include CT scan, CT angiography, MRI, and MRI angiography.

From this sample, the most frequently performed test was MRI, conducted on 36 patients, accounting for 87.8% of the sample. Among these 36 patients, 34 underwent further examination with MR angiography (94.4% of patients with MRI also underwent MR angiography). CT scans were performed on 16 patients, representing 39% of the sample, with 14 of them including CT angiography (87.5% of patients with CT scans also underwent CT angiography). Additionally, considering both tests, 12 patients (29.3%) underwent both CT scan and MRI (Figure 10).

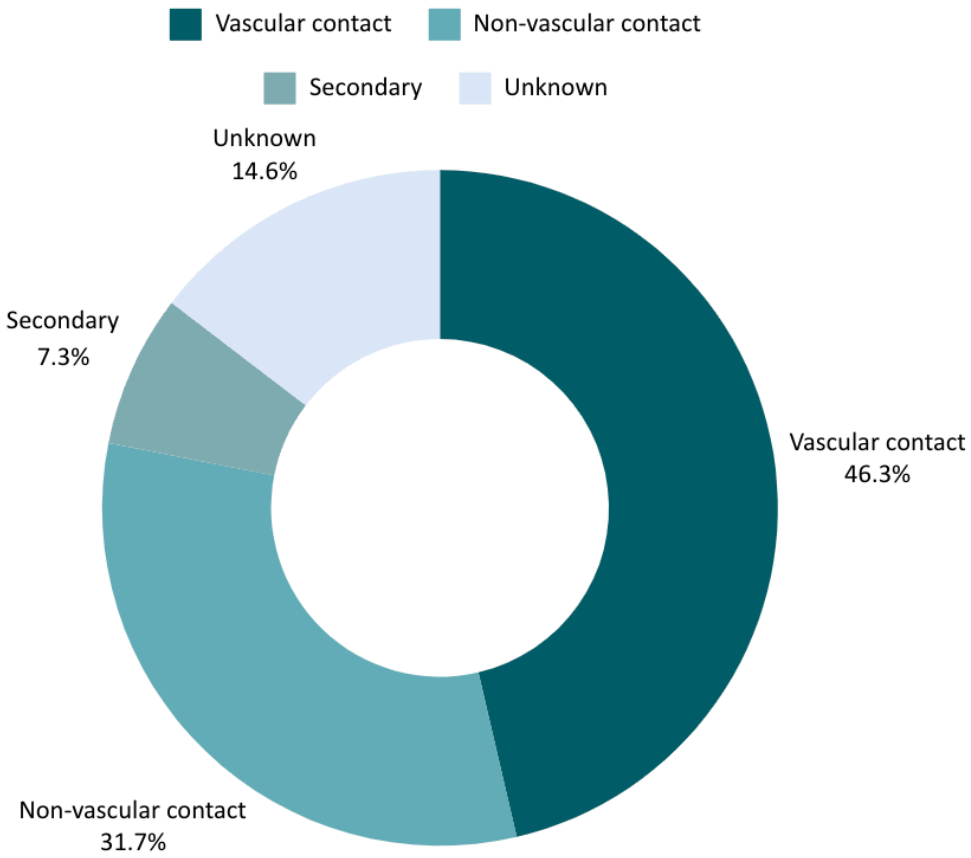
Figure 10. Imaging tests performed.



Mainly, these imaging tests are carried out with the aim of determining whether patients have trigeminal neuralgia due to compression caused by vascular crossing or, conversely, whether the pathology is caused by other secondary conditions or unknown causes. The results of the complementary tests (as shown in Figure 11) indicate that vascular compression was found in 19 patients in the sample (46.3%). Normal MRI findings with no vascular contact or causes responsible for the pathology were found in 13 patients

(31.7%). Lesions different from vascular contact responsible for the pathology were observed in 3 patients (7.3%), two of them with trigeminal neuralgia secondary to multiple sclerosis and the other secondary to ophthalmic herpes. Additionally, there are 6 patients (14.6%) for whom we do not have the results of the complementary tests because they were performed in private centers or other reference centers, and the results have not been provided, or because the imaging tests were conducted in the past when the resolution available today did not exist.

Figure 11. Imaging tests results.



7.6.1. Relation between having a vascular contact and the branch involved

We analyzed whether the presence of vascular contact causing the pathology affects one branch or another of the trigeminal nerve more than the other. For this analysis, we used the Chi-square test and found no significant differences between vascular contact and the main affected branch of the trigeminal nerve (p=0.4).

7.7. Oral preventive treatments

In the 41 patients of the sample, all the previous preventive treatments taken orally were analyzed. Up to six lines of oral medical treatment were studied, including the number and percentage of patients who reached each treatment line, the medications they took in each line before moving to the next, and before moving on to advanced therapies. The maximum dose of each treatment received and its side effects were also analyzed.

