International Journal of
Health Science

ISSN 2764-0159 vol. 5, n. 33, 2025

ARTICLE
Acceptance date: 28/10/2025

MOST RELEVANT EPIDEMIOLOGICAL, CLINICAL, AND IMAGING CHARACTERISTICS IN A SERIES OF 80 DOMINICAN PATIENTS AFFECTED BY REFRACTORY TRIGEMINAL NEURALGIA TREATED WITH STEREOTACTIC RADIOSURGERY USING GAMMA KNIFE

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Abstract: Objectives: To determine the most relevant epidemiological, clinical, imaging, and structural characteristics of 80 Dominican patients affected by refractory trigeminal neuralgia treated consecutively at the Dominican Gamma Knife Center over an 8-year period. **Material and Method:** Retrospective study of 80 patients (47 women, 33 men) with refractory trigeminal neuralgia treated at the Dominican Gamma Knife Center between March 2011 and March 2019. All patients underwent a 1.5 Tesla MRI scan with 1-1.5 mm slices for three-dimensional reconstruction, including the following sequences: FIESTA, T1 without and with contrast, FLAIR, T2, and TOF. In addition to their epidemiological characteristics, the etiological type of neuralgia (essential or secondary), side of symptoms, affected branch(es), size of the trigeminal cistern (large, intermediate, small), nerve trophicity (eutrophic, atrophic, dystrophic), the presence or absence of neurovascular conflict with precision of side (homolateral or contralateral to the pain), affected trigeminal segment (proximal, intermediate, distal), caliber of the compromised artery (small, medium, large), correlation of trigeminal trophicity with respect to the presence or absence of neurovascular conflict and arterial caliber. The images were examined by the Principal Investigator (PI) on the Elekta Gamma Plan 11 stereotactic image management platform at the Dominican Gamma Knife Center. The data collected was processed using measures of central tendency and Pearson's correlation-dispersion coefficient on the Microsoft Excel 2016 platform. **Results:** Women predominated in our population (58.75% vs. 41.25%). The prevalent age range was between 50 and 79 years (71.25%). Essential trigeminal neuralgia (72%) was more frequent than secondary trigeminal neuralgia (28%). The right side (57.5%) was more affected than the left (42.5%). The most affected isolated branch was the upper maxillary (15.69%). The most frequent combination of branches was upper maxillary with lower maxillary (29.41%). Large trigeminal cisterns predominated (66.25% right, 72.5% left) over intermediate cisterns (25% on both sides). Most symptomatic nerves were atrophic or dystrophic. In contrast, unaffected nerves were predominantly eutrophic. Although the symptoms were always unilateral, the presence of neurovascular conflict was detected bilaterally in 75% of cases. The artery causing the conflict was of medium caliber in more than 50% of cases; it was only large caliber in 5% of cases on the right and in 3.75% of cases on the left side. On both sides, the proximal segment of the trigeminal nerve was the most frequent site of neurovascular conflict. Trigeminal atrophy was more frequent with larger arterial caliber. **Conclusion:** This is the first time that a large group of Dominican patients affected by refractory trigeminal neuralgia has been reported in the international medical literature. A detailed analysis of their epidemiological, clinical, and imaging characteristics is presented to facilitate comparison with other published series. Particular emphasis is placed on the size of the trigeminal cistern, the trophicity of the nerves studied, the type of artery involved in the neurovascular conflict, its location, and its impact on the morphology of the trigeminal nerve, aspects for which there is little data in the specialized literature on the subject.

KEYWORDS: Refractory Trigeminal Neuralgia, Neurovascular Conflict, Atrophy, Dystrophy, Trigeminal Eutrophy.

INTRODUCTION

Refractory trigeminal neuralgia is a nosological entity feared by all neuroscientists[1]. The difficulty in controlling this pain has been a challenge for even the most experienced therapists for centuries[2], with suicide being a tragic outcome in many cases throughout history. The etiology of so-called Essential Trigeminal Neuralgia, not caused by trauma, infection, neoplasia, or demyelination, is usually related to the impact of the arterial pulse in contact with a demyelinated area of the nerve, and in many cases is doubtful or questioned[3] **.** The emergence of neuromodulatory drugs that act on sodium receptors, such as carbamazepine and oxcarbazepine, has played a key role in controlling the condition in its early stages[4] . Many. of these cases will inevitably worsen, making surgical intervention essential at some point [4] .Local injections of alcohol, glycerol, or local anesthetics into the affected trigeminal branch have long been abandoned due to their ineffectiveness and discomfort [4].

Percutaneous compression of the Gasser ganglion with a Fogarty balloon is a minimally invasive and effective method that requires an operating room and anesthesia[4]. The same is true for radiofrequency thermocoagulation using a transforaminal electrode[5]. The most effective treatment in cases of severe neurovascular conflict has been neurovascular decompression, involving the insertion of a Teflon mesh to separate the nerve from the artery via a posterior fossa approach, with the associated morbidity and mortality that this may entail [4]. In recent years, the use of radiosurgery using Gamma Knife has gained momentum due to its high efficacy, minimal morbidity, and zero mortality [6,8].

Given its occurrence in all corners of the world with an incidence of 100 per 100,000 patients per year in some Asian countries[7], refractory trigeminal neuralgia is a widely known entity, although its diagnosis is still unfortunately made after several unnecessary failed tooth extractions.

We found it interesting to determine the basic epidemiological variables and the clinical and imaging presentations of refractory trigeminal neuralgia in the Dominican population, which is predominantly mestizo like that of many Caribbean and Central American countries, in order to gain an understanding of these realities in this part of the world.

MATERIALS AND METHODS

This retrospective study was conducted on a population of 80 patients suffering from refractory trigeminal neuralgia, treated consecutively between November 2011 and August 2018 at the Dominican Gamma Knife Center (CGKD) belonging to the Center for Diagnosis, Advanced Medicine, and Telemedicine (CEDIMAT), located in the Plaza de la Salud in the city of Santo Domingo, Dominican Republic. All patients whose trigeminal neuralgia was related to a tumor or vascular process demonstrable by imaging were excluded. We reviewed the general statistics of the population treated during those eight years of CGKD activity, specifying the number of procedures performed and the type of pathology managed, determining the percentage occupied by each of them within the total therapeutic activity deployed. We determined the gender and age of each patient, establishing the predominant ranges in each section. We specified the type of trigeminal neuralgia according to its etiology: essential (no identifiable cause) or secondary to a specific circumstance or pathology. The affected side of the face and the territory of the trigeminal branch where the pain was experienced were carefully determined. We analyzed in detail the size, content, and anatomical relationships integrated in the trigeminal cistern, that important and highly variable space through which the trigeminal nerve passes and where the neurovascular conflicts that affect it occur [9]. We classified it as absent, small, intermediate, or large according to its dimensions determined by visual inspection by the PI after comparing them all with each other. We paid particular attention to the trophicity of each trigeminal nerve, both healthy and diseased, trying to understand the impact that the presence or absence of neurovascular conflict could have on the structure of the nerve[10]. We classify trophicity into three groups, according to its morphological appearance in each millimeter-thick MRI slice: eutrophic, dystrophic, and atrophic, determined by visual inspection performed by the PI after comparing them all with each other. The trophicity of the right and left trigeminal nerves, both healthy and diseased, was determined. We then proceeded to determine the relationship between neural trophicity and clinically evident suffering in the trigeminal nerve territory.

The neurovascular conflict was attempted to be pinpointed in each of the 1 to 1.5 mm MRI sequences performed: FIESTA, T1 with contrast, T1 without contrast, T2, TOF. Since contrast-enhanced computed axial tomography with thin slices of 1 to 1.5 mm was used in patients treated with the Gamma Knife model 4C, an attempt was also made to locate the neurovascular conflict in this imaging modality. Four groups of neurovascular conflict were identified: bilateral, contralateral to the pain, ipsilateral to the pain, and no neurovascular conflict. The caliber of the artery causing the neurovascular conflict was determined on both the right and left sides in four groups: small, medium, large, and no neurovascular conflict. The position of the neurovascular conflict was located according to the three most important points of the nerve between its origin in the REZ (Root Entry Zone) [10] and its final destination in the external pore of Meckel's cave, passing through the middle of the trigeminal cistern. Thus, four groups were determined on both the right and left sides: proximal, intermediate, distal, and absent. We wondered whether the trophicity of the trigeminal nerves was related to the caliber of the artery responsible for the neurovascular conflict, so we compared the different degrees of trigeminal trophicity on both sides with large, medium, small, or absent arterial caliber. The data collected was processed using measures of central tendency and Pearson's correlation-dispersion coefficient using the Microsoft Excel 2016 platform.

