

Radiation mechanisms of pain control in classical trigeminal neuralgia

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Abstract

Classical trigeminal neuralgia is a chronic pain condition that was clinically recognized centuries ago. Nevertheless, the pathological mechanism(s) involved in the development of classical trigeminal neuralgia is still largely based on the theory of peripheral versus central nervous system origin. Limitations of both hypotheses are discussed. Evidence of radiation effects in the electrical conduction of peripheral nerves is reviewed. Results of experimental studies using modern and current radiosurgery techniques and doses are also brought to discussion in an attempt to elucidate the radiation mechanisms involved in the conduction block of excessive sensory information triggering pain attacks. Clinical features and prognostic factors associated with pain control, recurrence, and facial numbness in patients submitted to surgical procedures for classical trigeminal neuralgia are discussed in the context of the features related to the pathogenesis of this condition. Studies focusing on the electrophysiology properties of partially demyelinated trigeminal nerves submitted to radiosurgery are vital to truly advance our current knowledge in the field.

Key Words: Demyelination, pain control, pathogenesis, radiosurgery, trigeminal neuralgia

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INTRODUCTION

Different mechanisms that ultimately modify pain sensory information within the trigeminal pathway may account for the variable response in patients treated with the available surgical procedures for trigeminal neuralgia (TN). In general, the five most common procedures available for the treatment of classical TN are successful to the order of at least 90% pain relief.^[6,9-11,35,37,39,41,46,47,51,52,56,57,59,60] Largely all of them are directed to disturb the conduction of the nerve, justifying their designation as ablative procedures, with the exception of microvascular decompression (MVD). MVD is directed to the root entry zone (REZ), aiming to

interrupt the constant pulsation of a blood vessel into the myelin of the trigeminal nerve.

Radiosurgery directed to the REZ in the affected side, similar to the other destructive techniques used to treat TN, leads to control of the pain in a high percentage of the cases.^[30,31,59] This review is directed at the mechanisms of pain control in classical TN,^[32] making a parallel of radiosurgery with other surgical techniques used to achieve pain control. A review of the experimental work available is brought into light to discuss the effects of a high dose of radiation to the proximal portion of the trigeminal nerve, which leads to successful treatment of TN in a large fraction of patients.

DEFINITIONS

Classical TN is the term coined by the last classification of the International Headache Society^[32] to define the following: usually unilateral facial pain in one or more branches of the trigeminal nerve, characterized by sudden and excruciating electrical shocks, triggered by brushing the teeth, shaving, drinking cold or hot liquids, touching of the face by cold wind, or tactile stimulation at the so-called trigger points. Each attack lasts from seconds to minutes and may repeat itself many times per day. It can be so intense that patients may be unable to talk or eat. There are periods of remission throughout the course of the disease. Specific imaging work up can reveal a vascular conflict at the nerve or can be absolutely uneventful. This condition is also known as idiopathic, essential TN, or type I trigeminal pain,^[13,20] according to other classifications.

Secondary TN is defined by the presence of structural damage to the trigeminal system such as a demyelination, tumor invasion/compression, giant aneurysm, arteriovenous malformation (AVM), and herpes zoster infection. If the pain features mimic classical TN, it is classified as typical. If constant, aching and/or burning pain is present, it is classified as atypical.^[32] In this paper, discussion will be focused exclusively on classical TN.

PATHOGENESIS OF CLASSICAL TRIGEMINAL NEURALGIA

Aretaeus de Cappadocia was the first to attempt to describe TN. In 1773, John Fothergill provided an accurate clinical description of this painful syndrome. Even though it is a recognized condition for centuries, there is no consensus about the pathological mechanism(s) leading to the most common neuralgia observed. All theories proposed to date are susceptible to criticism since flaws exist when it comes to explain all the features of TN.

Peripheral origin of trigeminal pain

TN has been identified as a peripheral neuropathy since the neurovascular conflict theory was proposed by Peter Jannetta in 1967.^[33] Since then, this has been the most accepted theory explaining the origin of trigeminal pain. Walter Dandy made the initial observations of vascular impingement into the trigeminal nerve in 1925.^[16]

The root entry zone (REZ) of the trigeminal nerve lies about 2–3 mm away from the surface of the pons. It is characterized by the transition between the central myelin produced by the oligodendrocytes and the peripheral myelin produced by the Schwann cells. The latter is known to be significantly more resistant to injuries, including repetitive vascular pulsation at the myelin sheet, which provides insulation of the trigeminal nerve.