All patients were under treatment at the moment of the study. Of the 41 patients in the sample, 100% received first-line oral treatment, 34 patients (82.9%) reached second-line treatment, 26 patients (63.4%) reached third-line treatment, 18 patients (43.9%) reached fourth-line treatment, 12 patients (29.2%) reached fifth-line treatment, and 2 patients (4.9%) reached at least six lines of treatment.

As an initial medical treatment for TN carbamazepine was prescribed most commonly. Carbamazepine was used as first line treatment in 31 patients (75.6%). In the second line, pregabalin was the most used drug in 7 patients (20.6%). Clonazepam was used in the third line by 6 patients (23%). In the fourth line, lacosamide was used by 5 patients (27.7%). In the fifth line, baclofen, phenytoin, and lamotrigine were the most used, each by 2 patients (16.7%), and in the two patients who reached the last line of treatment, pregabalin was used in one (50%) and amitriptyline in the other (50%) (Table 10).

Table 10. Oral preventive treatment lines.

	1st line (n=41)(%)	2nd line (n=34)(%)	3rd line (n=26)(%)	4th line (n=18)(%)	5th line (n=12)(%)	6th line (n=2)(%)
Carbamazepine	N=31 (75.6%)	N=2 (5.9%)	N=3 (11.5%)	N=1 (5.5%)	-	-
Pregabalin	N=4 (9.8%)	N=7 (20.6%)	N=1 (3.8%)	-	N=1 (8.3%)	N=1 (50%)
Gabapentin	N=2 (4.9%)	N=5 (14.7%)	N=2 (7.7%)	N=2 (11.1%)	-	-
Oxcarbazepine	N=1 (2.4%)	N=5 (14.7%)	N=1 (3.8%)	-	N=1 (8.3%)	-
Eslicarbazepine	N=1 (2.4%)	N=3 (8.8%)	N=5 (19.2%)	-	-	-
Amitriptyline	N=1 (2.4%)	N=1 (2.9%)	N=1 (3.8%)	N=1 (5.5%)	N=1 (8.3%)	N=1 (50%)
Duloxetine	N=1 (2.4%)	-	-	-	-	-
Clonazepam	-	N=4 (11.7%)	N=6 (23%)	N=2 (11.1%)	N=1 (8.3%)	-
Baclofen	-	N=3 (11.7%)	N=2 (7.7%)	N=4 (22.2%)	N=2 (16.7%)	-
Topiramate	-	N=2 (5.9%)	-	-	N=1 (8.3%)	-
Lacosamide	-	N=1 (2.9%)	N=1 (3.8%)	N=5 (27.7%)	N=1 (8.3%)	-
Phenytoin	-	-	-	N=1 (5.5%)	N=2 (16.7%)	-
Lamotrigine	-	-	N=1 (3.8%)	-	N=2 (16.7%)	-
Pimozide	-	-	N=1 (3.8%)	N=1 (5.5%)	-	-
Dexamethasone	-	-	-	N=1 (5.5%)	-	-
TOTAL	N=41 (100%)	N=34 (82.9%)	N=26 (63.4%)	N=18 (43.9%)	N=12 (29.2%)	N=2 (4.9%)

7.7.1. Lines of treatment according to vascular contact

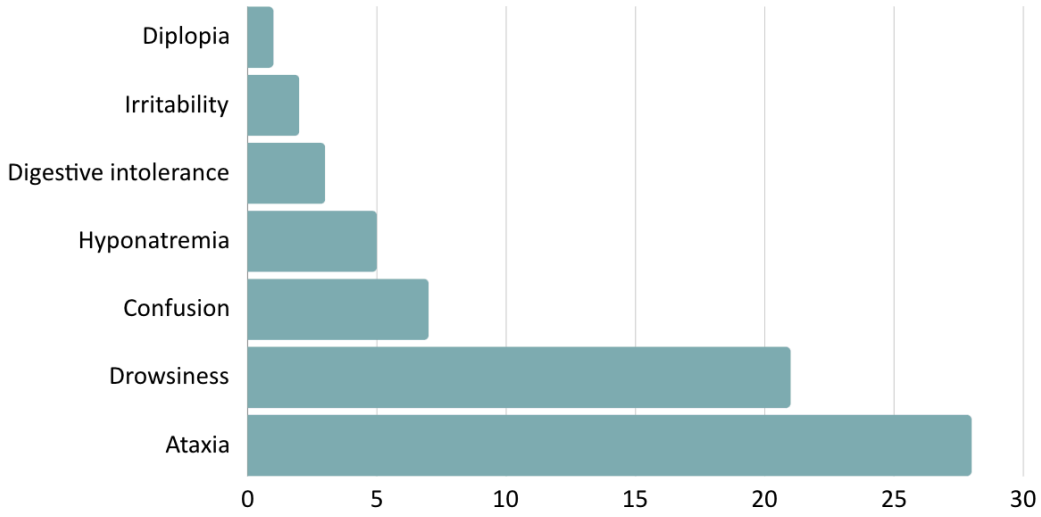
It was analyzed whether the presence of vascular contact, demonstrated by imaging technique, necessitated more lines of treatment in these patients compared to those who did not have this contact, potentially indicating refractoriness to medical treatment. For this analysis, the non-parametric Mann-Whitney U test was performed. A p-value of 0.85 was obtained, indicating that there were no significant differences in the lines of treatment achieved by patients who have vascular contact compared to those who do not.