RESULTS

This retrospective study was conducted on a population of 80 patients suffering from refractory trigeminal neuralgia, treated consecutively between November 2011 and August 2018 at the Dominican Gamma Knife Center (CGKD) belonging to the Center for Diagnosis, Advanced Medicine, and Telemedicine (CEDIMAT), located in the Plaza de la Salud in the city of Santo Domingo, Trigeminal neuralgia accounted for 11.9% of all therapeutic activity at the CGKD up to that point, with meningiomas being the most frequently treated pathology, at 23.7% (Graph 1). Graph 2 shows that 47 women (58.75%) and 33 men (41.25%) were treated, most of whom were between the ages of 50 and 79 (Graph 3). The type of trigeminal neuralgia was essential (no known cause) in 72% of cases and secondary (trauma, dental procedure, multiple sclerosis, herpetic neuropathy, etc.) in 28% of patients (Graph 4). The most frequently affected side of the face was the right, accounting for 57.5% of cases (Graph 5). The most frequently affected isolated trigeminal branch was the upper maxillary branch in 15.69% of cases. The most frequent combination of branches was the maxillary and mandibular branches, accounting for 29.41%. All three trigeminal territories were affected in only 5.88% of cases (Graph 6). Figure 7 shows our classification of the different types of peritrigeminal cisterns found in our patients. Taking advantage of the excellent 1.5 and 3 Tesla MRI images, FIESTA sequence, the PI analyzed the extent of the trigeminal cisterns, both right and left, of all patients, comparing them with each other (Figures 8 and 9), classifying them as Large, Intermediate, Small, or Absent. We found that they were Large in more than 60% of cases on both sides. On the left, there were no Absent cisterns, but on the right, we found two patients without an identifiable trigeminal cistern. Small cisterns accounted for less than 10% on both sides. Intermediate cisterns accounted for 25% of cisterns on both the right and left sides. We analyzed each affected trigeminal nerve and compared it with the healthy opposite nerve, looking for changes in its usual structure, classifying them as eutrophic (those with usual morphology and average volume), dystrophic (those that showed distortion from the usual shape in their path), atrophic (with flagrantly decreased volume). Graph 10 provides a fairly objective idea of this issue through simple observation. Analyzing Graphs 11 and 12, we note that eutrophic trigeminal nerves predominated on both sides in more than 50% of cases. However, the presence of atrophy was noticeable in more than 25% of the nerves studied on both the right and left sides. We analyzed the predominant trophicity in the affected nerves versus the unaffected nerves, and the results are shown in Graphs 13 and 14: eutrophic nerves accounted for up to 75% of asymptomatic trigeminal nerves and only 29.55 to 31.43% of symptomatic nerves. We paid close attention to the presence of vascular structures in contact with both painful and asymptomatic trigeminal nerves. Graph 15 shows an example of a neurovascular conflict of the affected side, visible in FIESTA sequences, T1 with contrast, and even in CT with contrast. According to the data presented in Graph 16, only 7.5% of the 160 trigeminal nerves studied did not show vascular contact. Seventy-five percent of patients had bilateral vascular contact. Only 11.25% of the cases presented had neurovascular conflict only on the side of the pain. In 6.25% of cases, the neurovascular conflict was contralateral to the pain and did not exist on the side of the pain.

An essential aspect to note in this investigation was the caliber of the vessel involved in the neurovascular conflict. This was determined by simple inspection of high-definition MRI images, especially in the FIESTA sequence, by the IP after comparing all the peritrigeminal vessels found in the patients. They were classified as small, medium, and large on both the right and left sides (Graph 17). The results can be clearly seen in Graphs 18 and 19: medium-caliber arteries predominated in more than 50% of cases on both sides. In our series, large-caliber arteries were only detected in a maximum of 5%.

We were also interested in the portion of the intracisternal path of the trigeminal nerve where the neurovascular conflict was verified. As can be seen in Graph 20, we distributed them according to the guidelines found in the international literature[18]: proximal, intermediate, distal from the origin of the nerve in the pons to its entry into Meckel's cave. Analyzing Graphs 21 and 22, we note the predominance on both sides of the proximal position of the vessel involved in the neurovascular conflict, with more than 30%. The intermediate and distal positions were found around 25% on both the right and left sides.

Finally, we analyzed the relationship between the trophicity of the trigeminal nerves studied in relation to the caliber of the artery causing the neurovascular conflict. As can be seen in Graphs 23 and 24: when there is no conflict, the nerves appear eutrophic up to 81.82% on the left. When the artery is small in caliber, eutrophic nerves still constitute up to 66.67% on the same side. However, when the artery is large in caliber, eutrophic nerves fall to 25% on the right and 0% on the left.

DISCUSSION

To our knowledge, this is the first report on the clinical and imaging characteristics of refractory trigeminal neuralgia in a large group of Dominican patients[11].

It is very important to note that among all the pathologies treated with the help of Gamma Knife at the CGKD, trigeminal neuralgia accounted for 11.9% of all cases, surpassed only by meningiomas (23.7%), pituitary adenomas (16.4%), and arteriovenous malformations (15.8%). This far exceeds multiple metastases (9.5%), acoustic neuromas (6.8%), and cavernomas (4.4%) (Graph 1).

Females predominated in our series, as is well established in the international literature[12] (Graph 2).

The age of our patients was consistent with what is universally observed: trigeminal neuralgia is not a disease of young adults and is very rare before the age of 30[13], t only one of our 80 patients fell within that age range (Graph 3). Fifty-seven of those 80 patients were between 50 and 79 years old, representing 71.25% of the study population.

According to some sources, neurovascular conflict involving an artery dependent on the superior cerebellar artery, inferior cerebellar artery, or petrosal vein may explain 80 to 90% of cases of refractory trigeminal neuralgia[14]. In these publications, tumors (meningiomas, acoustic neuromas, epidermoid cysts), arteriovenous malformations, saccular aneurysms, or multiple sclerosis may explain the remaining 10 to 20%. Patients with neurovascular conflict, which is almost imperceptible to the naked eye and can only be detected using the FIESTA sequence of a 1.5 or 3 Tesla MRI with 1 to 1.5 mm slices, fall within the category of essential trigeminal neuralgia, which only accounted for 72% of our population. We excluded all patients with trigeminal neuralgia caused by tumors or vascular pathology from the outset. Therefore, the remaining 28%, consisting of secondary trigeminal neuralgia, was related to trauma, dental procedures, multiple sclerosis, or postherpetic neuropathy (Graph 4).

The right side of the face has been reported to be affected more frequently than the left side, although the cause of this occurrence is unknown[15]. Our results with regarding the laterality of pain follow the same pattern: the right side (57.5%) was significantly more frequently affected than the left (42.5%) (Graph 5).

In the literature consulted, the maxillary superior and maxillary inferior branches are the most frequently affected[16]. When we analyzed the isolated branches in our population (Graph 6), the ophthalmic branch (11.76%) predominated over the inferior maxillary branch (9.8%), although the superior maxillary branch exceeded both (15.69%). The clinical presentation with more than one branch affected (62.74%) predominated over that of a single branch (37.25%), with the combination of upper and lower maxillary being the most frequent (29.41%).

The size of the peritrigeminal cistern, which according to data collected in highly influential reports "impacts the pathogenesis of essential trigeminal neuralgia, facilitating neurovascular conflict, especially in young patients"[17] was carefully analyzed in this study based on its appearance in thin 1 to 1.5 mm slices of 1.5 or 3 Tesla FIESTA MRI sequences, classifying them as absent, small, intermediate, and large (Graphs 7, 8, and 9). On both sides, large cisterns constituted more than 66%. On the left, there was no absence of cisterns, while on the right, there were two cases. Small and Intermediate cisterns constituted 32.5% on the right and 27.5% on the left. This is very valuable information "for surgical planning and potentially for predicting evolution" [17] .

The trophic state of the trigeminal nerves, especially if they are exposed to a neurovascular conflict, is relevant for analyzing the degree of suffering experienced, even guiding the most appropriate therapeutic decision: surgical decompression or another less invasive method[18] . Based on their comparative appearance with respect to the healthy side, using mainly 1.5 or 3 Tesla MRI FIESTA sequence images with thin slices of 1 to 1.5 mm, we were able to classify the trigeminal nerves as eutrophic, dystrophic, or atrophic (Graph 10). Eutrophic trigeminal nerves predominated on both sides (53.85% on the right, 65% on the left). Atrophic nerves accounted for about 30% on both sides (Graphs 11 and 12). When we analyzed the trophicity of asymptomatic nerves and compared it with that of affected nerves (Graphs 13 and 14), it was striking to note that the percentage of eutrophic nerves decreased from 75% to 29.55% on the right side and from 40% to 31.43% on the left side. Following the same comparative process, we realize that asymptomatic trigeminal nerves are atrophic in only 16.67% on the right and 30% on the left, while affected nerves show atrophy in 38.64% on the right and 54.29% on the left. This confirms the useful basic pathophysiological concept demonstrated in numerous studies: a nerve that suffers, a nerve that atrophies[18] .