Damage to the most sensitive portion of the myelin (central myelin) is the most accepted source for classical TN.^[42,44] Frequently, vascular conflicts are observed where there is contact of the superior cerebellar artery at the REZ of the trigeminal nerve.^[6,33] However, the neurovascular conflict theory is not justified in all cases. Some patients present with a clear neurovascular conflict, but on the opposite side of their pain. There are vascular compressions noticed in thin-cut magnetic resonance imaging (MRI) scans, which do not necessarily correlate with a clinical diagnosis of trigeminal pain. And lastly, there are cases where a neurovascular conflict cannot be diagnosed in the MRI scan. Barker *et al.*^[33] described cases where the MRI was negative but a tiny vein compressing the nerve was observed intraoperatively. Recently, specific MRI sequences such as 3-D constructive interference in steady state (CISS) or three-dimensional fast imaging employing steady-state acquisition (FIESTA) and 1-mm slice thickness cuts provide exquisite visualization of the trigeminal pathway [Figure 1a].^[15] Many neurosurgeons indicate MVD only in cases where a neurovascular conflict is diagnosed in the MRI.

Unfortunately, animal models used to study the physiopathology of TN are not convincingly representative of all key features defining this condition.^[19] Injection of substances that induce epileptogenesis, lesions in the trigeminal nerve, root, or ganglion, have been attempted, but the clinical symptoms do not resemble the classical features of TN. Animals seem to experience important numbness and scratch their faces many times constantly. In other experiments, animals exhibit permanent

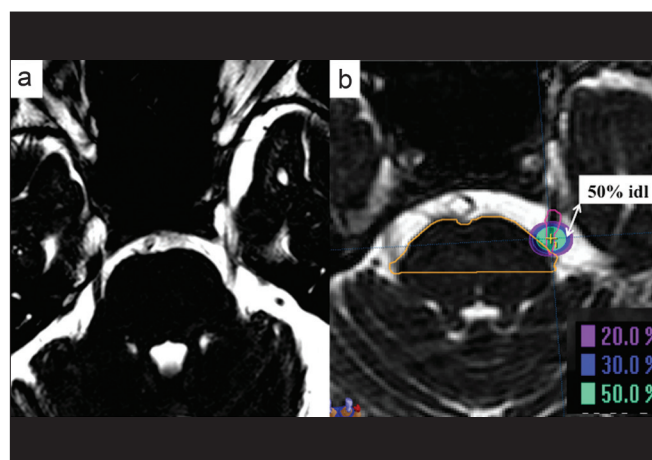


Figure 1: (a) Axial magnetic resonance imaging (MRI) showing the exquisite visualization of the trigeminal nerve provided by the fast imaging employing steady-state acquisition (FIESTA) or constructive interference in steady state sequence (CISS). The trigeminal nerve can be visualized since the exit in the lateral portion of the pons until the division into roots (VQ,V2,V3) inside the Gasserian ganglion. (b) Axial slice, FIESTA MRI showing a typical radiosurgery plan performed at University of California at Los Angeles. The prescription dose is 90 Gy delivered at the root entry zone. The isocenter is positioned with the 50% isodose line tangent to the pons

allodynia. Even though allodynia and hyperesthesia are noticed in some patients during exacerbation periods of acute pain attacks, it is not a common feature during periods of remission or eventual pain attacks.

Some of the animal models inducing trauma in the trigeminal roots showed data that would actually support the peripheral origin of trigeminal pain. Generation of extra action potentials to orthodromic stimuli was observed in 23% of the nerves submitted to suture lesions at 3 weeks postoperatively, but not at 1 or 6 weeks postoperatively.^[12] The areas of demyelination showed conduction delay, which would allow reflection of action potentials, leading to re-excitation of the intact areas of the axon itself. Consequently, the demyelinated area has the ability to produce after-discharge generation.^[14] Moreover, depolarization of large myelinated fibers (A β , tactile fibers) can lead to depolarization of non-myelinated neurons in the brainstem by primary afferent depolarization. Therefore, by amplification, tactile information can excite nociceptive axons in the brainstem and produce pain.^[43,44]

Since the neurovascular conflict theory is not irrefutable in all circumstances, other theories came about aiming to conciliate the neurovascular principle with other possible pathophysiological factors.