7.7.2. Side effects of oral drugs

The main side effects experienced by patients after receiving oral medical treatments have been analyzed. The overall side effects experienced by patients across any line of treatment are described (Figure 12), focusing primarily on first-line treatment drugs. In subsequent lines, some patients take concomitant treatments, making it impossible to discern which of the drugs the patient is taking is responsible for such side effects.

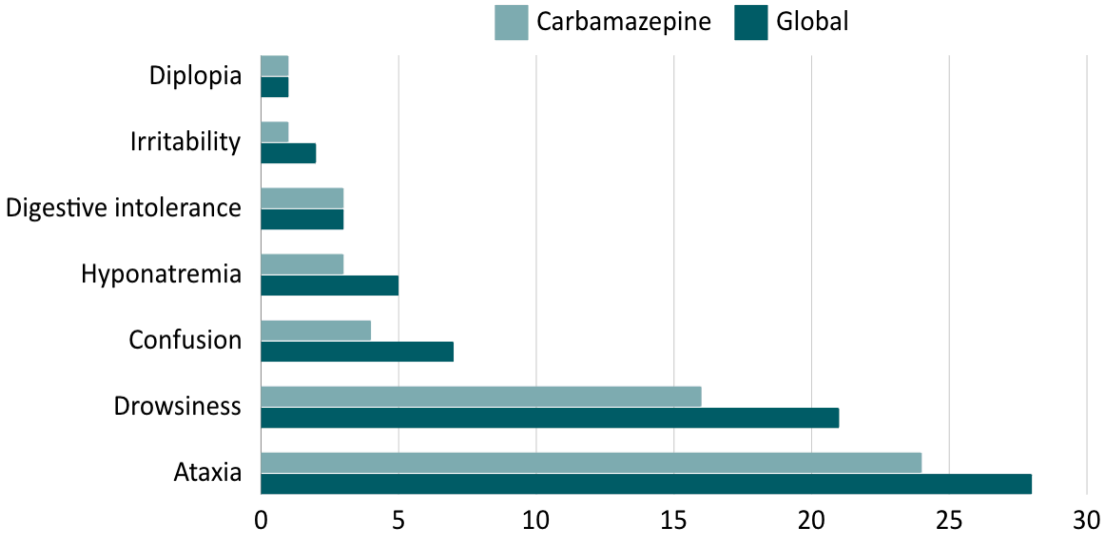
The most common overall side effects of patients under oral preventive treatment were gait instability (28 patients; 68.3%) and drowsiness (21 patients; 51.2%). Other side effects reported by patients were confusion (7 patients; 17.1%), hyponatremia (5 patients; 12.2%), digestive intolerance (3 patients; 7.3%), irritability (2 patients; 4.9%) and diplopia (1 patient; 2.4%).

Figure 12. Overall side effects of the sample.



As carbamazepine is the most frequent treatment and used by the majority of patients in the sample, we studied the side effects of carbamazepine treatment. The most common side effects reported by those patients taking carbamazepine as first line treatment were gait instability (24 patients; 77.4%) and drowsiness (16 patients; 51.6%), followed by confusion (4 patients; 12.9%), hyponatremia (3 patients; 9.7%), digestive intolerance (3 patients; 9.7%), irritability (1 patient; 3.2%) and diplopia (1 patient; 3.2%) (Figure 13).

Figure 13. Comparison of overall side effects with carbamazepine derivate.



Regarding other first-line drugs, of the patients treated with pregabalin, only one patient (25%) out of the four treated with this drug reported a sensation of instability (ataxia). Of the two patients treated with gabapentin, one patient (50%) reported drowsiness. The patient treated with eslicarbazepine (100%) reported drowsiness after taking it. No patients reported significative side effects with the intake of oxcarbazepine, amitriptyline, and duloxetine.

7.8. Advanced therapies

The advanced therapies used in trigeminal neuralgia that have been analyzed and described in this study include treatment with botulinum toxin, decompression surgery, rhizotomy, and gammaknife. 25 patients (61%) underwent invasive treatments, including microvascular compression, gammaknife, OnabotulimtoxinA treatment and radiofrequency thermoablation. Of the patients in this sample, 17 patients (41.5%) were treated with botulinum toxin. Decompression surgery was performed in 7 patients (17.1%), rhizotomy in 11 patients (26.8%) and gammaknife in 3 patients (7.3%), there are patients who have received more than one advanced therapy.

Additionally, among the 19 patients who were found to have vascular contact on imaging tests, it was analyzed how many of them underwent decompression surgery and how

many did not. It was found that decompression surgery was performed in 7 patients (36.8%), while 12 patients (63.2%) did not undergo surgery.