When we focus on the existence or absence of neurovascular conflict, defined in this research as contact between the trigeminal nerve and a vascular structure of any diameter or origin, as can be clearly seen in Graph 15, we find (see Graph 16) that in our patients it existed on both the painful side and the healthy side in 75% of cases. This confirms the impression given in articles specializing in the subject: contact between the trigeminal nerve and a vascular structure can be routinely observed in many asymptomatic patients[19], categorically stating that alterations in nerve trophicity such as thinning, grooving, tattooing, or distortion must be found to establish that the neurovascular conflict is significant enough to justify decompressive surgery[18,19]. Given the extraordinary variability in the presentation of this entity, we are not surprised to find that only in 11.25% of cases did the neurovascular conflict appear solely on the side of the pain and that in 6.25% of cases the neurovascular conflict was contralateral to the pain and did not exist on the side of the pain (see Graph 16).

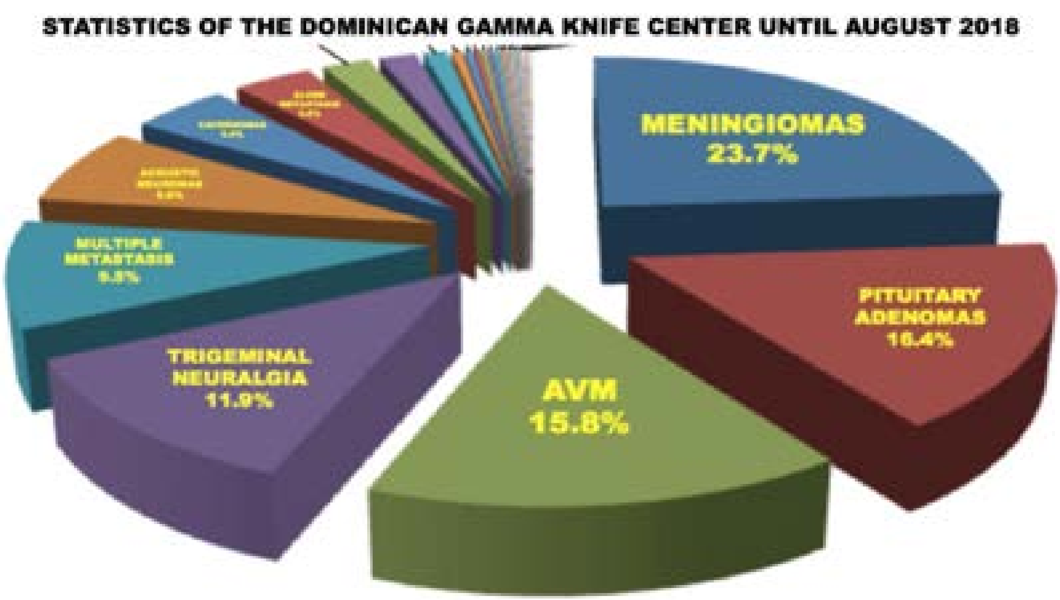
When assessing the caliber of the vessel involved in the neurovascular conflict according to the classification of Small, Medium, and Large shown in Graph 17, it was evident that the predominant caliber was Medium (52.50% on the right, 67.5% on the left, see Graphs 18 and 19). The extremes were less common: small caliber 25% right, 15% left; large caliber only 5% on the right and 3.75% on the left. The articles found in the vast literature reviewed refer to the arterial trunk (superior cerebellar and anterior inferior cerebellar) from which the branches that produce the neurovascular conflict derive, but they do not specify their caliber [20] .

When analyzing the portion of the intracisternal path of the trigeminal nerve where contact with the vascular structure in question takes place and then classifying them as Proximal, Intermediate, and Distal, as shown in Graph 20, we realized that both at right as on the left, this occurred predominantly in the proximal portion of the trigeminal nerve: 32.5% on the right and 35% on the left (see Graphs 21 and 22). The least frequently affected portion of the nerve was the distal portion, located at the entrance to Meckel's cave: 26.25% on the right and 23.75% on the left. Many of the articles reviewed on this anatomical detail of the neurovascular conflict do not accurately account for its location [21,22].

We were also struck by the relationship between the trophicity of the nerves analyzed and the caliber of the artery causing the neurovascular conflict (see Graphs 23 and 24). On both the right and left sides, there is an inversely proportional relationship between the caliber of the artery and the number of eutrophic nerves. On the right, when the caliber of the artery was large, the percentage of eutrophic trigeminal nerves fell to 25%. On the left, the percentage was zero. However, when the arterial caliber was medium, small, or absent, the proportion of eutrophic trigeminal nerves was above 63% on the left and 48% on the right.

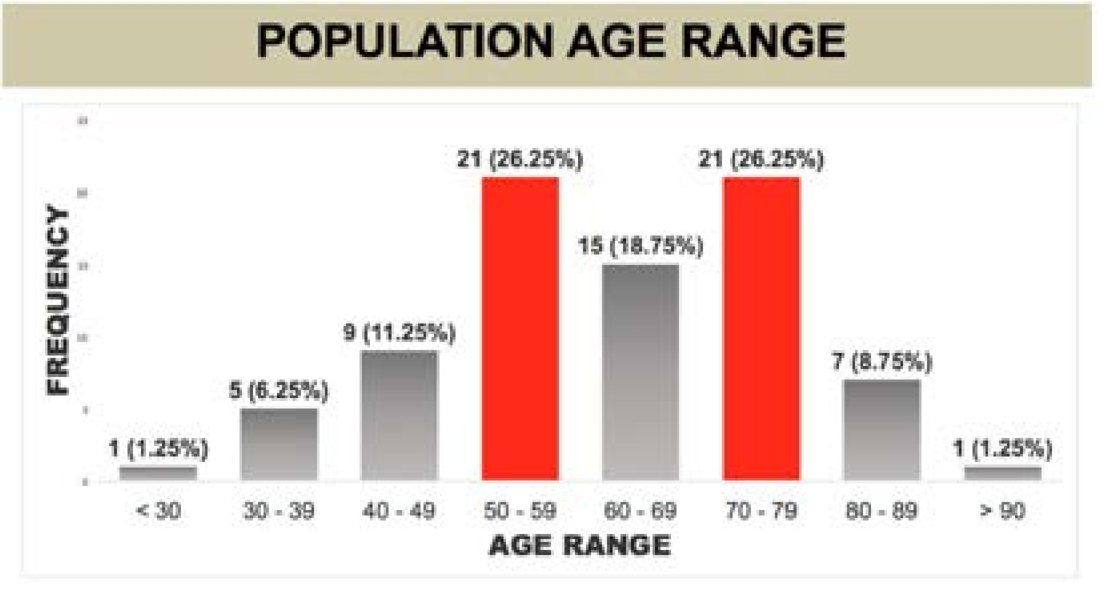
CONCLUSION

This large group of Dominican patients affected by refractory trigeminal neuralgia that we report bears a close resemblance to other series reported in the specialized literature in this field in terms of its epidemiological and clinical aspects. However, with regard to imaging details such as peritrigeminal cistern size, trophicity of the nerves studied, type of neurovascular conflict, caliber of the vessel involved, its location, and impact on trigeminal morphology, this study provides more accurate and detailed data than is usually reported. We trust that it will be taken into account for comparison, refinement, and optimization in future research.



Graphic 1.

Graphic 2.



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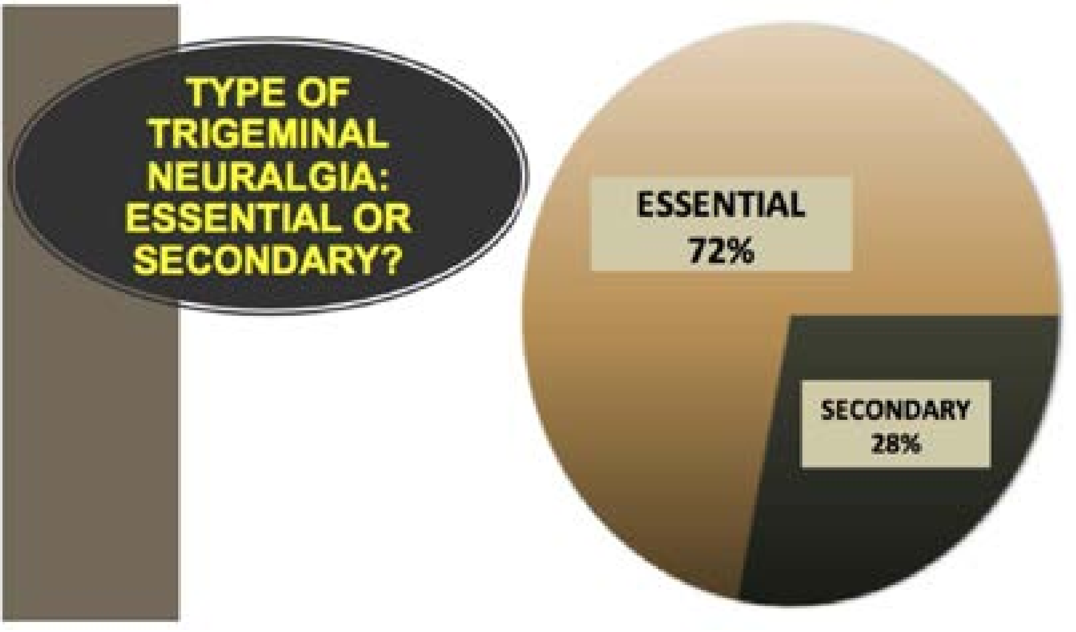