Central origin of trigeminal pain

In 1756, Nicolas Andre coined the term Tic Douloureux to define TN, which is a direct allusion to the similarities between the pain attacks and a seizure. Episodic recurrence of pain attacks in the absence of neurological deficits reinforced the resemblance with epilepsy.

There are certain features of the trigeminal pain attacks that challenge the validity of a pure peripheral pathophysiological mechanism for the genesis of TN.^[19,25,44] These factors are:

- delay between the trigger point stimulation and the trigeminal pain attack;
- pain attack is self-sustained, its magnitude is larger and outlasts the duration of the starting sensory trigger stimuli; and
- refractoriness following the pain attack, which consists of absolutely no response to stimulation or to a milder pain attack.

Moreover, demyelination by itself is not enough to generate the pain attacks. Myelinated axons composing the trigeminal nerve are related to thermal and touch inflow, not pain. Partial myelin damage should generate patches of numbness in the hemiface rather than pain, which is sometimes accompanied by hyperesthesia.

Experimental studies evaluating the effect of carbamazepine, phenytoin, and baclofen injections in the *subnucleus oralis* of the spinal trigeminal nucleus

revealed a dual mechanism of action: facilitation of segmental inhibition and decrease of excitatory stimuli coming from the periphery.^[22-24] These findings were not observed when phenobarbital was applied to the neurons at the *subnucleus oralis*, in accordance with the clinical observation that phenobarbital is not effective in the management of classical trigeminal pain. The corroboration between the central nervous system mechanism of action observed in animal studies and the clinical efficacy of the drugs used to treat TN suggests that a central mechanism is also part of the process to develop classical TN. Even though the initial process triggering TN may have a peripheral origin, it is necessary to have a central component to actually lead to the self-outlasting pain attack paroxysms in the absence of major sensory deficits. The common use of MRI in the modern era reveals vascular conflict in the REZ of the TN in the absence of pain or any other symptoms, corroborating the hypothesis of centrally generated TN.

Neuroplasticity and the hypotheses of TN pathogenesis

A conciliatory theory proposing peripheral and central nervous system events that would ultimately lead to TN has been suggested.^[25,44] In addition to increased generation of stimuli, mechanisms involved in suppressing afferent stimuli should be somewhat impaired (i.e. the dorsal root reflex). Pre-synaptic inhibition occurs via axo-axonic GABAergic synapses in the trigeminal nuclei.^[53] The peripheral nerve damage would disrupt the dorsal root reflex, therefore allowing the excessive peripheral sensory information to reach trigeminal nuclei relays above the brainstem level.

However, not all experts refute the sole peripheral origin of TN. For instance, the ignition hypothesis^[19] aims to explain the self-duration of the pain attacks and their spread beyond the area of the original stimuli. It has been shown that few dorsal root ganglia neurons of peripheral nerves can act as active pacemakers and sustain continuous discharges.^[1] This phenomenon has also been observed in areas of demyelination of sensory ganglia neurons, independently from the tactile stimuli originating the depolarization. Ephaptic transmission between axons would facilitate the recruitment of an increasingly larger population of neurons, which would in turn amplify sensory input to the trigeminal nucleus. Analysis of surgical specimens of patients with TN showed the lack or decrease of the insulation between the nerve fibers, providing the substrate for electrical axon-to-axon crosstalk.^[42,44] The spontaneous pacemaker areas could also explain the occurrence of pain attacks in the absence of stimulation in the trigger points. The authors also comment on the crossed after-discharge mechanism which is non-synaptic and non-ephaptic coupling.^[19] Neurotransmitters and potassium ions are released in the

interstitial space after an excitatory discharge of some sensory neurons. Other neurons are excited by diffusion of these mediators. This type of spread of excitatory stimuli would set the stage for transmission from A β fibers to c-fibers (nociceptive). The refractoriness period could be explained by the release of potassium ions due to activation of potassium channels by calcium, leading to neuronal hyperpolarization. Partial remyelination and normalization of membrane channels would account for the periods of remission.^[19,44]