7.8.1. Time from symptoms onset to completion of advanced therapies.

We have analyzed the time in years between the beginning of the clinical manifestations of the disease to the use of advanced therapies. In the case of decompressive surgery, the mean was 4.57 ± 3.65 years, with a range 2-12 years. For rhizotomy the mean was 11.09 ± 7 years, with a range 3-24 years. Finally, in the case of gammaknife, one patient underwent this therapy 4 years after the onset of symptoms, another 15 years and the last after 26 years.

7.8.2. Efficacy data on advanced therapies

7.8.2.1. Patient's impression

To quantify the improvement of patients after the use of advanced therapies, data were collected on the improvement reported by each patient after the use of advanced therapies (Table 11). In case of decompressive surgery 4 patients (57.1%) reported complete improvement after de surgery. After rhizotomy, 4 patients (36.4%) and after gammaknife 2 patients (66.7%) reported total resolution of pain. 2 patients (28.6%) reported partial improvement after decompressive surgery. 1 patient (14.3%) reported no improvement after decompressive surgery, 7 patients (63.6%) after rhiztomy and 1 patient (33.3%) after gammaknife procedure.

Table 11. Improvement after advanced therapies.

	Complete improvement	Partial improvement	No improvement
Decompressive surgery (n=7)	N=4 (57.1%)	N=2 (28.6%)	N=1 (14.3%)
Rhizotomy (n=11)	N=4 (36.4%)	-	N=7 (63.6%)
Gammaknife (n=3)	N=2 (66.7%)	-	N=1 (33.3%)

7.8.2.2. Oral drugs used by patients three months after advanced therapy

We analyzed whether the use of advanced therapies reduces the number of oral preventive drugs used by patients 3 months after therapy.

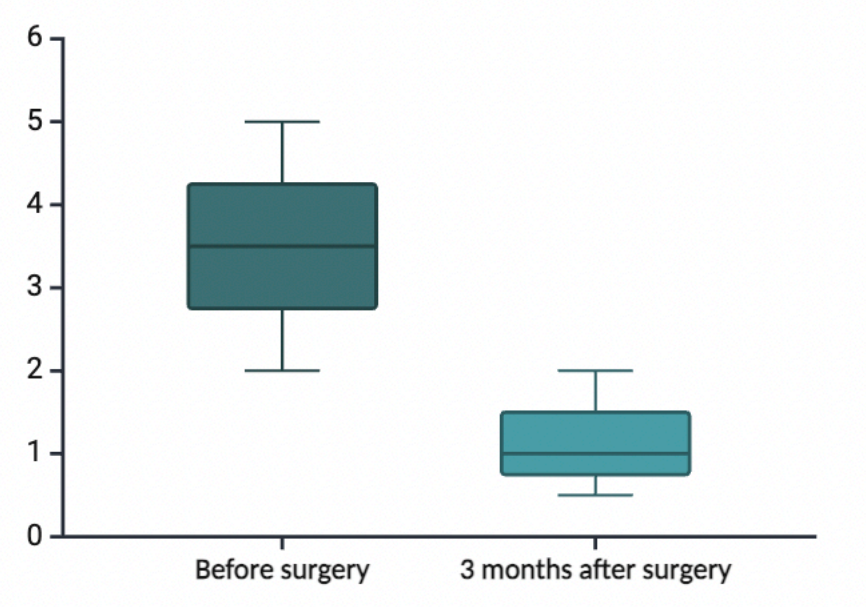
The Kolmogorov-Smirnov test was used to determine the normality of the sample population. A normal variable was obtained when analysing decompressive surgery, so we used Student's t-test for paired samples. In the case of rhizotomy and gammaknife, non-normal distributions were obtained, so the Wilcoxon test was used for the analysis (Table 12).

Table 12. Drugs before and 3 months after advanced therapies.

	Drugs at three months	Test (statistical significance result)
Decompressive surgery	Average of 2.286 fewer drugs at 3 months	Student's t-test for paired samples (CI 95% 0.62-3.95)(p=0.015)
Rhizotomy	Median of 2 drugs before and 2 drugs after 3 months	Wilcoxon test (z=-0,5) (p=0.56)
Gammaknife	Median of 4 drugs before and 3 drugs after 3 months	Wilcoxon test (p=0.31)

We have found that at 3 months post-decompressive surgery, patients require on average 2,28 fewer drugs than before undergoing surgery (CI 95% 0,62 – 3.95 p=0.015) with this result being statistically significant (Figure 14). In the case of rhizotomy, it was observed that the median number of drugs used before the intervention was 2 , which remained the same at 3 months post-intervention. For gammaknife treatment, a median of 4 drugs were used before the intervention and a median of 3 drugs at 3 months post-treatment, but these last two results not being statistically significant (p>0.05).

Figure 14. Drugs before and after 3 months of decompressive surgery.



6. Discussion

This study analyzed the clinical characteristics and treatments received by a cohort of patients with refractory trigeminal neuralgia from diagnosis to the date of data collection (January 2024) in a third level hospital such as the Marqués de Valdecilla University Hospital. This is a descriptive study of great interest for daily clinical practice as it provides data to aid diagnosis and especially for the treatment of these patients. Further, most of the findings in this study are similar to those in previous reports.

