Research Article

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Theoretical, Practical, and Clinical Aspects of a Novel Approach to the Treatment of Chronic and Episodic Cluster Headaches

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ABSTRACT

Importance: *Chronic and episodic cluster headaches are a worldwide distributed problem that significantly impairs sufferers' ability to function and perform their daily activities. Puzzling triggers and treatment approaches are burdensome and costly. A new approach to chronic and episodic cluster headaches may light up long-term and curative treatment and a new understanding of trigger(s).*

Objective: *The objective was to redefine the cause of the cluster headaches, diagnosing the evidence of a neuroma in the distribution of a zygomaticotemporal nerve, and the long-term symptom free resolution of cluster headaches.*

Design: *A single center, randomized, interventional, prospective clinical trial. Allocation is selective and ambulatory. Anticipated all gender and races aged 20-70 years old.*

Primary outcome and measures: *Evidence of Neuroma by histopathologic examination, long-term efficacy in relieving cluster headaches over 270 days. We were looking at other possible correlating findings. An interventional prospective clinical trial per protocol; clinicaltrial.gov Identifier NCT 04845451.*

Results: *Our data showed that nearly 100% of patients responded with complete relief of their cluster headaches symptoms. However, there were migraine symptoms on the opposite side after completing the original procedure, which we also addressed.*

Conclusion and relevance: *Systematic data collection included cluster symptoms, frequency of attack cycle, and intended pain severity. Our data collected over 270 days demonstrated long- term relief of cluster headaches symptoms. We addressed additional findings of trigeminal neuralgia by treatment of symptoms at the opposite site after resection of Neuroma using a De Novo formula/procedure. Corresponding resolution of cluster headaches by excision of a single neuroma in the property of zygomaticotemporal nerve may light future approaches to cluster headache resolution.*

Keywords

Clinicaltrial.gov Identifier NCT 04845451, Cluster headaches, Trigeminal neuralgia, Cephalelgia, SUNCT, Neuroma, diagnostic and curative.

Abbreviations

ECCH: Episodic & Chronic Cluster Headaches.

Introduction

It is unclear whether Cluster Headaches stem from the development and presence of a neuroma in the vicinity of trigeminal peripheral nerve branches, particularly the Zygomaticotemporal Nerve. Relevance in clinical examination of cluster headaches patients points at this anatomical location. In our search for headache literature for a similar notion, we could not find a similar clinical

approach to this matter yet—our evidence and observational-based exposure to a few cases and results encouraging potential for this study. Results may support our hypothesis, and approach.

Diagnostic and therapeutic procedures may lead to a new viewpoint in resolving episodic- chronic cluster headaches. Our goal was to enter a different path in understanding the cause of cluster headaches than the current conventional drug related popular one. Our years of observation and clinical studies were concentrated on Illuminating the cause of Migraine and cluster headaches. Our curiosity cleared the path for better understanding of the cause cluster headaches and the specific behavior of trigeminal nerve in affected individuals.

Rationale

Cluster Headache, described by different exposure and behavior, is a common chronic severe, disabling, devastating disease with potentially suicidal attempts and actions. The estimated prevalence of cluster headaches in the U.S. adult population is roughly 125-150/100,000, with a male-to-female ratio of 2.5:1 [1]. Description of the disorder relates its recognition to the family of autonomic trigeminal neuralgia. However, the cause is still puzzled among neuroscientists.

Millions of hours of productive life are lost, not to mention billions of dollars flow yearly in unsuccessful pharmaceutical and innovative electromagnetic device investments. Many hypotheses and theories are presented desperately to explain and solve this tribble puzzle in the human species.

Pharmacological modulation can allow for cell-type-specific activation or inhibition of neural activities. However, pharmacological modulation is limited by poor temporal and spatial resolution due to the slow and diffusive nature of drug delivery, including continuous pure oxygen inhalation. Therefore, our hypothesis may bypass the exhaustive pharmaceutical approach to treating cluster headaches in all its extensions.

Experimental Approach Redefining an Empirical Expectation

Based on our practical experience in the field of episodic and chronic migraine headaches, we desperately encountered a severe case of cluster headaches that we did not diagnose as cluster headaches at the beginning. After two years of challenging efforts to rule out all the possible causes of these individuals' "trigeminal Cephalgia," we came upon the last resource of surgical exploration of the painful location of an initial trigger of Pain over the right temple. This action took place to prevent the individual's planned suicidal attempt. Intraoperatively, we encounter minimal tissue not responding to a high dose of local anesthetic. The decision was made to excise this tissue in rapid action. The specimen has been sent to pathology for verification of the excised material. It revealed evidence of" Fibro-vascular tissue, mature adipose tissue, and focally prominent neural tissue, cannot rule out neuroma" (Case#: P15-0043733 MR#:34805064.04/30/2016). However, we did not ask for an immunohistochemical examination to determine the nature of the Neuroma. Primarily, we did expect a neuroma vs. neurinoma in our attempted exploration. This individual demonstrated complete freedom of his chronic episodic cluster headaches symptoms from 04/31/2016 to 02/10/2021. The case wasn't included in our clinical trial.

Discriminative observational study

Systematic tracking of over 250 and more YouTube videos of cluster headaches sufferers and followers consequently encouraged us to share our findings with a limited number of patients in a mini-surgical procedure to explore and respect a possible neuroma of the zygomaticotemporal branch at the affected side. But, again, we noticed individual sufferers, without exception aiming their fingers at one point and almost to the same point.

Our hypothesis is based on the empirical and anatomical morphology of the faulty Neuroma with a predisposition to the zygomaticotemporal nerve by the presence of automatism of a periodic pattern. A profound anatomical knowledge was imperative. A minimal exploratory surgical procedure of the anterior temporal and mid-temporal area, the location of the triggering Neuroma, and its resection may permanently end cluster headache symptoms.

Males overwhelmed females with Cluster Headaches, including episodic, chronic cluster headaches (ECCH), which are well documented in many clinical studies and journals.

An aggravated number of ECCH individuals presented right-sided rather than left-sided. 90%- 95% indicates a pre-attack loci source at the anterior-distal 1/3 of the temporal region. 10-20 mm above the height of the lateral epicanthus and 10-20 mm in front of the hairline. Border marked in a circle, Figure 1. Almost always most of the individuals with cluster headaches indicated the same location as trigger and start point of the explosive symptoms.