Pain duration has been identified as a predictor of recurrence in the series of patients treated with MVD, after disease chronicity of at least 7 years.^[6,9] It may suggest that the chronicity of the underlying untreated condition may correlate with the degree of changes in the trigeminal pathway (from initial myelin damage to central sensitization of the brainstem trigeminal nucleus), and therefore with the probability of achieving successful outcomes with surgery. Patients with longer pain duration have higher likelihood of being treated with multiple surgical techniques and likely represent a more difficult subpopulation to treat. The multivariate analysis performed on these studies did control for prior surgical procedure as a covariate, which strengthens the correlation between pain duration and recurrence. Yet, all these studies were retrospective and, to our knowledge, no study has prospectively evaluated chronicity of neuralgia and recurrence. These studies did control for prior surgical procedures as variable, which strengthen the findings about pain duration and higher risk of pain recurrence. Nevertheless, these studies are all retrospective. To our knowledge, disease duration has not been identified as prognostic factor for pain control or recurrence in radiosurgery series.

Neuroplasticity-induced changes in the spinal nucleus would be expected to lead to other sensory features such as hyperalgesia, allodynia, and burning type of pain. Based on clinical observations, some patients with a long-standing history of TN describe a constant background pain defined sometimes as dull and even burning. Still, the most bothersome symptom is the electrical shock-like pain. Other patients, even when submitted to prior surgical procedures, do not report a constant type of pain and report only typical features of classical TN pain, which would reinforce the peripheral theory of TN pathogenesis. It is definitely more common to notice a clear pain “transformation” in patients submitted to multiple surgical procedures, whereas concomitant development of facial numbness is frequently observed.^[6,9,48] The effect of surgically induced damage to the trigeminal system is an important confounder for the interpretation of these findings and may account in large part for these observations. Patients suffering pain attacks requiring intravenous phenytoin infusion frequently present with allodynia. However, allodynia usually subsides once some

degree of pain control is achieved, after therapy with intravenous phenytoin. These mixed clinical observations highlight the difficulty to explain all the features related to classical TN by the most common postulated hypothesis.

EFFECTS OF RADIATION ON THE PERIPHERAL NERVES

Experimental work delivering ionizing radiation to peripheral nerves of cold- and warm-blooded animals showed that abolishment of nervous conduction is clearly dependent on the total radiation dose. Several studies reported complete blockade of peripheral nervous conduction following doses of radiation ranging from 1500 to 3000 Gy in cold-blooded animals.^[5,27,28] The threshold is lower for warm-blooded animals, showing increased nerve susceptibility to ionizing radiation. For example, 450 Gy led to complete conduction block within 1 hour following radiation in rabbit nerves. Still, radiation resistance of the peripheral nerves is remarkable.^[28] *In vivo* irradiation of cold-blooded animals is in agreement with *in vitro* experiments.^[27] Upon delivery of 1500–2000 Gy, paresis or paralysis was observed. Deficits, however, were absent with doses up to 800 Gy. These doses are evidently not used in clinical practice.^[39-41,48,51,52,59]

The literature is controversial in regards to lower doses of radiation. Some studies reported that relatively lower doses of radiation up to 100 Gy did excite the nerve membranes transiently,^[4,7,36] while others failed to notice any effects on amplitude, conduction velocity, or membrane resistance.^[4,26,54,55] Conflicting experimental results can be explained by the diversity of protocols, nerve preparations and conservation, radiation doses, rates and schemes of radiation delivery (continuous vs. cumulative fractions), electrophysiology technique, and time interval between radiation delivery and nervous conduction recording. Experiments conducted before 1960s failed to demonstrate any changes in nerve conduction during or after low radiation doses.^[34,50] During 1960s, many investigators^[3,4,7,36,55] reported on the excitability of peripheral nerve conduction at radiation doses around 100 Gy. The justification for their findings in opposition with the findings previously published relied on the fact that the doses used were too low, way below 100 Gy, and recordings were made on the tissue innervated by the nerve rather than on the nerve fibers.

Papers published in 1970s criticized the peripheral nerve choices of authors showing excitability and attributed their “excitability” findings to artifacts generated by injury currents.^[26,54] The methodology used in 1970s consisted of voltage clamp techniques instead of laying a section of the nerve between two wires, as was used in the experiments in the 1960s.