8.1. Demographic research

Analyzing the demographic characteristics of the patients in the sample, aspects such as their age and sex stand out. The mean age of the patients at the time of inclusion in the study was 67.9 years. 53.7% of the patients in the sample were female, which is in line with what is expected in the general population, because there is literature describing that trigeminal neuralgia is a disease more prevalent in women than in men[(6)]. In the patients included in our study, the mean age of symptom onset was 54.3 years as published in other series[(7)]. It is reported that patients with secondary trigeminal neuralgia debut earlier than those with other forms of trigeminal neuralgia; in our study, patients with trigeminal neuralgia secondary to MS debuted at 51 years of age, this is similar to the age of those with other forms of trigeminal neuralgia and it has also been described that they may debut at older ages. Furthermore, the sample of patients available in our study of secondary trigeminal neuralgia is very limited, so this is not a result that can be extrapolated to the general population[(21)].

8.2. Medical history research

We analyzed the personal history of each patient to see if it was related to the development of the disease. Among the cardiovascular risk factors, 34.1% of the patients in our sample had HBP, 26.8% were smokers, 4.9% had migraine, and 2.4% had ataxia, epilepsy, ophthalmic herpes and syncope. On the other hand, we did not find any patients with a personal history of diabetes mellitus. Available studies suggest that patients with hypertension or arteriosclerosis (with cardiovascular risk factors) have an increased risk of trigeminal neuralgia due to functional and morphological changes that alter the vascular nerve supply[(15)]. In our analysis we have found that HBP is the most prevalent personal history in the sample and could correlate with what is described in the literature but it should be noted that the average age of the patients in this sample is over 50 years old so it is common for older patients to have a higher number of cardiovascular risk factors than those who are younger. In addition, it has also been described that patients with migraine are at higher risk of developing the disease, although there is no complete evidence on this[(1)]. There are other pathologies related to a higher risk of developing TN such as rheumatoid arthritis and temporomandibular joint pathology although due to the low sample volume we do not have any patients with these diseases[(1)].

8.3. Diagnosis

8.3.1. Time to diagnosis and place of diagnosis

The mean time from the onset of symptoms to diagnosis was 6 months with an interquartile range of 24 months, with patients being diagnosed immediately after the onset of symptoms and patients taking years to be diagnosed. These data were obtained knowing the time to diagnosis for 38 patients, since in three of them it was not known how much time had passed from the onset of symptoms to the final diagnosis because they had been diagnosed in other reference centers. The majority of the patients, 65.9%, were diagnosed in the Neurology Department by neurologists. 12.2% by a General Practitioner in the Primary care, 9.8% in the Emergency Department and a minority of patients had been diagnosed by their dentist or in the Pain unit. The average time from the onset of symptoms to final diagnosis and the most frequent place of diagnosis inform us that it is important to make the clinical characteristics of the disease known in other hospital departments, especially in the Emergency Department and Primary Care, in order to make the diagnosis of the disease prior to consultation with the neurologist. Even though TN has a typical clinical picture, diagnosis it is often missed or delayed in clinical practice, although patients suffering from this pain are more likely to consult their Primary care physician or dentist, studies have shown that diagnosis is mainly made by a neurologist or headache specialist[36].

8.3.2. Characterisation of trigeminal neuralgia

The lateralization of pain in our patients was analyzed. A total of 63.4% of patients presented pain on the right side of the face while 36.6% presented pain on the left side and no cases of bilateral pain were recorded. This is in line with the texts published to date, which show differences of approximately 60% on the right and 40% on the left side[1,5]. Anatomical variation and asymmetry can be observed on the right and left sides of the foramen ovale or foramen rotundum[37]. Previous reports suggested that due to this difference in size of the foramen rotundum, the smaller foramen could lead to a secondary compression of the maxillary nerve in the cases of TN caused by vascular compression[38]. This phenomenon could be a causative factor of the higher incidence of right-sided TN.

In addition, we have also studied the branch affected in each patient and the possible combinations of these branches. We found that V2 is the most affected branch of the trigeminal nerve (34.1% of the patients in the sample), followed by V3 (31.7%) and the combination of V2+V3 (12.2%), with V1 being the least affected branch (7.3%), these data are very striking as this order of involvement corresponds fully with the existing literature on the disease and important studies of the disease published in leading journals such as Cephalalgia or the New England Journal of Medicine[1,6,9,19].

In terms of pain triggers, patients reported pain when chewing, talking, touching or washing their face, brushing their teeth, shaving and swallowing, common triggers in the general population with trigeminal neuralgia[27].