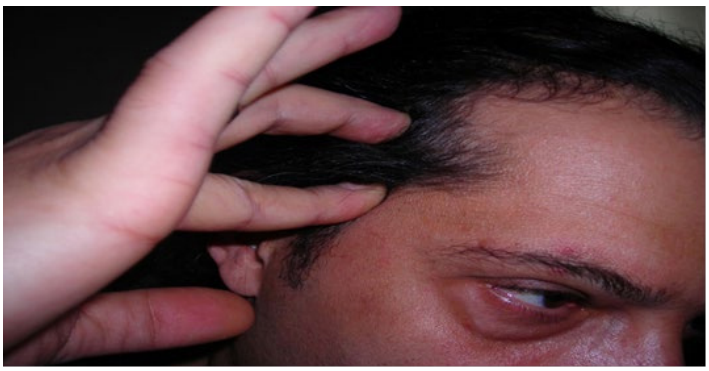


Figure 1: Cluster headaches trigger location identified by a patient; permission provided.

Pre-attack event reported typical symptoms of tingling dysesthesia, numbness, and short-lasting impulses 10-20 minutes before the catastrophic start of physical symptoms of severe Pain, ophthalmoplegia, congested sinus associated with rhinorrhea,

lacrimation, accompanied by facial hyperhidrosis and forehead, rare occipital Pain, and restlessness.

Hypothesis

Based on personal experiences, clinical reviews, and anatomical studies of trigeminal nerve branches presenting the autonomous symptoms, we materialized our hypothesis:

An anatomical coordinate communication of a Cluster Circuit turned on by ZT-neuroma, a malicious, non-traumatic, neoplastic tissue coding and decoding itself upon autonomic release of neurotransmitter(s). Exhaustion of neurotransmitters in the synaptic vesicles turns out the explosions of Pain off until the next refill of neurotransmitters in the presynaptic vesicles is warranted.

Poor results of preventive or abortive pharmaceutical arrangements, including Onabotolinum toxin A, lidocaine-corticosteroid cocktail, and the latest monoclonal antibodies, are abandoned mainly by sufferers after few attempts. An attempt utilizing pure Oxygen inhalation and psychedelics are not always helpful either.

This study is based on our experimental minimal surgical procedure to diagnose and resect a ZT- neuroma in our temple of patients suffering from ECCH. The goal is to shed this speculation in a novel analysis of events to end devastating catastrophic headaches.

Descriptive anatomy of cluster headaches path

Comprehensive descriptive anatomy of the first and second division of the trigeminal nerve containing the morphologic-anatomical status of single branches may light our hypothesis. C.H. patients universally indicate the anterior temporal region as the triggering point. The temporal part contains deep, superficial muscle and fascia, which receives motoric innervation from the Tertius division of the trigeminal nerve. Superficial temporal dermatome innervated by Temporozygomatic, and zygomatic nerve divided in the zygomaticofacial Nerve of V-II division.

Branches of temporal nerves from facial nerve connecting and bypassing temporal fascia to innervate temporoparietal muscle posteriorly, Figure 2.

The ophthalmic nerve is the first branch of the trigeminal nerve. It arises from the convex surface of the Gasserian ganglion in the dura of the lateral wall of the cavernous venous sinus under CN IV and above the maxillary nerve, as seen in Figures 3 & 4.

Sobbota/Becher: Atlas des Anatomie des Menschen, 16 Auflage 1960. Urban und Schwarz. Muenchen/Berlin. Cited for scientific purposes with the friendly permission of Elsevier-de.

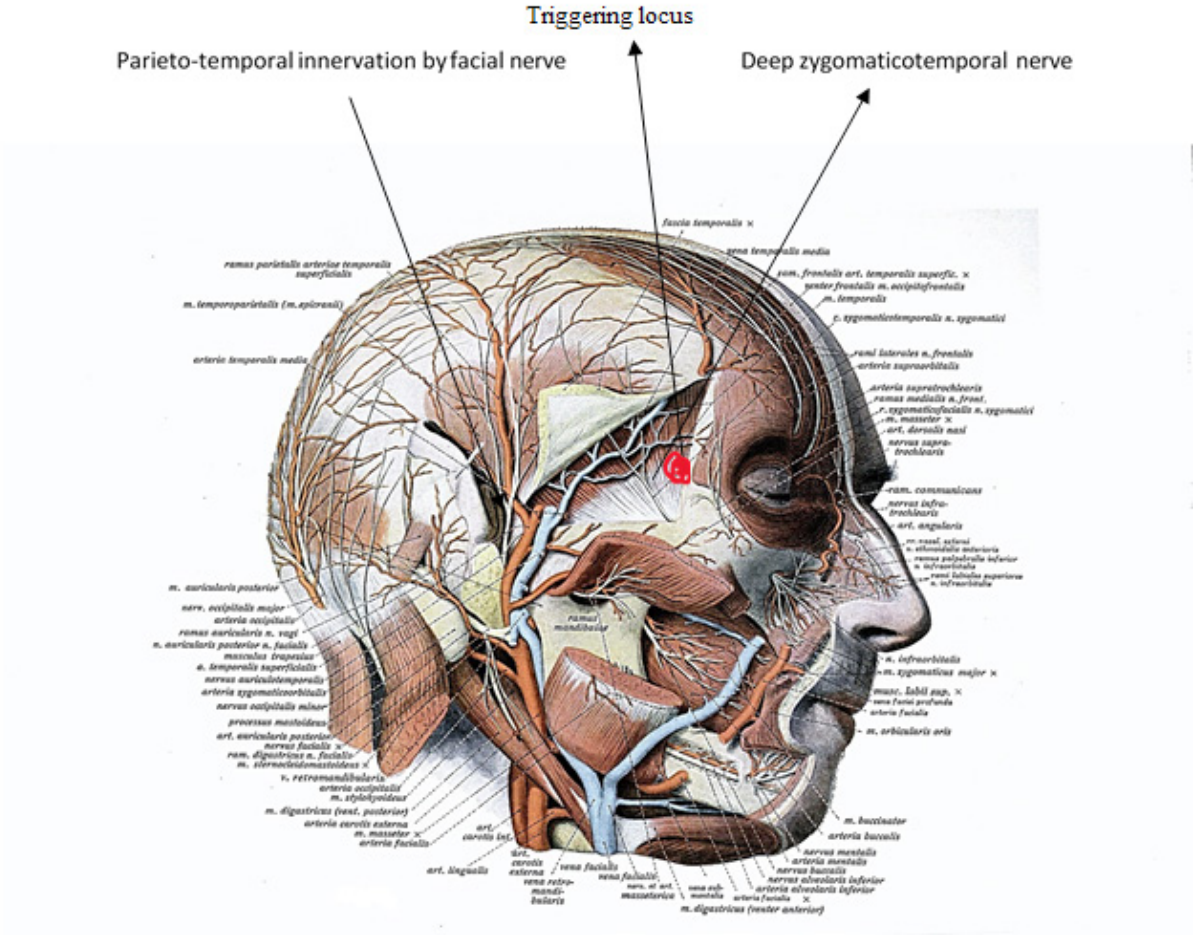


Figure 2: Sensory branches of the Ophthalmic and Maxillary division Cited for scientific purposes with the friendly permission of Elsevier- de.