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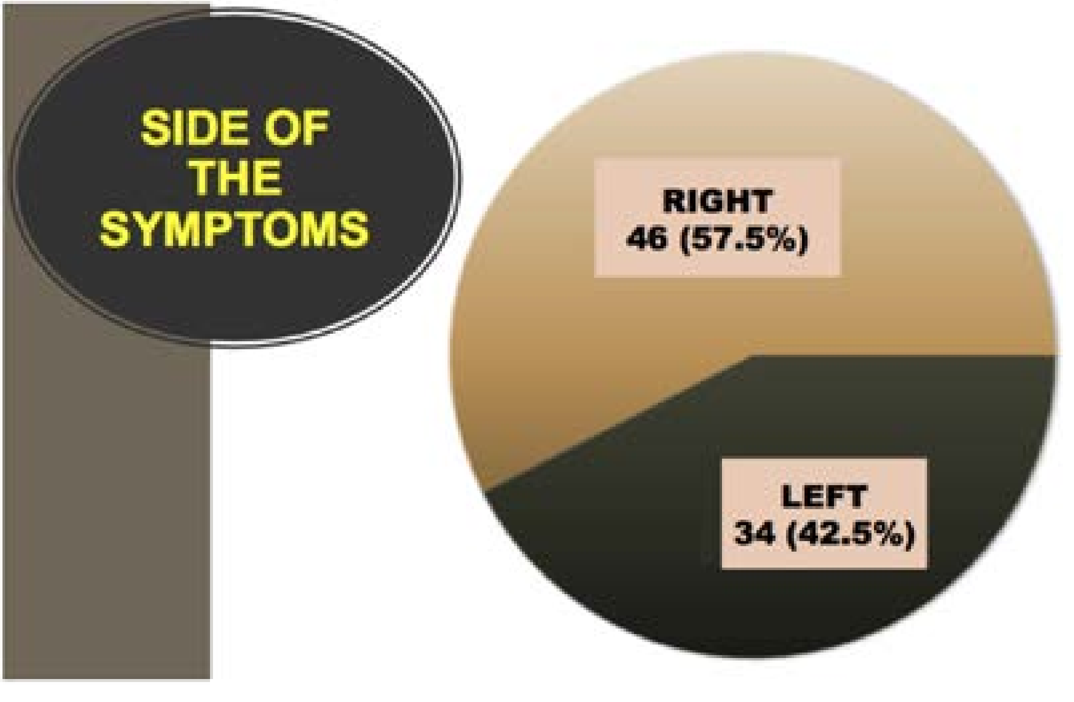

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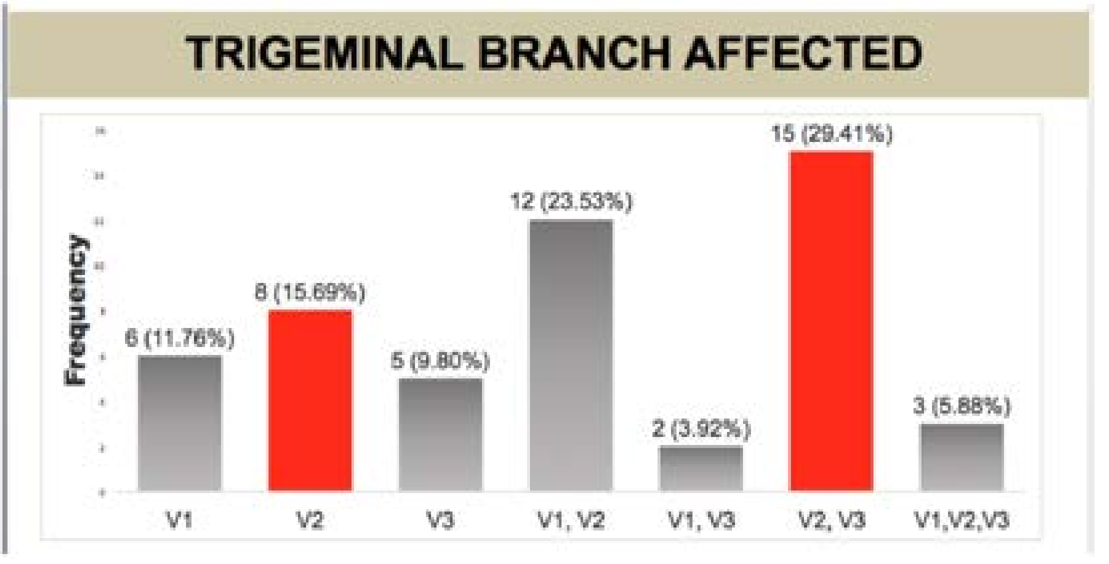

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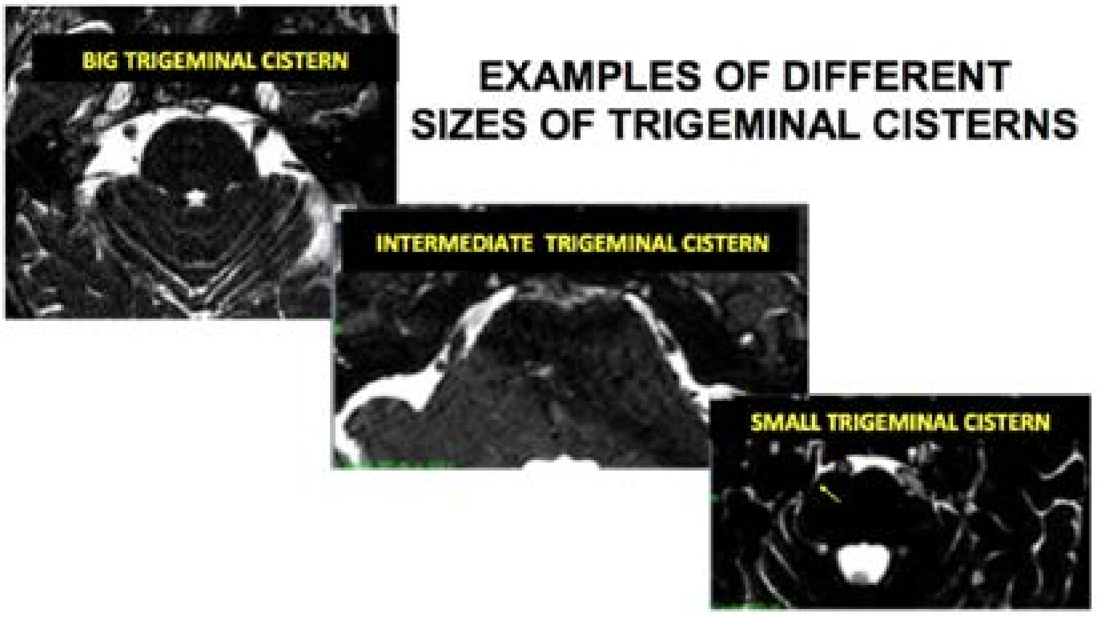

Graphic 7.

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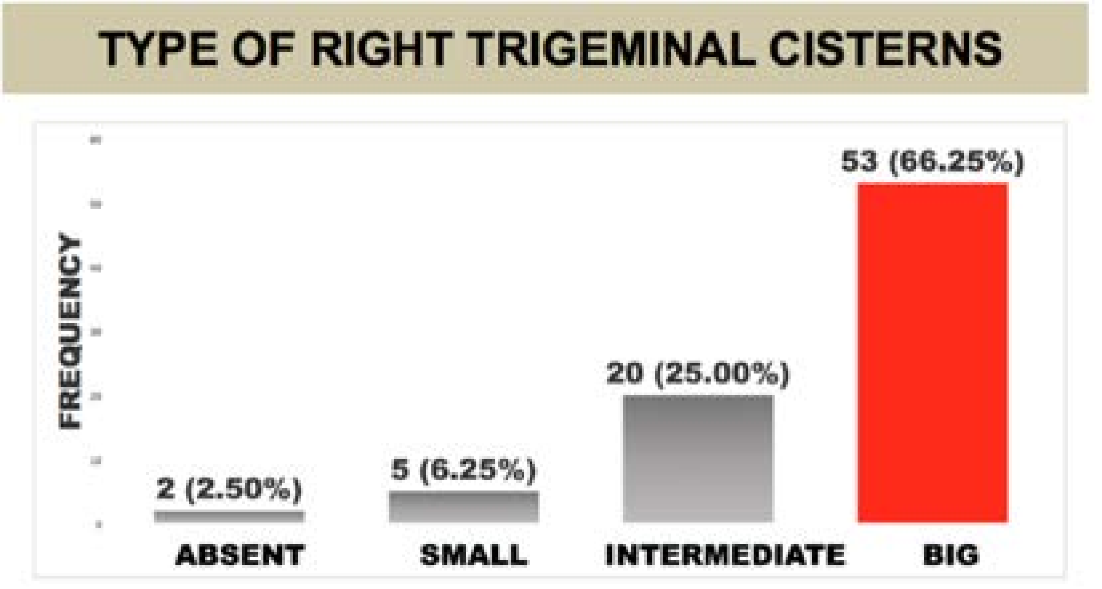