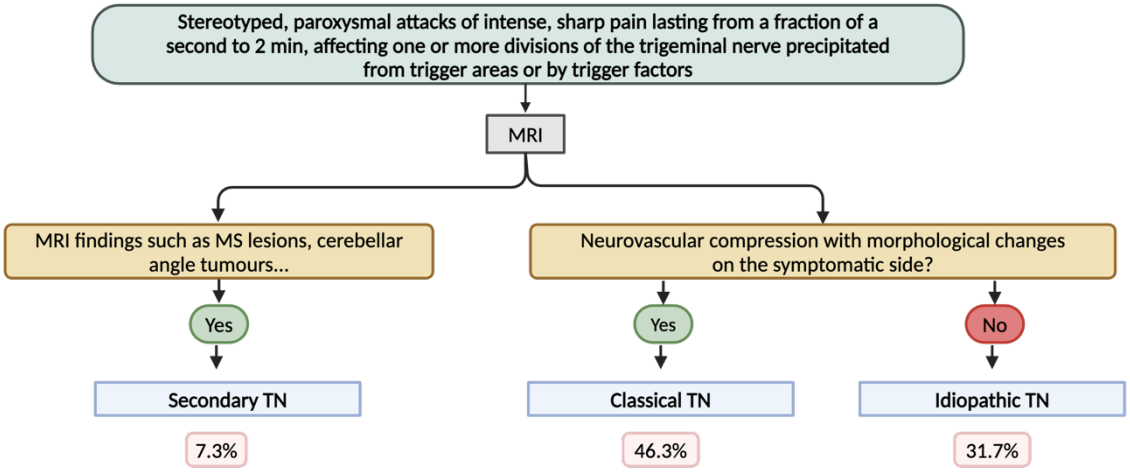
8.4. Neuroimaging tests and classification of TN.

For the diagnosis of this disease, the most important thing is a correct clinical history and physical examination of the patient, taking into account the clinical characteristics of the disease. However, it is common to perform complementary imaging tests at diagnosis or during follow-up to see if there are findings that explain the disease. Commonly used imaging tests are MRI, MRI angiography, CT and CT angiography. Further, neuroimaging studies, especially MRI, are important for the classification of TN into either primary or secondary TN, which is typically caused by MS or a brain tumor in the posterior cranial fossa.

The European Academy of Neurology (EAN) and the American Academy of Neurology (AAN) recommend MRI as the first imaging test to be performed in the study of trigeminal neuralgia[1,9]. In our patients, therefore, the most frequently performed imaging test was MRI (performed in 36 patients, 87.8%); this MRI was extended to angioMRI in 94.4% of the patients who had MRI. On the other hand, CT scanning was performed in less than half of the patients in the sample (39%), this is because CT scanning is only recommended for the study of TN in those cases in which MRI is not available or is contraindicated as it has limited efficacy in the study of the disease[1,20].

As results of the imaging tests, vascular contact was found in 19 patients of the sample (46.3%), no significant findings were found in 13 patients (31.7%) and lesions other than vascular contact but responsible for the disease were found in 3 patients (7.3%), two of them with lesions compatible with MS and another with herpes ophthalmicus. In addition, there were 6 patients (14.6%) for whom we do not have the results of the imaging tests because they were performed in private centers or other reference centers and they did not provide the results of these tests. These findings allow us to classify trigeminal neuralgia into its different types according to The International Classification of Headache Disorders Third Edition (ICHD-III), so those patients who met the clinical criteria for the disease and who also had a vascular contact responsible for the symptoms were classified as Classic trigeminal neuralgia. In patients in whom other lesions have been found to be responsible for the disease, such as in cases of MS or ophthalmic herpes, we classified it as Secondary trigeminal neuralgia, and finally, those patients who met all the clinical criteria for the disease but no significant findings are found in the complementary tests were classified as Idiopathic trigeminal neuralgia (Figure 15). It is important to note that the resolution of imaging techniques is constantly advancing and it is possible that many patients with idiopathic trigeminal neuralgia have a vascular contact that has not been seen because the imaging tests were performed years ago when the resolution of MRI was poorer or may not even be possible to see with the resolution available today.

Figure 15. Classification of TN according to MRI findings in our patients.



There are articles that describe that the existence of a vascular contact causes greater involvement of some branches of the trigeminal nerve than others[1]. We have analyzed this in our sample without finding significant differences.

8.5. Treatment

The initial treatment of TN is usually pharmacological monotherapy. However combined therapy with different types of anticonvulsants or antidepressants can be used if the effect of monotherapy is lacking and patients with refractory NT sometimes need advanced therapies or neurosurgery. In our sample, the oral preventive treatments and advanced therapies undergone by the patients in the sample have been analyzed.

8.5.1. Oral preventive treatment

In the case of preventive oral treatment, we have analyzed up to 6 lines of treatment in our patients, including the number and percentage of patients who reach each line of treatment, which drug they took in each line before moving on to the next, and prior to advanced therapies. We have also seen that the starting and maintenance doses administered to our patients are those described and recommended in the current literature for the treatment of this disease[9,29].