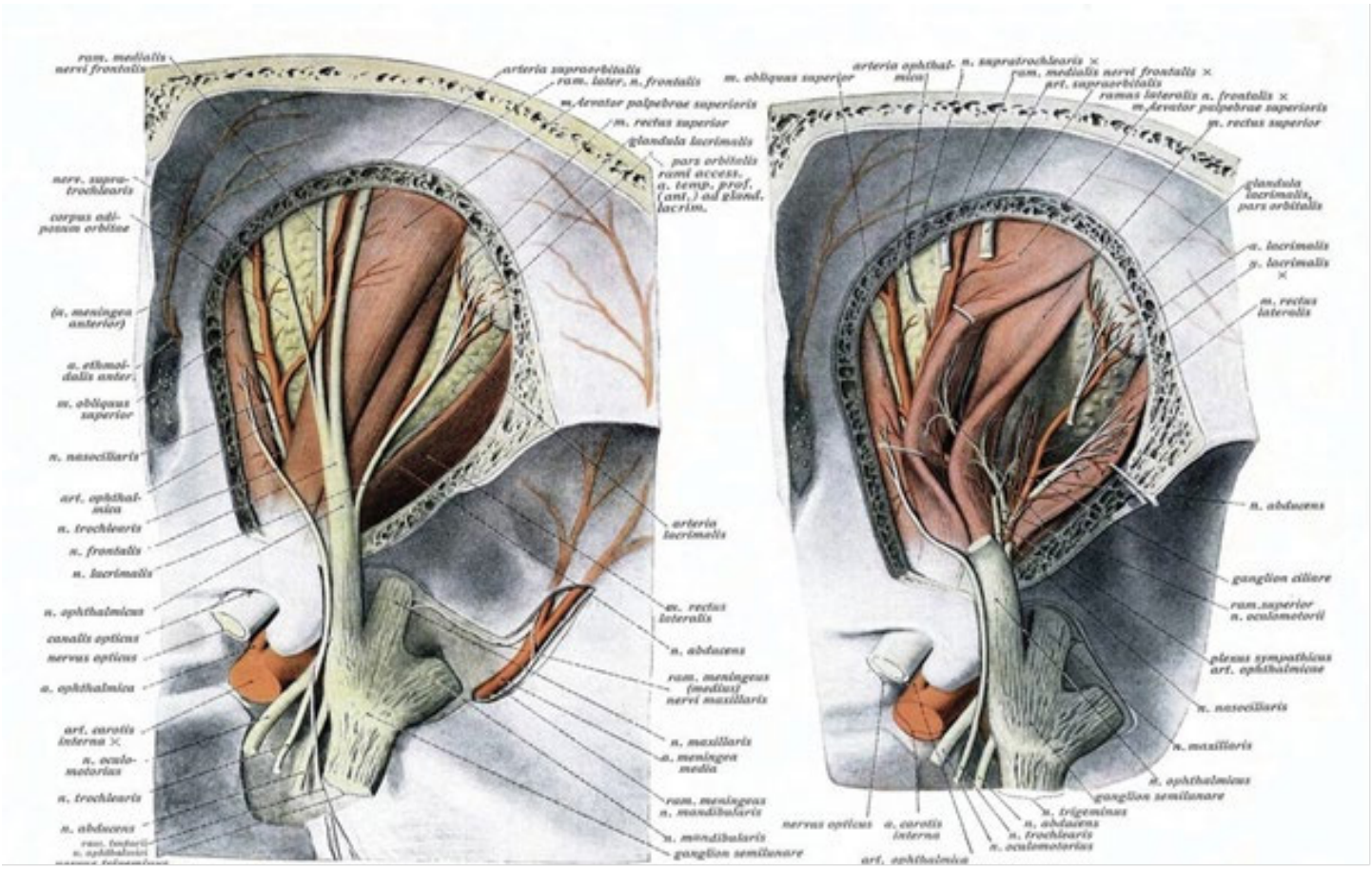


Figure 3: 1st Division: The Ophthalmic Nerve.

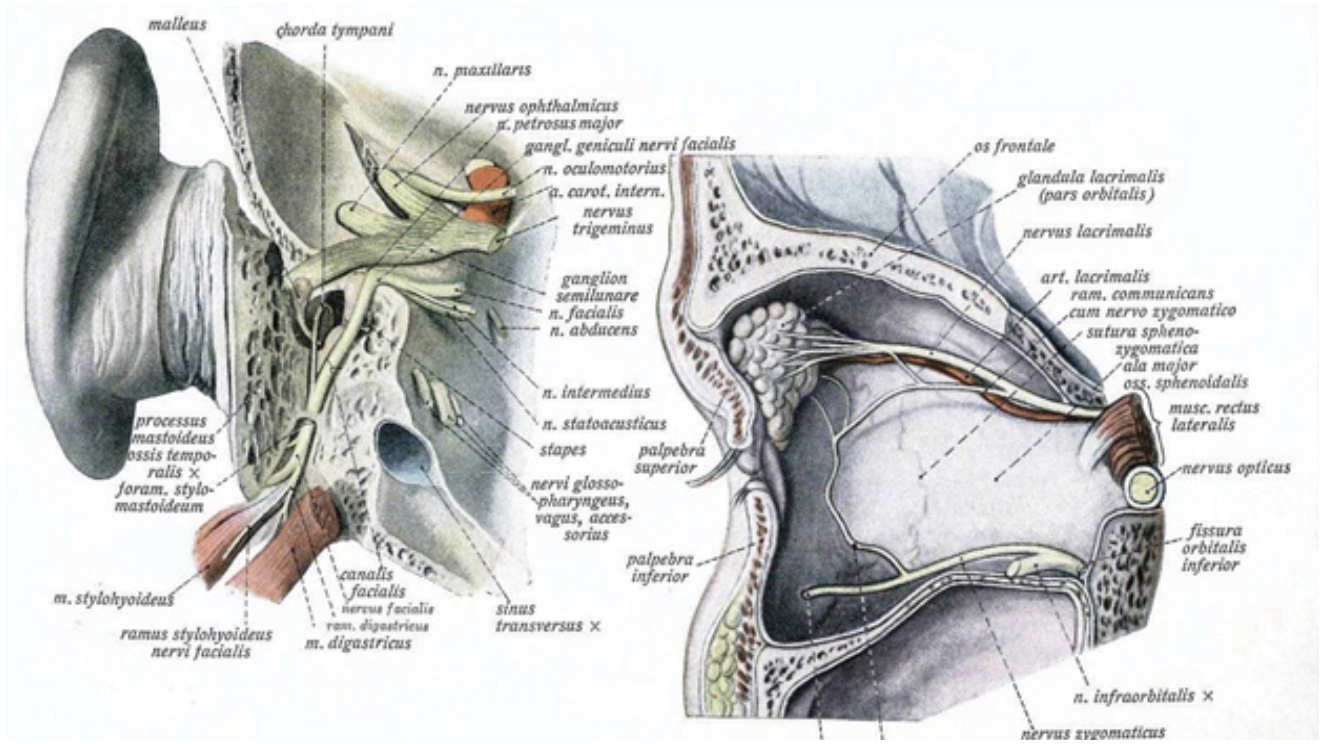


Figure 4: Intraorbital relationship of communicating ramus with Zygomatic and frontal nerve Sobbota/Becher: Atlas des Anatomie des Menschen, 16 Auflage 1960.Urban und Schwarz, Muenchen/Berlin. Cited for scientific purposes with the friendly permission of Elsevier-de.