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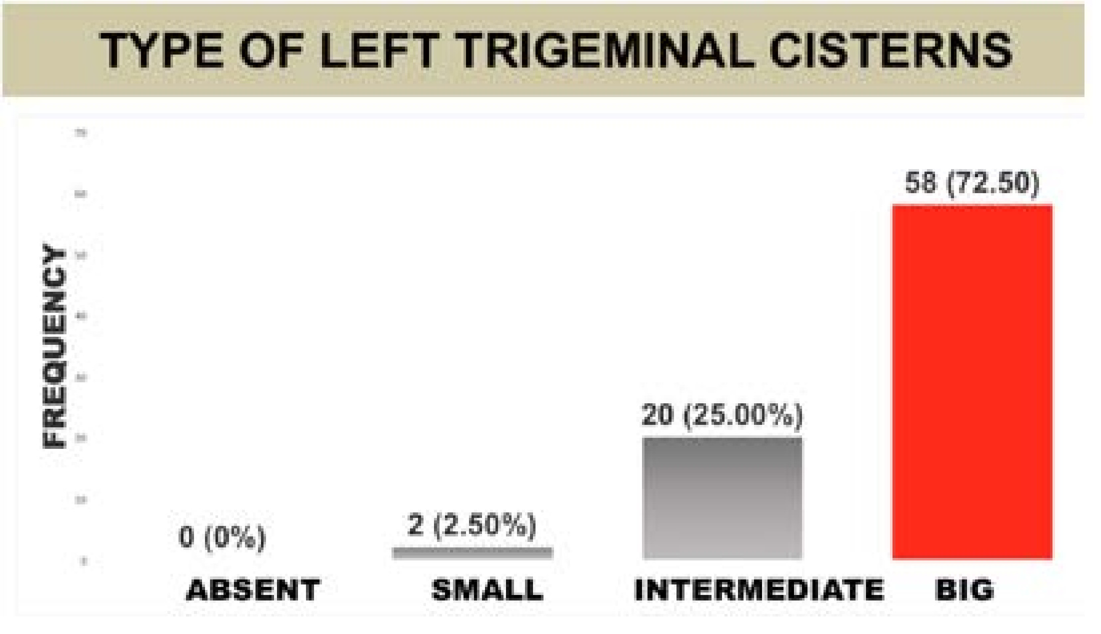

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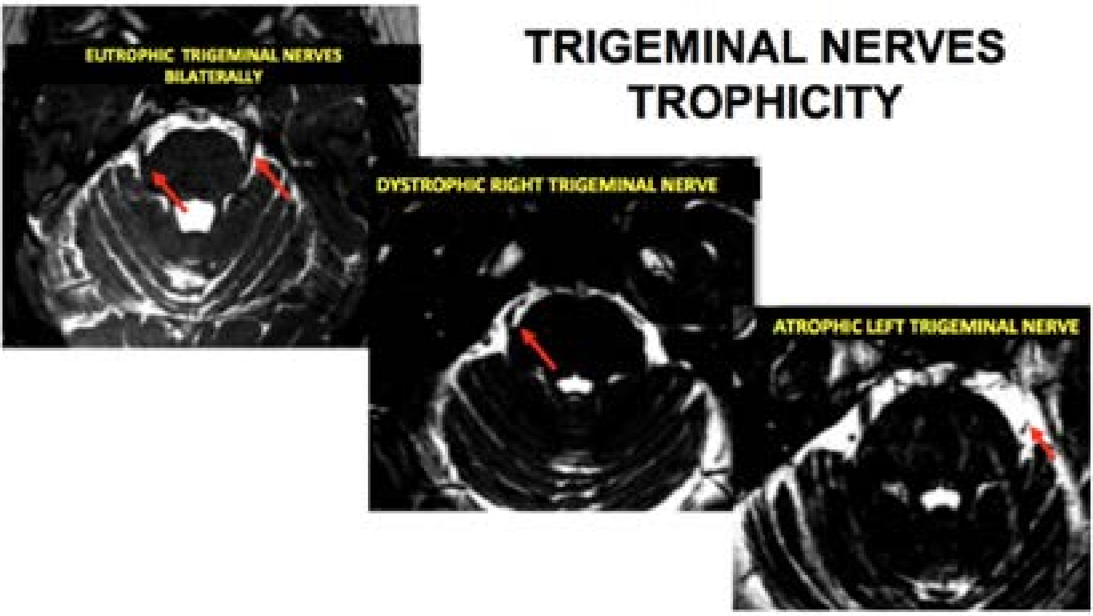

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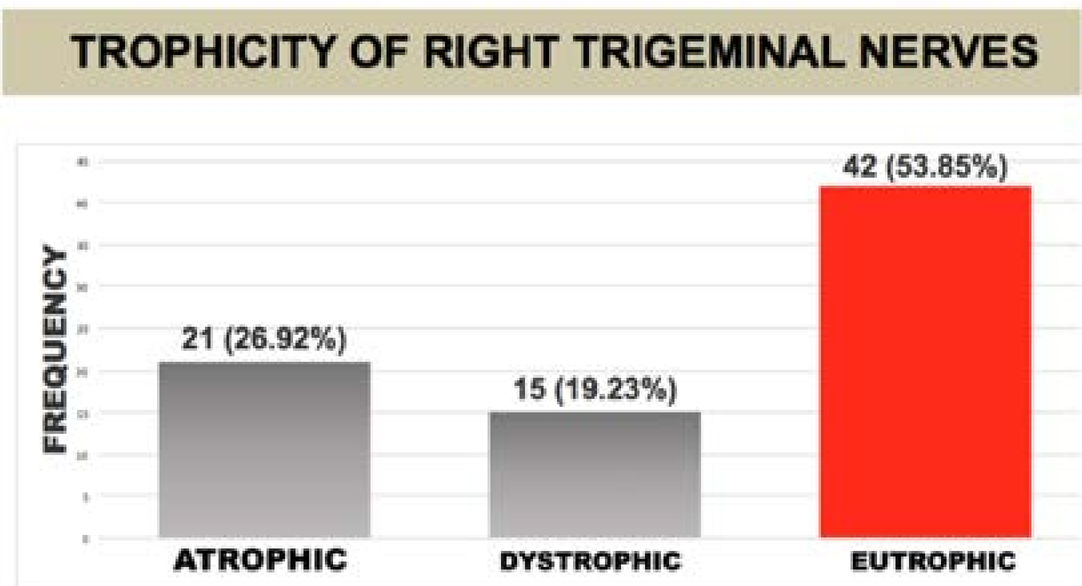

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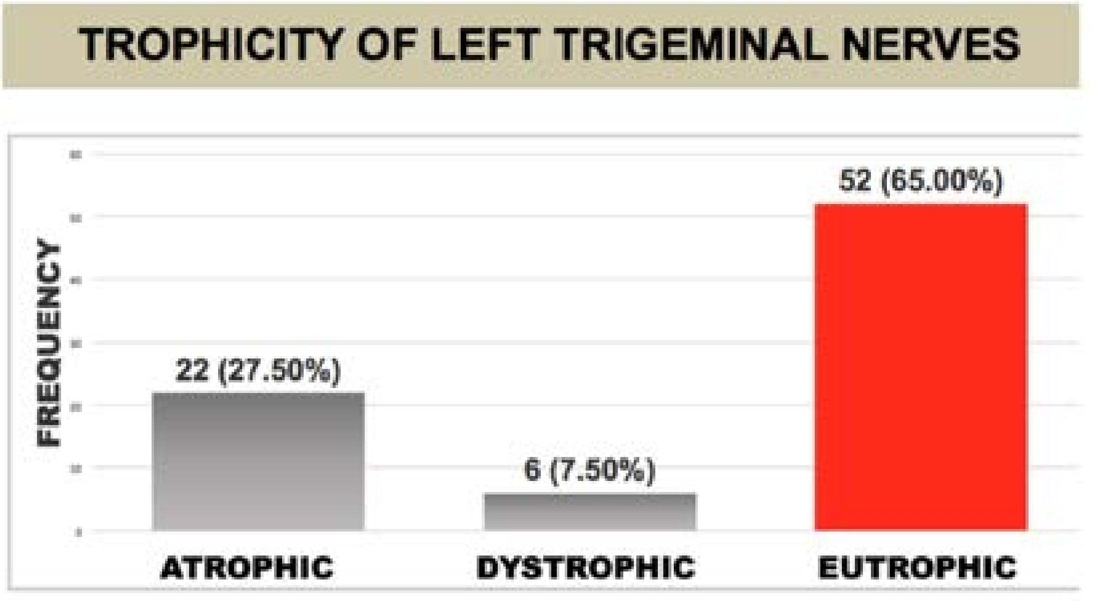