In our study, carbamazepine was the most prescribed drug as first-line treatment, used in 31 patients (75.6%) of the sample. This indicates a good approach to the initiation of trigeminal neuralgia treatment in our center, as carbamazepine is the only drug with Class I efficacy (Grade A recommendation) in the treatment of trigeminal neuralgia[9]. The second most commonly used drug in first-line treatment was pregabalin in 9.8% of patients, followed by gabapentin in 4.9% of patients. After carbamazepine, the drugs with the most evidence for the treatment of trigeminal neuralgia are oxcarbazepine and eslicarbazepine (Class IV, Grade C recommendation) however in our sample, after

carbamazepine, the most commonly used drugs are pregabalin and gabapentin, this is because in our sample the population has a high average age and in long-lived patients these two drugs have shown better tolerance compared to first and second line drugs that produce more side effects[20]. Furthermore, it has been reported that drugs such as gabapentin and pregabalin are more effective in cases of postherpetic trigeminal neuralgia[11], and in our sample the patient with postherpetic trigeminal neuralgia started first-line treatment with pregabalin.

8.5.1.1. Oral preventive drugs side effects

The overall side effects of patients with any drug and in any line of treatment have been collected and described. In addition, the adverse effects of first-line drugs were studied, since in successive lines of treatment there were patients taking more than one drug and it would be impossible to discern to which drug the reported adverse effect is attributed.

In terms of overall adverse effects of taking any preventive oral treatment, 28 patients (68.3%) experienced instability/ataxia, 21 patients (51.2%) drowsiness, 7 patients (17.1%) confusion, 5 patients (12.2%) hyponatremia, 3 patients (7.3%) digestive intolerance, 2 patients (4.9%) irritability and 1 patient (2.4%) diplopia. Furthermore, if we analyze the adverse effects among the 31 patients taking carbamazepine exclusively in the first line of treatment (most commonly used drug in the treatment of the disease) we find that 24 patients (77.4%) experience instability/ataxia, 16 patients (51.6%) experience drowsiness, 4 patients (12.9%) confusion, 3 patients (9.7%) hyponatremia, 3 patients (9.7%) digestive intolerance, 1 patient (3.2%) irritability and 1 patient (3.2%) diplopia. With these results we can state that most of the overall side effects of the patients were due to carbamazepine intake as they correspond to those described in the literature for this drug[22]. The side effects described above may condition the use of treatments and therefore their efficacy, making substitution necessary or leading to the need for advanced therapies.

8.5.2. Advanced therapies

The main advanced therapies in the treatment of trigeminal neuralgia are botulinum toxin, decompressive surgery, rhizotomy and gammaknife. 61% patients of the sample needed to undergo one of these advanced therapies, indicating refractoriness to oral preventive treatment. Moreover, the average time from the onset of symptoms to the use of the advanced therapies (with the exception of botulinum toxin) was more than 4 years in all cases.

The most commonly used advanced therapy, also because it is the least invasive, is botulinum toxin treatment in 17 patients (41.5%). Rhizotomy has been performed in 11 patients (26.8%), decompressive surgery in 7 patients (17.1%) and gammaknife in 3 patients (7.3%).

We analyzed how many of the patients with Classic trigeminal neuralgia, that is with a vascular contact demonstrated by neuroimaging, underwent decompressive surgery. We found that decompressive surgery was performed in only 7 of the 19 patients with a demonstrated vascular contact in this sample.

8.5.2.1. Efficacy of advanced therapies

We analyzed the efficacy of decompressive surgery, rhizotomy and gamma knife using two parameters, firstly the pain sensation reported by the patient after surgery and secondly the difference between the number of drugs used before the procedure and 3 months after the procedure.

In the case of decompressive surgery, 57.1% of patients reported a complete improvement in pain and 28.6% a partial improvement (only one patient reported no improvement at all). Furthermore, it was statistically significant that patients used an average of 2.29 fewer drugs 3 months after surgery. Both results are indicative of the good efficacy of this advanced therapy. If we analyze the fact that the majority of patients with vascular contact are not undergoing this intervention and at the same time we see the good results of the patients in whom it is being carried out, it would be interesting to raise awareness among the professionals in charge about indicating or carrying out more of this intervention, as in many cases the results are definitive and it means a change of life for the patient suffering from this painful disease. In addition, studies on patients who have undergone vascular decompression show results as good as those obtained in our study, with 83% of patients with pain relief and 63% of patients with fewer drugs or lower doses of drugs after surgery[35].

In the case of rhizotomy, 36.4% of patients reported complete improvement and 63.6% reported no improvement at all, and we found no significant differences in the number of drugs used by patients before and after surgery.

Finally, in the case of gamma knife, 66.7% of patients experienced complete improvement and 33.3% of them no improvement at all. We also found no significant differences in the number of drugs used before and after surgery. Although only 3 patients in the study had undergone this technique, the results may not be extrapolated to the general population due to the low sample size, although it is true that texts indicate that up to 34% of patients undergoing this test do not show pain relief after the procedure[19].

8.6. Limitations

This study includes several limitations.