The ophthalmic nerve carries sensory information from the scalp and forehead, the upper eyelid, the conjunctiva and cornea of the eye, the nose (including the tip of the nose, except alae nasi), the nasal mucosa, the frontal sinuses, and parts of the meninges (the dura and blood vessels). It innervates the temporal fascia and dermatome. The ophthalmic nerve receives sympathetic fibers from the cavernous sinus and communicating branches from CN III and IV. Before it exits the skull through the superior orbital fissure, it gives off a dural branch that divides into the frontal, lacrimal, and nasociliary Figure 4.

An anatomical feature of the ophthalmic nerve demonstrates nerves involved in the autonomic symptoms of ECCH. Figure 5 illustrates anatomical communication between the Z.T. nerves; Intraorbital communicating branches of the ophthalmic nerve, including the ciliary nerve, reach the zygomatic branch of the infraorbital Nerve (Maxillary division).

Relation of the supraorbital and infratrochlear branches, the anatomic relationship of both branches to the Optic Nerve demonstrates the main trunk of the supraorbital nerve extends through the bony foramen just 2-4 mm from the optic nerve. In addition, the ophthalmic branches run over the trochlea to reach their destination.

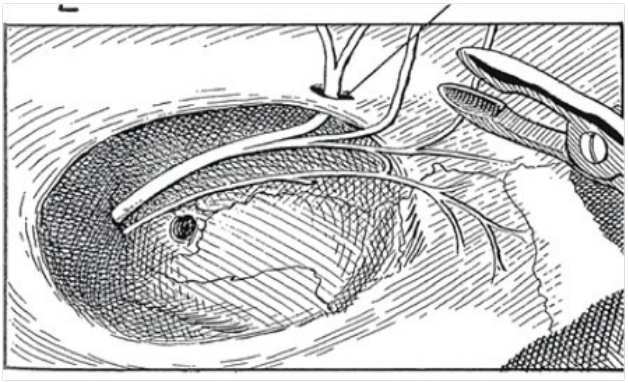


Figure 5: Intraorbital anatomic position of Optic Nerve and frontal Nerve (V-I).

Atlas of Neurosurgical Techniques. James L. Poppen, M.D. W.B. Saunders Company. Philadelphia and London 1960. This path easily transduces and propagates the electrical impulses/bursts from the Z.T.- Neuroma to the circuit. The extracranial circuit pathway includes:

1. Zygomatico-temporal-neuroma
2. Zygomatic Nerve
3. Intraorbital communicants' rami
4. Lacrimal Nerve
5. Ophthalmic nerve Intraorbital routing, supraorbital nerves, the upper eyelid, the conjunctiva and cornea of the eye, the nose (including the tip of the nose, except Alae nasi), the nasal mucosa, the frontal sinuses.
6. Optic Nerve via ophthalmic nerve branches overlaying the eye globe and propagation of electricity by adjacent ophthalmic Nerves 2-3 mm distance from each other, Figure 5.

Pterygopalatine ganglion in the center of all trigeminal nerve activities.

An intracranial CNS response follows in reaction to the perception of unexpected peripheral neural activities of a cluster of symptoms and Pain. Activation of the hypothalamic path projects an organized afferent fiber system in the trigeminal ganglion and responsible nuclei, respectively. Hypothalamic-cortical projections are functionally affiliated with activating an inhibitory preventive molecular response. A rami communicant of the zygomatic nerve (2nd division) with the trigeminal nerve's lacrimal nerve (1st division) inside the orbital cavity demonstrates an appropriate anatomical relationship.

Frontal nerve

Frontal nerves make the largest branch the first trigeminal division. It passes in the lateral part of the superior orbital fissure, below the lacrimal nerve and above CN IV, between the periorbital and superior palpebral levator. In the middle of the orbit, frontal nerve divides into the supraorbital (giant branch) and supratrochlear nerves.

The supraorbital nerve exits the skull through the supraorbital foramen. It supplies the upper eyelid and then turns under the frontalis muscle to provide the scalp with lateral. And medial branches. At the level of vertex, it intercommunicates to the branches of the greater occipital nerve bilaterally. The supratrochlear nerve exits the medial orbit and provides branches to the conjunctiva, the upper eyelid's skin, and the lower and medial parts of the forehead.

Maxillary nerve

The maxillary nerve carries sensory fibers from the lower eyelid and cheek, the nares and upper lip, the upper teeth, gums, the nasal mucosa, the palate, and roof of the pharynx, the maxillary, ethmoid and sphenoid sinuses, and parts of the meninges (Figure 6). The maxillary nerve is divided into three branches: the zygomatic, pterygopalatine (or sphenopalatine), and posterior superior alveolar nerves.

As it leaves the semilunar ganglion, the maxillary nerve passes through the dura of the lateral wall of the cavernous sinus. Maxillary division of the trigeminal complex exits the skull via the foramen rotundum and crosses the pterygopalatine fossa to enter the orbit, through the inferior orbital fissure, becoming the infraorbital nerve. Before entering. The foramen, it provides middle meningeal nerve, a dural branch. The zygomatic, pterygopalatine and posterior superior alveolar branches are given off in the pterygopalatinefossa.

The zygomatic branch divides into the zygomaticotemporal and supplies the deep temporal muscle portion and zygomaticofacial nerves.

The lateral wall of the orbit gives off a branch to the lacrimal nerve, which carries postganglionic fibers from the pterygopalatine ganglion for lacrimation. The zygomaticofacial is inferiorly situated and supplies the skin of the cheek.

The pterygopalatine (or sphenopalatine) nerves are two nerves that unite the sphenopalatine ganglion to the maxillary nerve.

Methods

In this clinical trial, we involved a limited number of human subjects for an interventional clinical trial. This approach is a pragmatic, cluster headaches-randomized clinical trial. No institutional review board (IRB) approval is obtainable. Based on our clinical interaction with headaches for the past two decades and our own pragmatic experiences, the decision was made to proceed with this crucial clinical trial.

Estimated Enrollment: 10, actual participant 4. Start date June 2021 Completed study 12/30/2022.

Participant Patients

Difficulty recruiting with a barrier of mistrust to any clinical trial for Cluster Headaches limited participation willingness. SARS-COVID-19 pandemic events were a second barrier.