Schwarz and Fox attempted to elucidate the mechanism involved in nerve conduction blockade triggered by ionizing radiation in a series of experiments. After a delay of 800–1000 sec and once a minimum threshold dose of radiation had been delivered to the nerve, there was decrease in the peak sodium current without further decrease in resting membrane potential. In a series of initial experiments, the minimum radiation dose able to trigger the sodium current decrease varied from 60 to 100 Gy. Nevertheless, in subsequent investigations, this phenomenon was not observed when doses below 100 Gy were delivered. Delay in developing conduction block after radiation delivery is not dependent on the dose delivery rate. This led to the currently accepted theory that slow chemical reactions leading to final block of sodium channels would be the mechanism involved in the process. In summary, nervous stimuli block would be the result of indirect destruction of ionic channels, mainly sodium.^[54]

All experiments described above measured the compound action potential of a given peripheral nerve. The final composition of the nerve ultimately determines the excitability profile observed after ionizing radiation delivery, when measuring the entire nerve rather than the axon. Different subtypes of fibers have different thresholds to radiation response. Gerstner^[27] showed that radiation threshold leading to conduction block was lower for fiber A gamma than for subtypes alpha and beta (1500 Gy vs. 3000 Gy, respectively). A histological assessment, using light microscopy, of a human trigeminal nerve sensory root showed myelinated type A fibers with an average diameter smaller than that of A fibers identified in the motor roots or in the ophthalmic, maxillary, or mandibular subdivisions.^[49] These findings are in accordance with the findings of Young and Stevens^[62] using electron microscopy.

Based on some of the facts reported above, some conclusions can be drawn:

- a. Peripheral nerves of warm-blooded animals are more sensitive to ionizing radiation than those of cold-blooded animals.
- b. Gamma fibers are more radiation sensitive than alpha and beta fibers.
- c. The most accepted theory explaining conduction block following ionizing radiation is that it happens through damage of sodium channels.

One particular study found decrease in the sodium peak current with radiation doses used for TN radiosurgery. We must take into account the fact that the human trigeminal nerve has a different fiber composition in comparison to the sciatic nerve, which was extensively used in cold-blooded animal experiments. The difference in fiber composition of the trigeminal nerve could potentially predispose to conduction block at a lower radiation dose threshold. Demyelinated areas, acting

as autonomous hyperexcitable pacemakers, may have a different density of membrane receptors in comparison to the intact segments of the nerve. This could imply more sensibility to radiation-induced electrical conduction block. It may also explain the clinical results observed with radiosurgery for TN using doses significantly lower than the ones required to block nerve conduction in intact peripheral nerve experiments. Histology data on trigeminal nerves submitted to radiosurgery are rare, but they suggest that radiation causes partial block of nerve conduction rather than complete nerve knockout. Obviously, physiological studies evaluating trigeminal nerves treated with radiosurgery are necessary to corroborate this hypothesis.

Genetics may play a role in the susceptibility of response to radiation among different individuals, accounting for the differences in the time required to experience pain relief after radiosurgery treatment. Very few patients experience pain cessation within days of radiation delivery. In average, patients present response within 4–6 weeks post-radiosurgery.^[59] And finally, there are the late responders, presenting pain relief many months after treatment. Genetic heterogeneity may lead to different radiation sensitivity profiles that would also explain radiosurgery failures. Maybe, some individuals required lesser amount of nerve fibers receiving a given threshold dose of radiation to trigger pain control (and facial numbness).

PARALLEL BETWEEN ANIMAL EXPERIMENTATION AND HUMAN FINDINGS

Even though far from ideal, findings from radiation experiments in peripheral nerves of different species can be extrapolated to parallel the radiation effects on the human trigeminal nerve. These approximations are the best we are able to gather at the moment.

Radiosurgery to the nerve – Pathological examination of experimental data

Our experimental data with 90 Gy radiation delivered to the peripheral nerve of the swine,^[18] i.e. spinal nerve as it exits the spinal canal, have shown that radiation induces partial nerve damage, seen as islands of axonal denudation inside the thickness of the nerve [Figure 2]. This finding correlates with the behavioral finding of lack of reaction of the animal when the dermatome site is tested with painful stimuli.