Our study included a relatively low number of patients (n=41) considering the overall prevalence of TN in Spain. Moreover, the data collected are extracted from the Headache Unit of a single tertiary hospital center; therefore, this may be a source of potential bias

when it comes to identifying different trends among the characteristics of the patients included in our study. Therefore, the generalizability to the general population of people affected of TN is limited.

Second, this study is limited by its retrospective design and includes only medical records. Regarding the retrospective individualized assessment of the patients, the duration of the retrospective study was different in each case, as the patients were diagnosed at different times. Consequently, there is a significant impact on disease monitoring and prognosis, as the therapeutic arsenal has changed over the last years.

Future studies with larger samples and multicenter studies that confirm the results described would be desirable.

7. Conclusions

In conclusion, the following ideas can be drawn from this work:

- TN is a disease that produces a lancinating and very sharp pain similar to an electric shock following the path of one or several branches of the trigeminal nerve.

- TN affects women more frequently, affecting more unilaterally and on the right side of the face. The most affected branches are V2 and V3 or the combination of V2+V3.

- The patients in this study were a cohort of patients from the Headache and neuralgias database of the Neurology Department of the Marqués de Valdecilla University Hospital diagnosed as TN and with specific treatment for this disease.

- It is an under-diagnosed disease. It takes an average of 6 months to be diagnosed, with a range of 24 months when it is a disease with a very characteristic clinical picture.

- The most frequently performed tests at HUMV are MRI and angioMRI.

- There are three types of TN: Classic, Idiopathic and Secondary. In our center, as in the general population, the most frequent of these is Classic followed by Idiopathic and finally Secondary.

- It is a very refractory disease to medical treatment, with patients reaching 6 different lines of oral preventive treatment.

- In the first line of oral preventive treatment, the most used drug is carbamazepine, followed by pregabalin and gabapentin.

- Carbamazepine is the drug with the most reported adverse effects, the most common being gait instability, followed by drowsiness and confusion.

- Advanced therapies used in treatment are botulinum toxin, decompressive surgery, rhizotomy and gamma knife. The most performed procedure in our hospital is botulinum toxin followed by rhizotomy, decompressive surgery and gamma knife.

- The most effective advanced therapy in our patients has been decompressive surgery, achieving a reduction of 2.28 drugs three months after the procedure.

- A study with a larger population would be necessary to extrapolate all the data analyzed to the general population.

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9. Acknowledgements

No me puedo creer que esté escribiendo esto ya, tengo tantas cosas que decir y tanta gente a quien agradecer que intentaré ser lo más breve posible. Escribir esta última página no solo es el cierre de mi TFG, es el cierre de una etapa de mi vida, una etapa de crecimiento profesional, pero sobre todo de crecimiento personal y de cierta forma también la constatación de haber cumplido un sueño. Llevo tanto tiempo esperando y ansiando que llegue este momento…

Al margen de la carrera, las etapas de la vida están muy marcadas por la gente que te acompaña en ellas y el lugar donde te encuentras, así que en primer lugar agradecer a mis amigos de aquí, por hacer de Santander mi casa, haberme hecho sentir tan querida, haber compartido tan buenos momentos, habernos reído tanto (y a veces también llorado). He sido tremendamente afortunada de encontrar esa clase de personas que sabes que son para toda la vida, sin duda me iría al fin del mundo con ellos.

Agradecer a mi familia, siento que más del 50% de estos 6 años se lo debo a ellos y sin duda no podría haberlo hecho sin su apoyo incondicional. Por sus consejos, por su positividad para contrarrestar en ocasiones mi negatividad, por empujarme para hacerme llegar más lejos, por creer en mí siempre.

Gracias a todos mis profesores durante la carrera, por compartir sus conocimientos médicos para formarnos como profesionales, transmitirnos su ilusión y amor por la profesión, pero sobre todo por compartirnos todas aquellas cosas que derivan de la experiencia y no aparecen en los libros. Trataré siempre de seguir vuestros consejos.

Agradecer especialmente a mis tutores Vicente González Quintanilla y Julio Pascual Gómez por haberme enseñado, guiado y orientado en la realización de este trabajo, dispuestos en todo momento a ofrecerme su ayuda y resolver mis dudas, no podría haber escogido mejor. Gracias también a Jorge Madera por echarme una mano en los temas relacionados con la parte estadística, sin él tampoco podría estar escribiendo esto. Y finalmente gracias a todo el servicio de Neurología del HUMV por acogerme durante mis prácticas como una más y enseñarme tanto de esta maravillosa especialidad, sois un 10 tanto a nivel profesional como personal.

Para finalizar quería agradecer a todos los pacientes, no solo a los que han sido incluidos en el estudio que ha permitido desarrollar este trabajo, sino a todos, que permiten que podamos aprender y mejorar, por hacer que todo esto tenga un sentido que no es otro que ayudar a los demás.

En resumen, ha sido un largo viaje, la montaña rusa de mi vida podría decirse, pero rodearse de tan buena gente lo hace todo más fácil, así que como diría uno de mis escritores favoritos, gracias a todas las personas queridas en las que vivo cada día.

Sinceramente, de corazón,

Carmen Castaño Ron