Communication with significant headache centers was fruitless. Recruitment for each participant took 5-7 months. Participants were recruited based on the clinical trial protocol with diagnosis and clinical documentation of cluster headaches. P. I. Candidates who performed the personal evaluation and verified data provided with electro-stimulatory implants were excluded. No Comorbidities for exclusion were selected. Participants are scheduled to arrive at our clinic for a direct interview and the procedure.

Active Comparator: Patients with ultimate diagnosis and history of Cluster Headaches, Hemicrania Continua, Trigeminal Autonomic Cephalalgia, and Trigeminal neuralgia. Based on ICDH 3 beta of International Headaches Society.

Intervention

1. Minimal surgical Procedure and exploration of the exposed area for the presence of Neuroma or hypersensitive tissue not responding to the local anesthesia. Verification and excision of the extremely painful tissue – Neuroma.
2. Pathologic examination of the resected specimen for the presence of abnormal nerve tissue.
3. Follow-ups with patients for wound evaluation and immediate care in person within the next two days continued by primary care physicians and telehealth communications.

Data collection

Based on the classification of episodic and chronic cluster headaches in years existing, severity before treatment study, and post-treatment summaries.

The number and percentage of patients who experienced No Evidence of Disease Activity (NEDA) in the treatment versus individuals continuing to share their symptoms, were 4 of 4. In addition, 100% reported being completely free of their cluster headaches symptoms in 30 days, 90 days, and 270 days by completing the follow-up questionnaires. One participant dropped out of our statistics to lose –to-follow-ups after responding to the 210 days questionnaire.

Laboratory assessment

All the resected and collected specimens revealed pathologic evidence of single prominent neural tissue and neural bundles per high-power field verified by microscopic examination, identified by Hematoxylin Eosin(H&E) staining. In addition, the S-100 immunohistochemistrical should be able to highlight the presence of neural clusters in collected specimens.

Safety, adverse events

Adverse events have been coded in the trial protocol using a medical dictionary for regulatory activities with severity graded by standard terminology criteria for adverse events—version 3.0 (CTCAE). An aggravated, acute, or chronic harmful event following a clinical trial study or medical treatment of a human being or animal species is a severe adverse event.

Handling missing data, outliers, visiting windows, and other information. Participated in Periodic teleconferences with the Principal Investigator and analytic team member (Clinical Monitor), organized to share and ensure communication for periodic findings and safety reviews according to CMWW&RLLC Procedure has been documented in the project hardcopy files and Electronic Medical Records (EHR).

Safety data, including adverse events, did not show any adverse events during and after the procedure within nine months after the procedure. The clinical trial strictly followed the determined protocol.

The primary analysis is determined by the presence or absence of a neuroma and the determination of elimination or continuation of the cluster headache symptom immediately and after that. Patients are evaluated in person on the day of arrival, the day of the procedure, and the following two days. We hold all their drugs upon the scheduled course. Their primary care physicians scheduled wound care and sutures removal.

Secondary analysis and protocol deviations

The efficacy of the treatment procedure determines secondary analysis in the long-term 1, 3, and 9 months. All participants expressed no pounding and Pain of the cluster headaches following the excision of the "nerve bundle." However, in the beginning, the first two participants noted migraine headaches severity of 5-7 on the opposite side, which they had never experienced. This finding evaluated and revealed a new knowledge and understanding of cluster headaches. This behavior of the trigeminal nerve system was expected.

Having expected additional autonomous symptoms challenging us, we agreed on the deviation from the protocol. We added simultaneous De-Novo treatment of the opposite side the following day after the surgical procedure. Completing the original course with new knowledge shared with new participants and utilized in our protocol. At the endpoint of data collection, the following three participants were free of any migraine headaches or trigeminal neuralgia in cranial or facial properties.

End of the clinical trial

The end of the clinical trial is foreseen at the end of the last participant's data collection per our protocol.

Outcomes

The primary outcome was the evidence of Neuroma, nerve fibers in the excised specimens. Secondary outcomes included the resolution of individual autonomic symptoms following the excision of neural tissue. In addition, the quality of lifestyle, the continuation of drugs utilized, including prescribed or illicit drugs, and self-rated improvement were evaluated.

Our approach intended an interventional procedure to treat without drugs and looked into other autonomous trigeminal craniofacial nerve system behaviors.

Current data demonstrate that Cluster and migraine headaches sufferers do not respond satisfactorily to various NSAIDs, Triptans, or monoclonal antibodies they took for their cluster headaches. Therefore, the first two participants were encouraged to return (out of state) to treat their migraine headaches. At this endpoint, we revised and completed our clinical trial protocol by implementing the second intervention of treatment of migraine headaches using a compounded drug in our De-Novo migraine treatment algorithm. Participants agreed with the treatment approach. Both received the De-Novo treatment. They were symptom-free for the next nine months of follow-up. Participants no longer utilized medications. One participant complained of Pain over the right jaw that caused symptoms of facial neuralgia and has been referred to his dentist for further diagnosis and management.

- All participants were suffering from cluster headaches in a typical fashion and were diagnosed by their primary care and neurologist or headaches centers with chronic or episodic cluster headaches for years. From 19 candidates, we selected 11; however, only five individuals were able to travel to our clinical trial site for active participation. Four Female and one Male participant were aged between 31-57 years.
- All participants had already exhausted conventional treatment modalities, drugs, or the use of oxygen inhalations for years.
- All participants screened their medical records for exclusion criteria. In addition, responding to questionnaires and in-person interviews verified the inclusion criteria for the 5 participants.

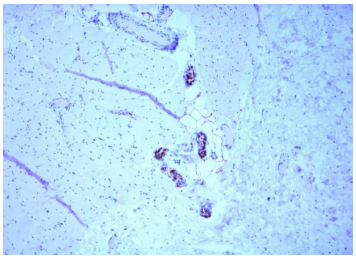
Results

From March 15, 2021, to December 22, 2022, 5-screened participants met the criteria for our interventional clinical trial. All four received the surgical procedure per protocol. Specimens were collected from all four procedures. Histopathologic examination using H & E, and S-100 immunohistochemistry stain highlighted in all four-specimen presence of neural tissue as follows:

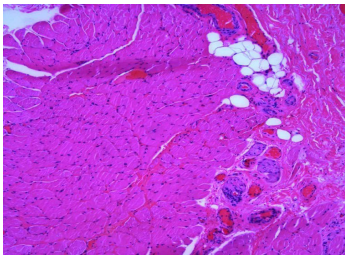
1. All resected and collected specimens revealed pathologic evidence of single prominent neural tissue and neural bundles per high-power field verified by microscopic examination, identified by immunohistochemistry of S-100 stain. The S- immunohistochemistrical stain highlighted these neural clusters. However, the histopathological antibody staining results demonstrated an isolated number of neural cluster (N.C) 9 (slide#1), N.C 4 (slide # 2), N.C 15 (slide # 3), N.C 2 (slide #4), and N.C several (slide #5) in the minimal excised tissue. In classical Description, expert dermatophatology evaluation did not show findings consistent with classically defined parameters for a neuroma. In addition, our pathological evaluation came short on evaluation of neuronal regulation of intrinsic and extrinsic signals of triggering potentials. Two important obstacles for future research are 1- materializing the cholinergic nature of the neuroma, 2-nature of intrinsic behavior of the neuroma.
2. We collected the Protocol questionnaires after one, three, and nine months. Preliminary results demonstrated no evidence of a continuation of cluster headaches symptoms for 270 days. One participant withdrew from follow-ups after seven months of follow-up. A very high percent positive response to the procedure result is associated with 100% positive histopathologic evidence of resected neuroma/neurinoma.