Identical histological findings have been observed in the trigeminal nerves of baboons.^[38] The study showed that radiosurgery doses of 80 or 100 Gy delivered to intact trigeminal nerves lead to progressive focal damage of the nerve. The histological changes are characterized by demyelination, axonal degeneration, and necrosis, depending on the maximal radiation dose. Histology was

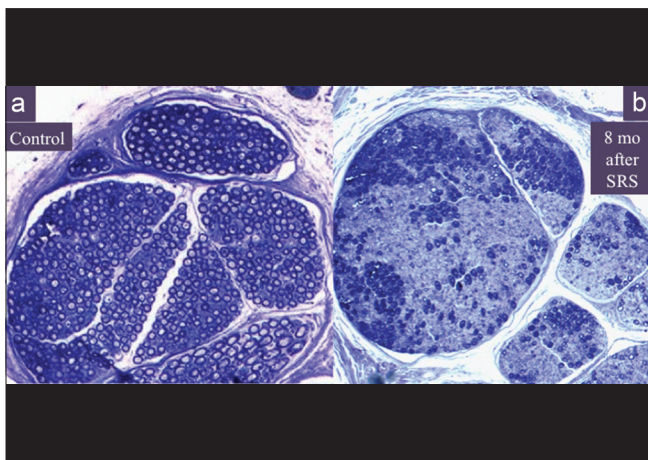


Figure 2: Axial spinal nerve stained with toluidine blue. (a) Control nerve. (b) Nerve irradiated with 90 Gy at 8 months after radiosurgery. Note the partial destruction of the fibers composing the trigeminal nerve

performed at one time point (6 months post-radiosurgery). No specific type of fiber within the trigeminal nerve was preferentially damaged by radiation, but only four nerves were studied and one of them showed almost complete nerve width necrosis. This particular nerve received 100 Gy.

Radiosurgery devices and doses used in clinical practice for the treatment of TN were applied in both studies. There are, however, important limitations. The irradiated nerves were intact. Unfortunately, data on radiosurgery effects in partially damaged nerves are not available. In swine, clinical outcome measures used to confirm accurate radiation delivery in the dorsal root ganglion were numbness and limb paresis. Patients with classical TN do not necessarily present with facial numbness after radiosurgery, and motor dysfunction of the masseter is not noticed. Moreover, pain control is achieved prior to the development of facial numbness. Obviously, neurophysiological studies of the irradiated nerves are the key to elucidate radiation mechanisms involved in pain control.

Radiosurgery to the nerve – Pathological examination of clinical data

Foy *et al.*^[21] described the case of a patient who presented with extremely refractory trigeminal pain despite undergoing surgical procedures such as MVD, glycerol injection, and radiosurgery. The patient responded to first radiosurgery and failed the repeated procedure. A small mid-cisternal segment of the nerve was submitted to histological analysis shortly after second radiosurgery failure and 16 months following the first radiosurgery procedure. No lesions were noticed in the specimen submitted to histology. Considering all the ablative procedures the patient had been submitted to, it is clear that the analyzed nerve segment rested outside the

area of the nerve targeted by the ablative procedures; otherwise, one cannot explain complete absence of histological changes on a nerve submitted to five different surgical procedures. Although extremely rarely performed in humans, histology on a nerve submitted to two radiosurgery procedures was, unfortunately, unrevealing.

Szeifert *et al.*^[58] reported on the autopsy results of a patient treated twice with radiosurgery. The first treatment was with 90 Gy targeted at the *pars triangularis* of the trigeminal nerve. The second treatment consisted of delivery of 70 Gy close to the REZ. The first and second radiosurgery treatments happened 11 months and 26 days, respectively, before the patient's death. Pathological examination of the entire nerve showed a focused fibrotic lesion with hyaline-degenerated collagen bundles and scattered fibrocytes at the site irradiated 11 months earlier. S100 immunoreactivity was absent inside the fibrotic lesion but was present in the surroundings of the lesion. At the REZ, acute demarcated changes were characterized by a necrotic center containing tissue debris and fibrinoid material. S100 positivity was also absent inside the necrotic center of the acute lesion but was present in the surroundings. S100 proteins are present in myelinated and non-myelinated Schwann cells in the nerve trunks, in Schwann-related cells of sensory corpuscles, and in peripheral neurons.^[29] Lack of immunostaining in the segments of the nerve irradiated suggests that radiation impairs both myelinated and non-myelinated nerve fibers.