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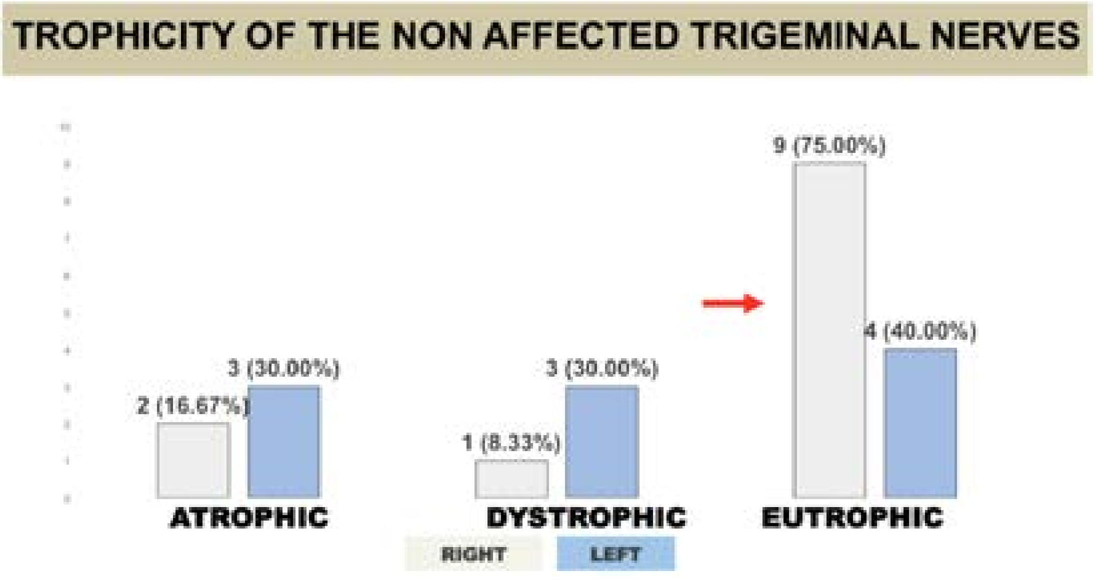

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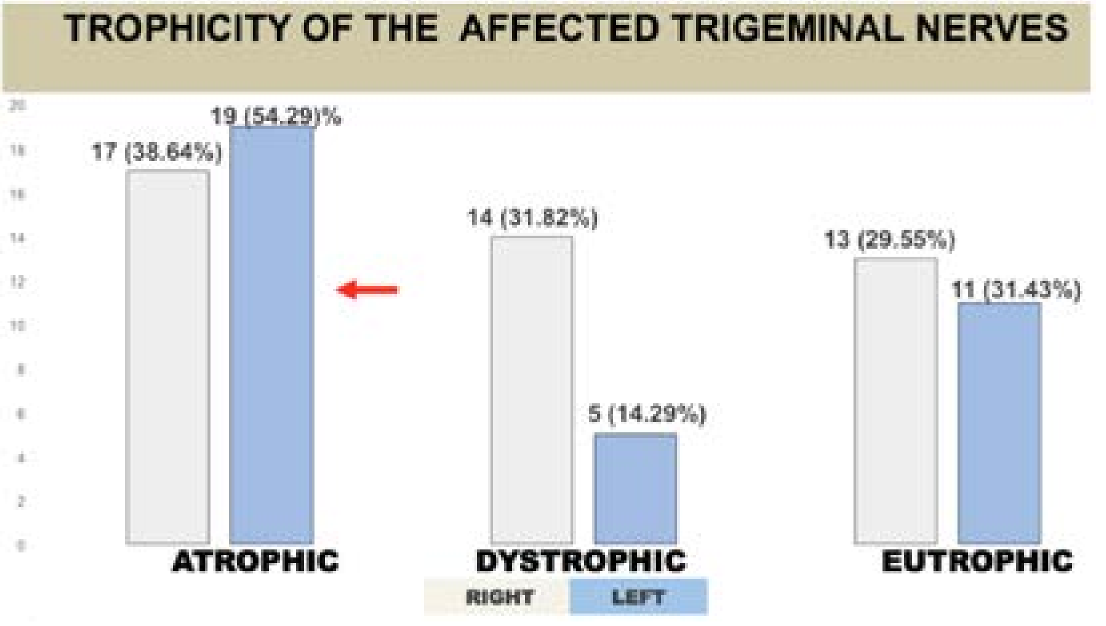

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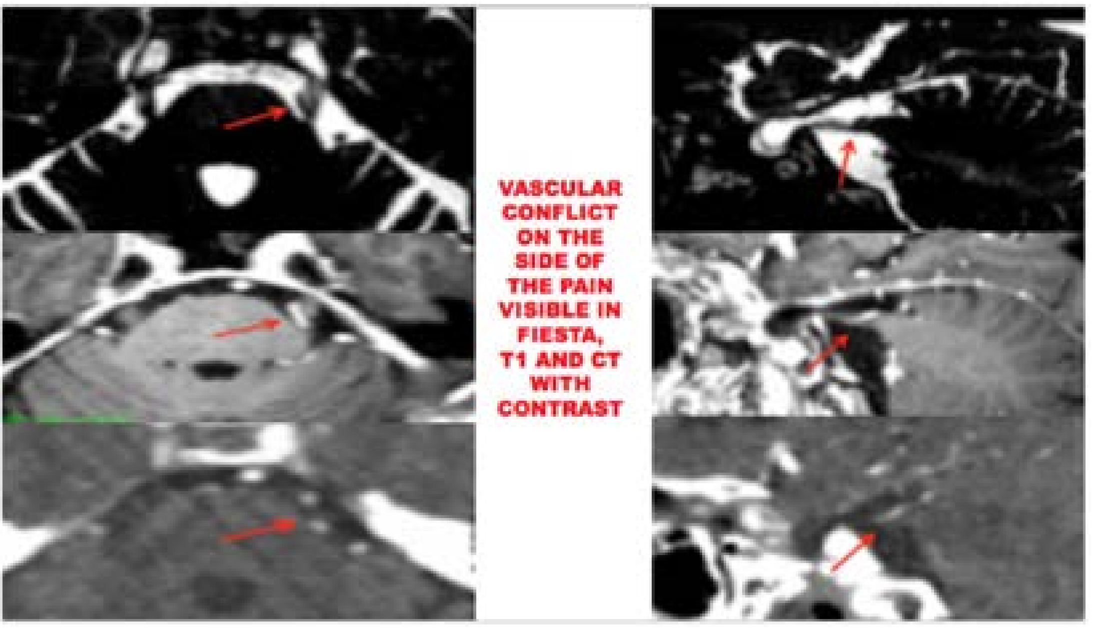

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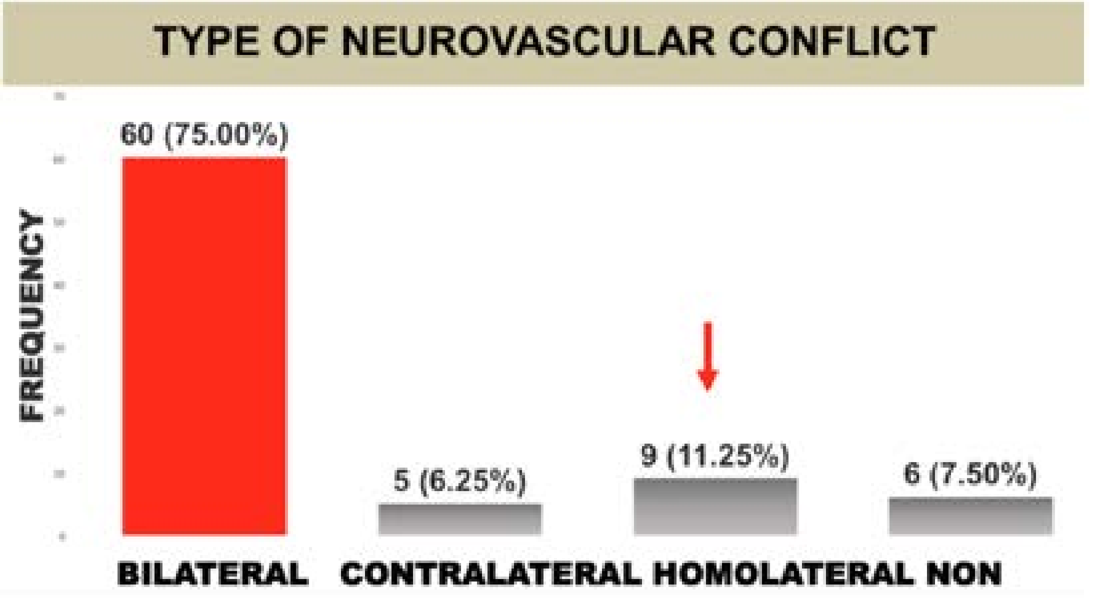