Microscopic imaging of the slides below provides detailed findings of excised pathologic nerve fibers.

#1 B22-252- male

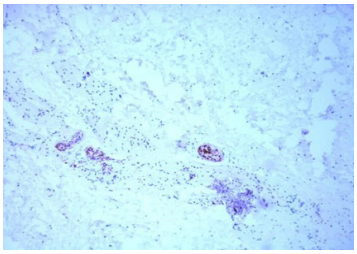


S-100 Staining

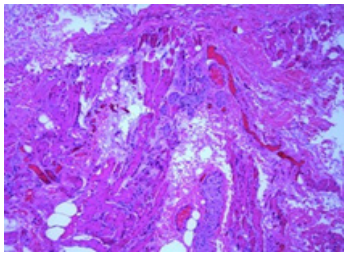


H &E Staining

#2 B22-12764- female

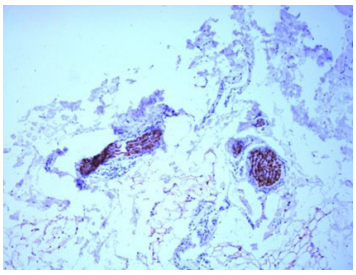


S-100 Staining

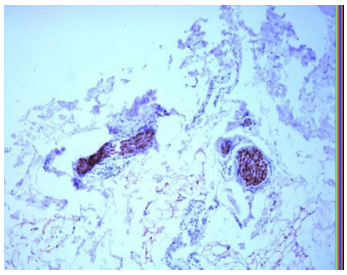


H &E Staining

#3 B 22-253- female

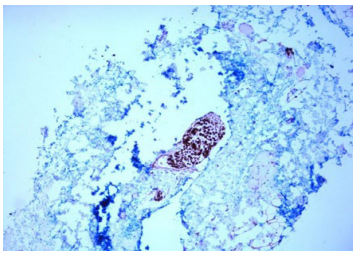


S-100 Staining

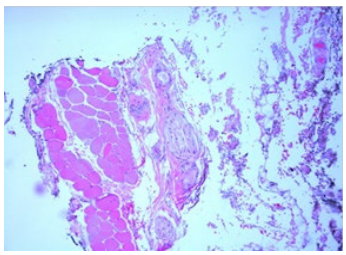


H &E Staining

#4 B 22-2784- female

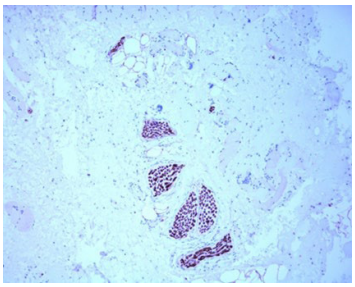


S-100 Staining

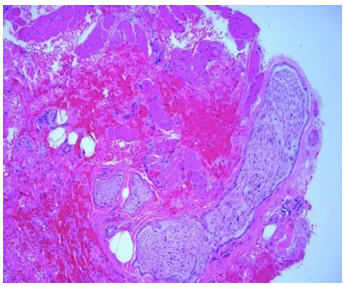


H &E Staining

#5 B 22-4372- female



S-100 Staining



H &E Staining

Discussion

Is there any evidence of trigeminal nerve tumors?

The hypothesis of a Zygomaticotemporal neuroma as a triggering key in the Cluster headaches autonomic symptoms followed by a search for neoplastic growth in the vicinity of the trigeminal nerve.

Pathophysiology of trigeminal nerve tumors a review of the literature

There is a preference for tumors of the trigeminal nerve complex. Neurinoma of the trigeminal nerve accounts for most of the trigeminal neoplastic tumors rather than neuroma. However, Neurinomas, mostly schwannomas arising from trigeminal complex intracranially, are rare. A critical review of the literature and reports did not demonstrate an extracranial neurinoma or intracranial Neuroma of the trigeminal complex. Most reported trigeminal neoplastic tumors consisted of neurinomas, meningioma, epidermoid cysts, osteochondral, or metastasis of other tumors. These tumors of the trigeminal nerve comprise only 0.2% of all intracranial neoplasms [2]. Trigeminal neurinomas are rare neoplasms reported by the incident of less than 1% of all intracranial neurinomas [3], and intracranial trigeminal tumors. An extracranial extension of the tumor with a well-defined perineural/meningeal membrane sheet is rarely reported [4]. The Ophthalmic and maxillary division. However, 2 cases of intracranial trigeminal Neuroma in patients with von Recklinghausen neurofibromatosis (NF1) were reported. These neuromas, however, did not demonstrate symptoms associated with trigeminal nerve neurinomas. The diagnosis was based only on incidental MRI findings, which showed a small nodular lesion [5].

Diagnostic symptoms of intracranial neurinoma of the trigeminal nerve range from disturbances in the adjacent cerebral nerves such as paralysis of the third, fourth, and sixth cranial nerves, clinically presenting exophthalmos and cavernous sinus syndrome, posterior fossa involvement (sensorineural hearing loss, tinnitus, cerebellar ataxia, and participation of intracranial nerves VII, IX, and XI. Bilateral trigeminal neuromas are extremely rare. However, its presence may account for a major expansion of neurofibromatosis [6].

The clinical course of patients' symptoms demonstrates explosive cluster headaches in any form, chronic or episodic C.H. Symptoms of peripheral Neuroma, in general, are different from neurinoma, Schwannoma, or Neurilemmal, which often get attention occupying space affecting the adjacent CNS nerves.

For instance, a neurinoma of the ophthalmic division presented hypoesthesia in the distribution of ophthalmic branches, exophthalmos, and visual disturbances upon the location of tumors [7]. On the other hand, the maxillary division's neurinoma does not demonstrate a different clinical course than the ophthalmic divisions.