RADIATION EFFECTS AND PAIN CONTROL

Radiofrequency rhizotomy, balloon compression, partial section of the nerve, and glycerol injection cause an abrupt disruption of the sensory transmission. The injury elicited by radiation implies a process leading to sub-total damage and partial block of sensory information overtime. Animal experiments established that the ability of radiation to completely block nervous conduction is dose dependent. It was also shown that there is a minimal time latency required to elicit conduction block independent of the dose rate and is conditional upon the delivery of a minimal total radiation dose. The minimal radiation effective dose varies according to the level of myelination of the nerve fiber. Radiation effect on myelinated fibers is likely due to inhibition of autonomous pacemakers that generate recurrent action potentials, which spreads to myelinated and non-myelinated axons by ephaptic and after-discharge potentiating mechanisms.

Pathological specimens of patients submitted to MVD showed that demyelinated areas are observed at the REZ. This is the site where the central myelin is more sensitive to injuries (compression, stretching, radiation). Blood vessels are commonly observed to touch the nerve precisely at the REZ. There are radiosurgery protocols

that limit the total dose of radiation to the brainstem surface to 12 Gy,^[52] while other protocols allow up to 45 Gy^[59] touching the surface of the brainstem. This implies a substantial variation of the radiation dose at the REZ. Since the time to response after radiosurgery varies considerably among responders, it may be that the extension of demyelinated areas submitted to the high dose of radiation influences the pace of pain response. We observed a shorter latency to achieve pain control after radiosurgery as the isocenter was brought closer to the brainstem surface overtime.^[59]

Clinical data suggest that pain outcomes tend to be better when the isocenter is positioned more proximally to the brainstem/REZ.^[8,30,31,59] This is not an unanimously accepted evidence^[52] and only a randomized trial will provide a definitive answer. Considering that a higher dose of radiation directed to the demyelinated area of the REZ would correlate with pain relief, the radiation dose needed to trigger a large clinical effect on pain control rate is likely larger than the currently used dose range in clinical practice. Otherwise, a larger clinical difference on clinical outcomes among the different protocols would have provided more convincing evidence. This causality hypothesis, at this point, is obviously speculative. However, it is somewhat supported by the experiments discussed in the earlier section.

It would be relevant for radiosurgery practice to determine the threshold dose of radiation to achieve conduction block in demyelinated portions versus intact trigeminal nerve segments. Also, experiments comparing radiation dose effects on partially damaged versus completely intact nerves will provide important information about the radiation mechanisms involved in the blockade of electrical axonal conductivity. These experiments may even contribute to validate the current hypothesis about the genesis of TN.

TECHNICAL ASPECTS OF RADIOSURGERY TREATMENT

Radiosurgery for TN is very challenging. The target has a diameter of 3 mm and the most commonly used collimator has a diameter of 4 mm [Figure 1b]. One important aspect involved in the time course of response of TN pain to radiosurgery is that it is probably related to the amount of radiation reaching the actual target, i.e. the site in the trigeminal REZ where demyelization is present. Our data showed that when we could confirm that the REZ was reached by the maximal radiation dose, as observed by contrast enhancement in the follow-up MRIs, patients presented excellent pain outcomes.^[30]

As the current thickness of the targeting MRI and computerized tomography (CT) scans is between 1 and 1.5 mm, the best possible targeting accuracy is of 0.75

mm, based solely on the imaging factor. We also need to consider that the expected accuracy of the stereotactic frame is 1.5 mm. This was shown in a multicentric study for functional neurosurgery that included our own center data^[63] and has also been previously reported by others.^[45] Therefore, the possibility of suboptimal maximal dose delivery is real. This is more so if one also includes the radiation delivery device accuracy of approximately 0.5 mm. After consideration of all factors, one could estimate a random mistargeting of at least 1.5 mm.