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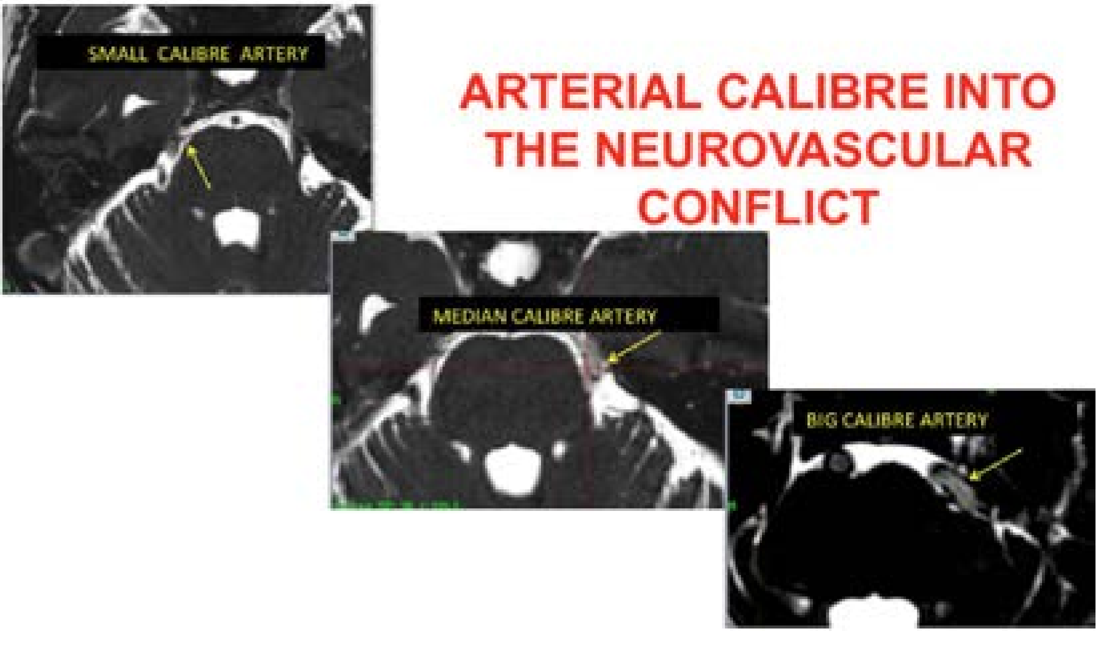

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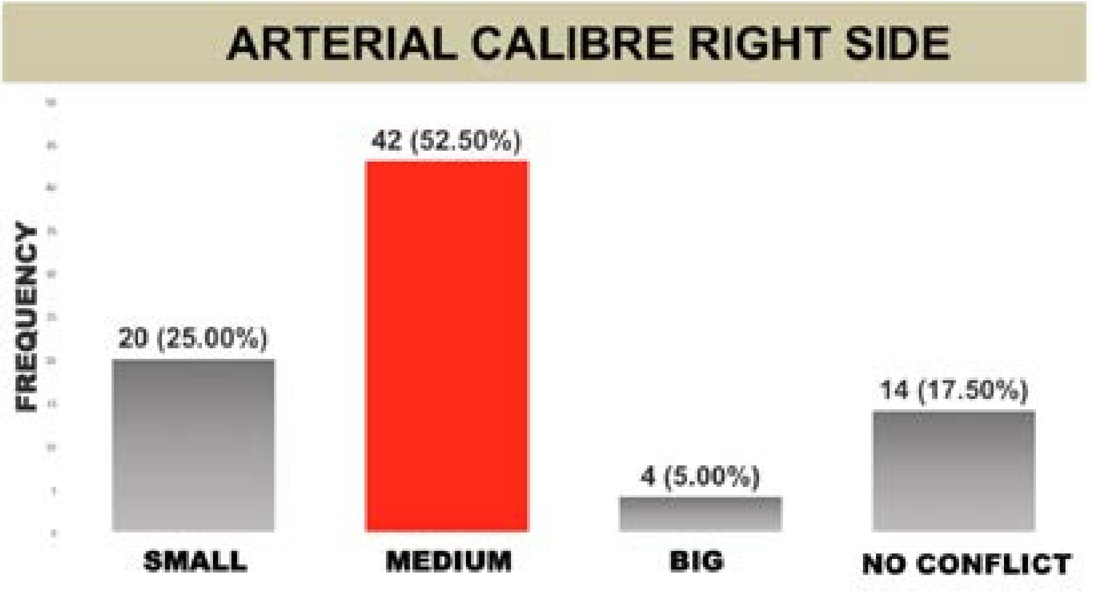

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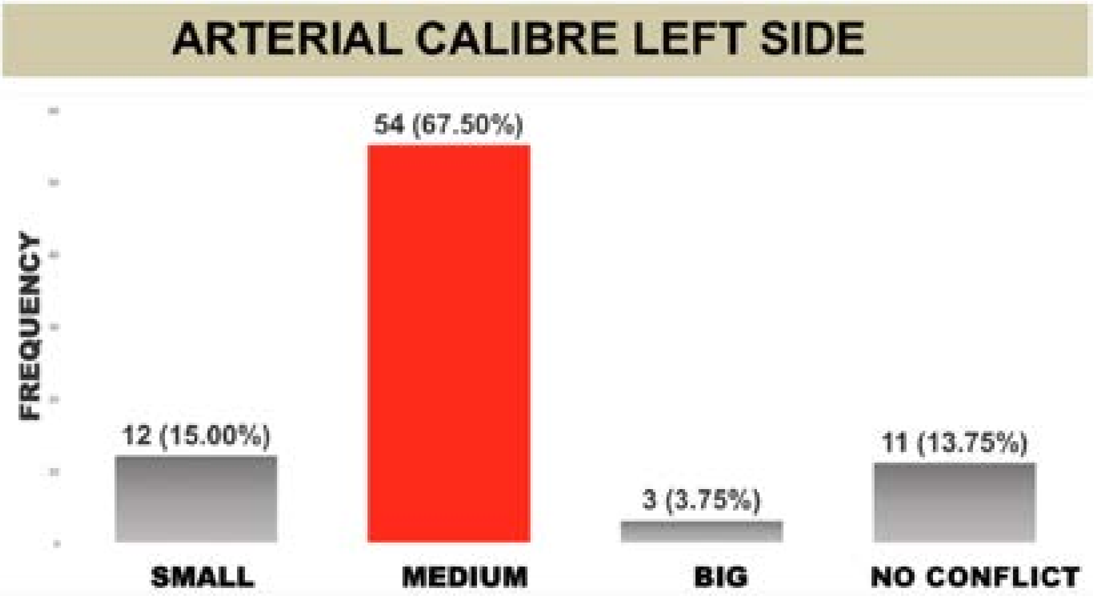

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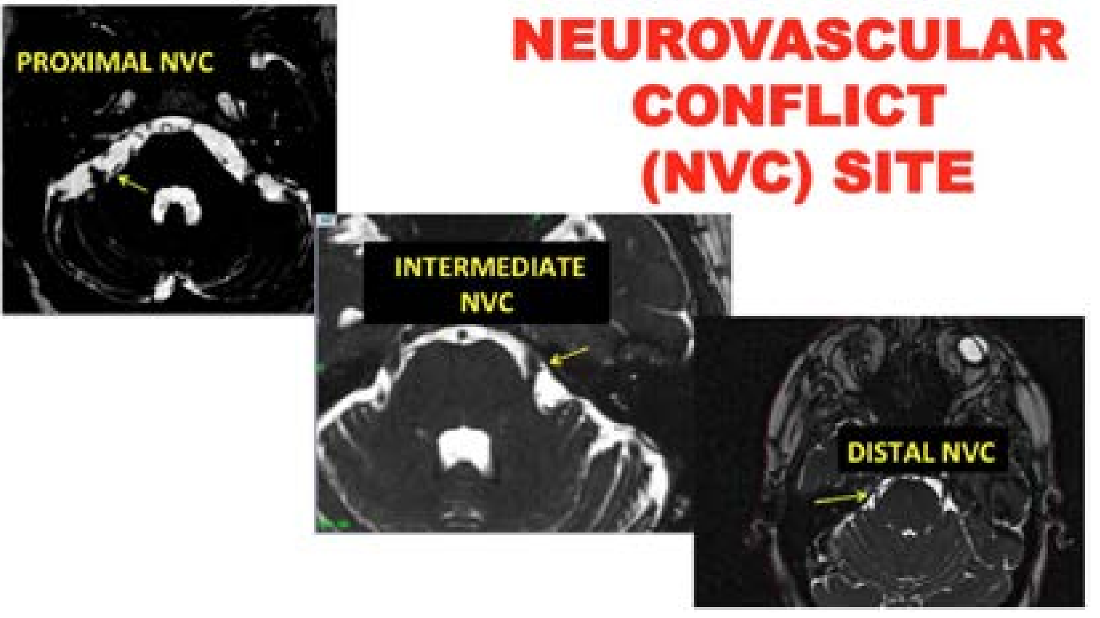