The author's further search in the literature did not appreciate an extracranial peripheral neuroma or neurinoma of the trigeminal nerve branches. However, this review demonstrates a preference for the trigeminal nerve for intracranial neoplastic tumors. Interestingly, symptoms of intracranial neurinomas of the trigeminal nerves, including the Gasserian ganglion, did not come out close to the clinical autonomic course of cluster headaches. Peripheral nerve neuromas are categorically separated into two groups:

- Traumatic Neuroma and Neuroma in continuity, a non-neoplastic proliferation of the nerve endings in response to trauma or surgery. The traumatic neuroma of a severed peripheral nerve is painful and disproportionately intense by touch. Major limb amputations may demonstrate Phantom Pain. There are no spontaneous pain discharges reported. Some autonomic reflex dystrophic symptoms may also occur during Neuroma activities.
- Spontaneous nontraumatic Neuroma of the brachial and lumbar plexus was observed more often.
- Palisaded encapsulated Neuroma appears as circumscribed dermal or subcutaneous nodule composed of Schwann cells and some neurofilaments within the lesion. They do not typically cause "pin and needles" nor produce intractable, severe Pain [8].

Characterization of Zygomatico-Temporal Neuroma in unilateral explosive autonomous cluster headaches

The hypothesis of Zygomaticotemporal-neuroma activities investigated as

- Zygomaticotemporal Neuroma is possibly composed of nonmalignant neoplastic proliferation of the axons, which has been determined in each case by immunohistochemistry verification in the resected specimen in our clinical study.
- A cluster circuit with frequent, intense impulses released for a particular limited time of neurotransmitter synthesis needed to be released by Neuroma considered circadian rhythmic Neuroma Activities.
- Rhythmicity of impulses seems to involve synthesis and release of neurotransmitter(s) (acetylcholine or catecholamine or other) [Subject to further immunohistochemistry examination] in presynaptic nerve endings and degradation in the postsynaptic vesicles [by acetylcholine esterase?]. However, the pattern of intense rhythmicity and frequent discharges may occur differently at a lower threshold in the Neuroma in everyone. The ZT-neuroma's automatic turn-on switches understand that mechanical and chemical stimulation cannot stop or stimulate its activities. Projection of Pain in circumscribed trigeminal nerve branches, and ganglia by increased electrical activity, are believed to be the pain process is strongly limited to a peripheral anatomical circuit and a local inhibiting mechanism. Therefore, simultaneous actions of the contralateral trigeminal nerve complex in the form of migraine headaches are inevitable. Furthermore, our clinical experiences in the past 20 years demonstrated the existence of bilateral craniofacial neuralgia simultaneously.
- Exposure of the contralateral side and other divisions and branches of trigeminal nerves were questioned about being addressed following excision of Z.T.- Neuroma
- Peripheral nerve stimulation is accompanied by a physiologic response in the relevant brain centers, such as the Hypothalamus, as metabolic activity is introduced by neuroimaging. The metabolic activities during the spontaneous Cluster Headache attacks are demonstrated by PET, fMRI subsequently as cortical-central pain processing. The central nervous system is always involved in painful events, including trigeminal neuralgia. Suppose we understand that Pain is a peripheral mechanism, not central. The brain, per se, does not carry pain receptors. Universally seen, the brain is a silent creature that depends on programming applications from internal or external physical environments by its autonomic sensory organs. The trigeminal ganglion is physiologically connected to the mid-brain and independently by its nucleus Solitarius.
- Involved ipsilateral sympathetic and parasympathetic ganglia in cluster headaches demonstrate connectivity to the processing pain centers in the brain, not vice versa. The brain is a motherboard, not an application. The brain is the guardian of living species' physical and functional existence.
- Strangely, the graphic Description of the nuclei of the brain shows that trigeminal nuclei, both sensible and motoric, originate and are embedded in the mesencephalon. The body of the trigeminal nerve then leaves the midbrain at the lateral aspect of the pons. Anatomic- morphologically, the semilunar ganglion lies between two layers of dura mater, which continue all three Trigeminal nerve divisions until it reaches the oval foramen. Dura mater encephali carries vasomotor nerve fibers and plenty of receptor entities that nourish the thinner inner layer of the Dura mater. Finally, the last nerve fibers originate from all three divisions of the trigeminal nerve and the apical part of the vagus nerve (X).
- The central sensory nucleus receives its afferents (as the sensory root) from the semilunar ganglion through the lateral part of the pons ventral surface. Its axons cross to the other side, ascending to the thalamic nuclei to relay in the post-central cerebral cortex. The descending sensory fibers from the semilunar ganglion course through the pons and medulla in the spinal tract of C.N. V to end in the nuclei of this tract (Figure 2 & 3) (as far as the second cervical segment).
- The axons of these nuclei cross to the opposite side, ascend into the spinothalamic tract, and relay in the thalamic nuclei; from there, they end in the cerebral cortex. The sensory nucleus of C.N. V is connected to other motor nuclei of the pons and medulla. In addition, the descending sensory spinal tract receives somatic sensory fibers from CN VII, IX, and X.

CNS Neuroimaging studies in an actual event of a cluster headache

No diagnostic tools are available to diagnose a small-diameter peripheral nerve or a small neuroma. A review of expert neuroimaging studies in patients with ECCH also studies the brain during different phases of C.H. reviewed from literature within headaches and specially C.H. prominent centers. This review did not demonstrate the presence of any" small vessel disease" periventricular calcifications of the brain in C luster headache patients. Therefore, it eradicates the possibility of direct vascular involvement in the etiology of ECCH. The brain of individuals during an activity of ECCH was studied by fMRI, PET Single Photon emission computed tomography (SPECT), Structural MRI, diffusion tensor imaging (DTI), and magnetic resonance spectroscope (MRS) [9].

Their finding concentrated on activities of several brain centers, including hypothalamic loci, focusing on metabolic changes during the spontaneous attacks, which provided theoretical consideration for the hypothesis related to the hypothalamic-trigeminal nucleus, circadian rhythm, and other brain centers as the cause of ECCH pain. Symptoms of a Neuroma activity in the territory of the peripheral trigeminal nerve, in particular Z.T. neuroma, demonstrate its exceptional circuit involvement as described above. In addition, brain centers are involved in the perception of and analysis of Pain to determine possible actions. We suggest that the external path easily transduces and propagates the neuroma electrical impulses to the circuit participants because of the autonomic character of the nerve connectivity they demonstrate. The circuit activities and brain metabolic activation cease by a

turn-off of neuroma impulses. A neuroimaging study during a Cluster headache episode and Pain-free episode by indomethacin induction revealed discontinuation of metabolic activities in the brain during imaging [10]. To our knowledge, CNS metabolic studies of the brain centers during acute cluster headaches did not come close to the trigeminal nerve's peripheral vicinity, including it intermediary ganglions.