Delivered doses vary from 80 to 90 Gy, through a 4-mm collimator, which results in prolonged treatment time. Radiosurgery devices used for treatment of this condition include: Gamma unit,^[8,41,46,51,48] dedicated Linac,^[31,59] and Cyberknife®.^[40] Depending on the age of the cobalt source of the gamma units, beam-on time may vary significantly and treatment time can be longer than 1 hour. The speed of radiation delivery (motor units per minute or MU/min) measured in Linac-based devices is a constantly evolving technological feature. Newer dedicated Linacs are able to deliver up to 2000 MU/min, while other devices, such as Cyberknife and older-generation dedicated Linacs, deliver maximum up to 600–800 MU/min. This difference directly impacts on radiation treatment duration. Ability to decrease the overall treatment time is a major trend in stereotactic radiation. The development of volumetric modulated arc therapy^[2] and rapid arc^[61] techniques in recent years is an example. It is intuitive that faster treatments would be associated with less patient mobility and increased radiation delivery accuracy. The trigeminal target lies in the pre-pontine cistern, surrounded by cerebrospinal fluid (CSF). Even though not considered in clinical practice, there is minimal respiratory movement of the cranial nerves while crossing CSF space within the skull. Minimal variations of the nerve position during extended radiation delivery time may unpredictably impact the overall results and contribute to explain why some patients fail radiosurgery and some patients respond sooner than others. Longer nerves, more brain atrophy, and differences in the angle of emergence of the nerve from the brainstem do not currently seem to be modifiers of radiosurgery planning due to lack of knowledge on their potential impact in the final clinical outcome. Despite the difficulty to measure and quantify the relevance of these anatomical characteristics, it is intuitive that prolonged radiation delivery time may amplify the impact of these factors on the results. Increased sub-millimetric mobility of the nerve in the cistern during radiation delivery may negatively affect the amount of clinically relevant fibers receiving the minimal radiation dose necessary to block excessive sensory information.

Total disease duration and periodicity of pain attacks at the time of radiosurgery treatment (multiple daily attacks vs. low frequency pain attacks vs. remission) may also be relevant in the context of radiation effects.

Radiosurgery is not delivered to patients under acute pain attacks because of the known latency necessary to trigger pain relief. If radiation controls excessive action potentials generated in the demyelinated areas by inducing changes in the density of the membrane ionic channels, it certainly cannot be used in patients under acute pain attacks who need an immediate method of pain control. Radiation would be expected to best work on patients treated while they experience low frequency of pain attacks. Abnormal re-myelination is considered by some experts to explain the periods of remission observed in the course of the disease. Adding radiation to remyelinated segments of the nerve may potentiate the block and/or generation of excessive sensory information. However, if experimental studies show that demyelinated areas present lower radiation dose threshold for impulse blocking than remyelinated or intact areas of the nerve, it may throw light on the optimal timing to radiosurgery treatment. Concomitantly, careful analysis of these variables in future series treated with radiosurgery may suggest which hypothesis seems to best explain how radiation leads to pain relief.

On the other hand, the potential effect of radiation on the trigeminal nuclei at the brainstem should be considered as a possible additional mechanism of radiation-induced pain control and facial hypoesthesia, noticed in some cases post-radiosurgery. The dose distribution achieved in our radiosurgery plans with the 5-mm collimator shows that only about 2.7 Gy and 0.9 Gy reach the area of the *nucleus principalis* and *spinalis* of the trigeminal nerve, respectively. When using the 4-mm collimator, these doses are even smaller. It has been shown by our group that radiosurgery delivered with the 3-mm collimator has the ability to modulate neurotransmitters in the brain.^[17] Whether these low doses reaching the *nucleus principalis* and the *spinalis* modulate the dorsal root reflex is to be investigated.

CONCLUSION

Based on the review of the experimental literature in parallel with the findings in humans undergoing procedures for TN, it is likely that any procedure tending to decrease the input of information from the trigeminal sensory fields across the junction of the peripheral portion of the trigeminal nerve with the central nervous system trigeminal pathways leads to pain control. Accepting the hypothesis that the transition of peripheral myelin (Schwann cells) to central myelin (oligodendrocytes) is the weak site of the nerve, and is therefore vulnerable to short circuitry formation, it is interesting to observe that the MVD results are, indeed, the most durable with the least disruption of the trigeminal system. It is likely that imprecision of the stereotactic technique with 1-1.5 mm error in a target of 3 mm leads to variation of dose to the REZ, potentially offering the basis to the variability in

the results achieved with this method and also justifying observed recurrences.

Experimental data on the effects of focused radiation on the electrophysiology properties of partially demyelinated trigeminal nerves are a major need to truly advance our current knowledge in the field. It should allow further refinement of radiosurgery protocols and, hopefully, improvement in clinical outcomes.

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