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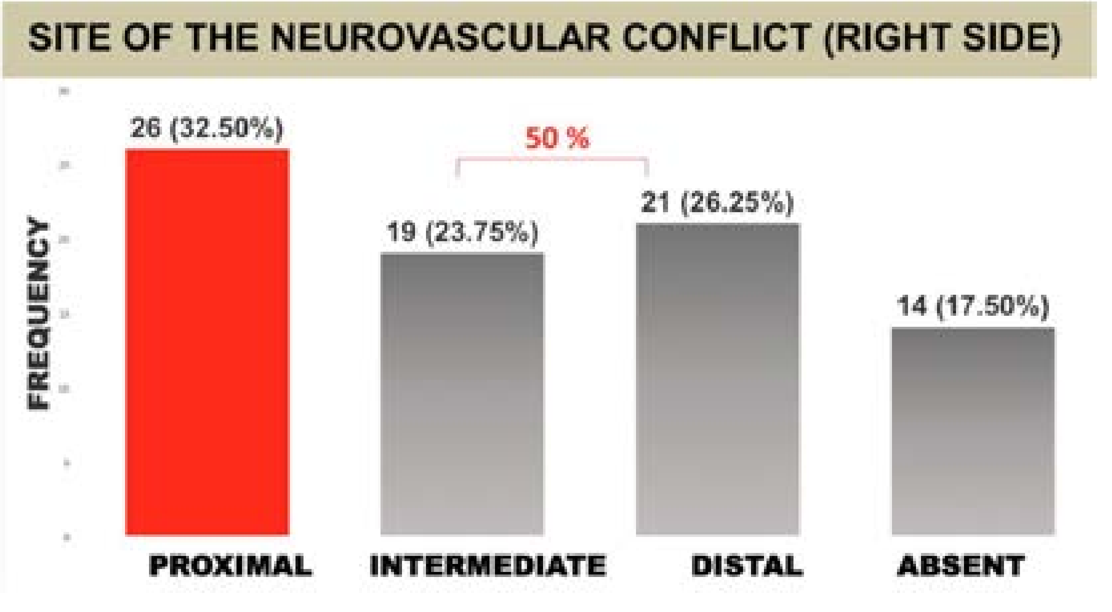

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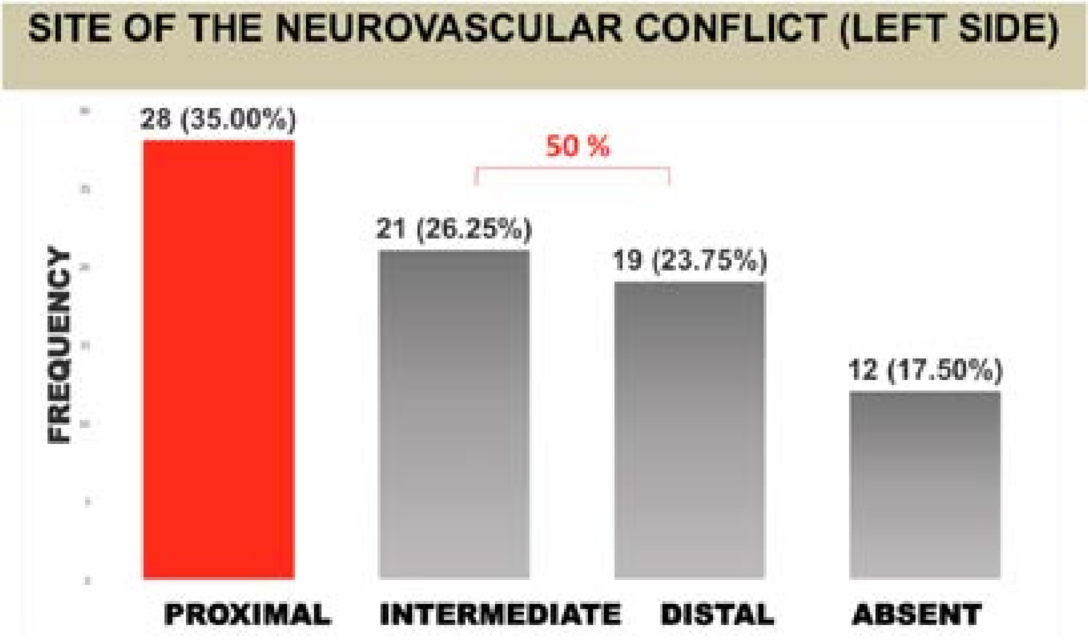

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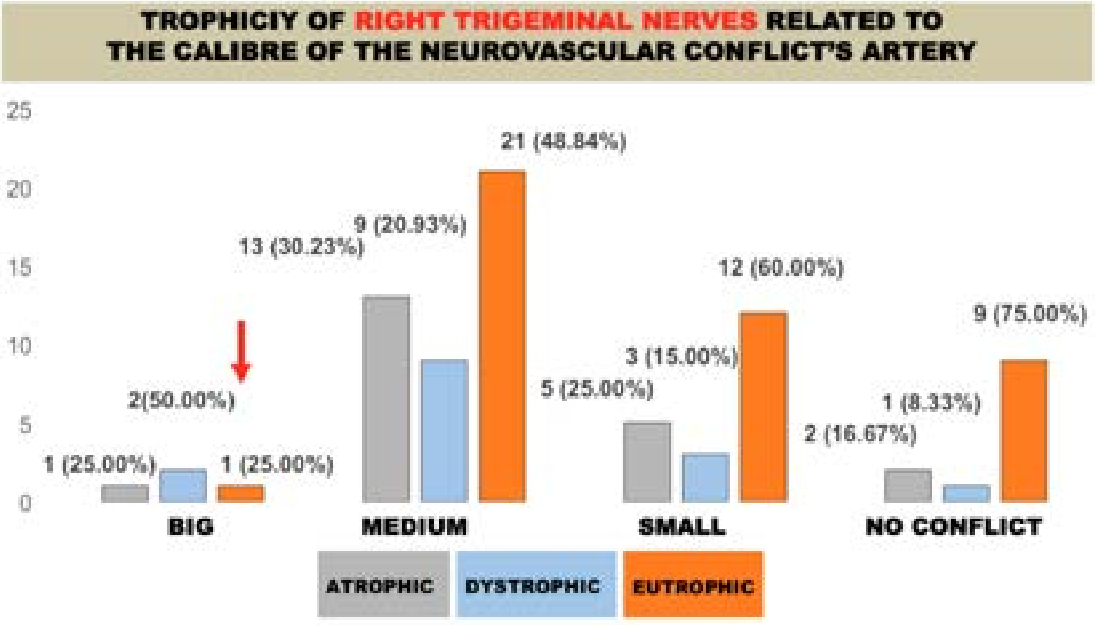

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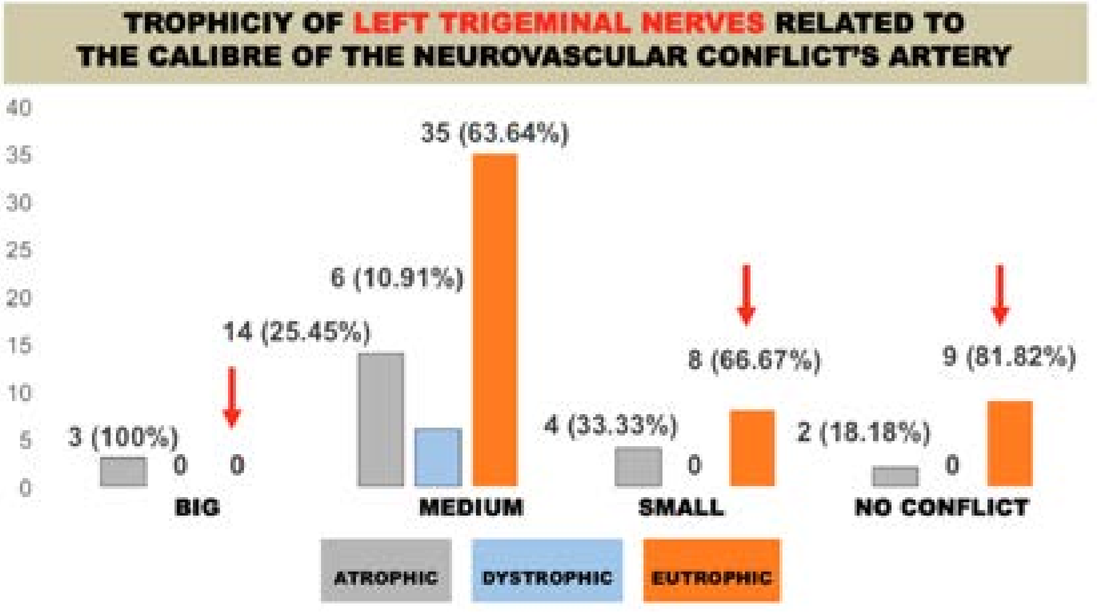

Graphic 24.

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