Cluster headaches are severe, debilitating, spontaneous, neuropathic sensory events in humans accompanied by localized starting dysesthesia, "pins and tingling" exaggerated to intense rhythmic impulses several times per day to weeks or months. Its' activity is exhaustive psychotically, physically, socially, and financially. Cluster headaches have existed ever since humans understood how to describe their body symptoms. Genetic exposure is speculated.

However, the possibility of an embryologic developmental malfunction is not yet discussed. Triggering an autonomic nerve ganglion by unknown internal or external stimuli is suspected of de-silencing the silenced equilibria environment of the autonomous system in the craniofacial property. The extracranial circuit component of ECCH reflects the anatomical nerve components participating reflection of the single circumscribed symptom:

1. ZT-neuroma
2. Zygomatic nerve V-II
3. Intraorbital communicants' rami
4. Lacrimal nerve V-I
5. Ophthalmic nerve Intraorbital routing, supraorbital nerves, the upper eyelid, the conjunctiva and cornea of the eye, the nose (including the tip of the nose, except Ala nasi), the nasal mucosa, and the frontal sinuses, V-I.
6. Optic Nerve via ophthalmic nerve routing and electricity propagation.
7. Pterygopalatine ganglion as a peripheral and CNS coordinator center.

An intracranial CNS reaction follows in response to the perception of Pain materialized in neuroimaging during the activity of ECCH.

We speculated that the Zygomaticotemporal Neuroma located in the temporal area is the only possible extracranial tumor of the trigeminal nerve of the maxillary division known to be now responsible for ECCH. The nature of Neuroma arises from nerve fibers with a special characteristic of all Neuroma tingling dysesthesia, followed by a spontaneous outburst of stimulatory electrical discharges, which affects specific nerves and distributary autonomic ganglions described below. This behavior-provoking, usually known as CNS neuropeptide, releases in recognition and processing of the pain signals. The periodic striking of the discharges in the Neuroma would be challenging in characterizing this phenomenon. Neuroma of the Zygomaticotemporal Nerve physiologically seen is directly associated with autonomic complex in the craniofacial region with a preference to Rt. Side of the face and male gender. It demonstrates additional autonomic effect at the ipsilateral frontal nerve and concomitant more significant occipital nerve irritation by connectivity to the frontal nerve at the vertex level. The contralateral trigeminal complex involvement seems rarely mentioned in the literature.

How to diagnose the presence of a Z.T. neuroma in ECCH-patients?

Unfortunately, there is no diagnostics imaging tool for identifying the smallest Neuroma of a Peripheral trigeminal nerve. However, our search showed "Raman Spectroscopy" may provide later clinical development. an excellent functional tool in detecting minor peripheral nerve abnormalities [11,12]. Therefore still, clinicians depend on their clinical judgment through observation and palpation.

Clinical diagnostic & procedure steps for resection of a Neuroma

1. To avoid misidentification of Neuroma, patients indicate using their index finger to palpate where tingling or vibration discomfort starts.
2. Fixation staining using injectable of a biodegradable methylene blue 0.01 ml through narrow gauge needles Gg 27-30.
3. Marking a lazy S incision line 2-3 mm from the Neuroma marking on the skin.
4. Local anesthesia was obtained using plain 2% or 1% lidocaine infiltration of the circumferential exploratory area.
5. Using a number 15 scalpel initiated an inch incision. Meticulous preparation of the subcutaneous tissue 25 mm at each side of the incision line. An ALM or Miltex cross Retractor provides appropriate visibility of the Z.T. nerve branches embedded in lipomatous and connective tissue over the temporal fascia.
6. Exploratory visualization of the marked subcutaneous tissue using binocular magnification eases visualization too. For example, using Adson tissue forceps with the side without grasping teeth, an exploratory touch of the above and distal marking would deliver the hypersensitive painful Neuroma tissue for a sharp excision using surgical scissors. Special attention is to be paid to the Neuroma since this tissue is susceptible and does not respond to a high dose of lidocaine. The patient may react by jumping or making a sharp, unexpected movement. In addition, all possible hypersensitive tissues may contain neuroma material, which needs to be excised. Only Nerve fibers related to the neuroma sacrificed. No hyposensitivity in the property of ZT-nerve should be expected. Figure 6.

Atlas of Neurosurgical Techniques. James L. Poppen, M.D. W.B. Saunders Company. Philadelphia and London 1960.

7. Excision specimens may be transferred to a container for pathologic examination and immunohistochemistry verification of Neuroma.
8. Wound irrigation, hemostasis of possible bleeding(s). Wound repair using 4/0 proline or Nylon. Sterile dressing with fine compression. No antibiotics if prep and draping are provided in an orderly surgical fashion.
9. Postoperatively, this procedure may demonstrate absolute resolution of the patient's Cluster Headaches symptoms.

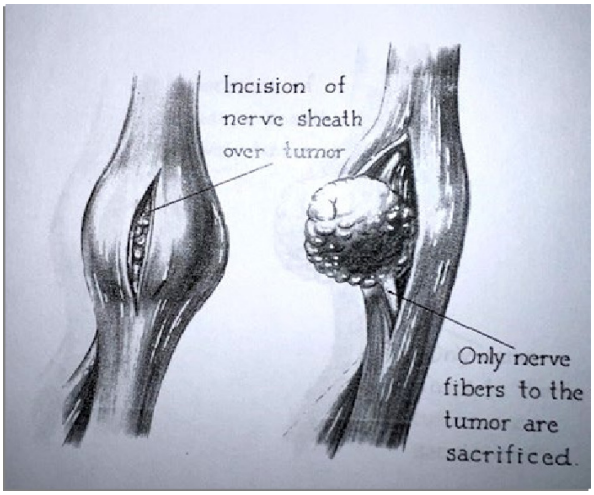


Figure 6: Visualization of a neuroma and its excision within a peripheral nerve branch.

Conclusion

Our study projected evidence of zygomaticotemporal Neuroma/ disorganized nerve bundle as a triggering source of the ECCH. This Subject of surgical exploration and resection might cure the long-term Episodic and chronic cluster headaches ECCH. It may light up puzzling questions and treatments, save a life, and ease the psycho-social and financial burden on individual patients and society.

The procedure is straightforward and accessible in the hand of an experienced physician, with no need for a reconstructive procedure. A pathologic examination of resected tissue is imperative and may increase clinical confidence in the expected result. However, a simultaneous treatment approach of the potential contralateral odds migraine type neuralgia makes it critical concerning the complete resolution of the craniofacial neuralgia of everyone to end disability. Our approach exhibits the possibility of discontinuation of desperately utilized Psychedelics, monoclonal antibodies, Oxygen use, and use of implanted electrostimulations.

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Research ethics and patient consent

Ethics and Consent: All patients provided written consent upon face-to-face encounter for each and one procedure, and publication of the data in the scientific journals and online media.

Data availability

All collected data including electronic communications and images are available and protected Electronic Medical Records EHR by Dr. Owiesy a Principal Investigator.

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