Entrapment Neuropathy: A Concept for Pathogenesis and Treatment of Headaches—A Narrative Review

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ABSTRACT: Entrapment neuropathy is a known cause of neurological disorders. In the head and neck area, this pathophysiological mechanism could be a trigger for headache. Over the last few decades, injection of botulinum toxin type A in the muscles that are causing the compression as well as surgical decompression have proved to be effective treatment methods worldwide for large numbers of patients with daily headaches. In particular the entrapment of the supraorbital nerves in the glabellar musculature and the occipital nerves in the neck musculature are triggers for headache disorders for which many patients are still seeking an effective treatment. This article reviews the literature and aims to bring the concept of neural entrapment to the attention of a wider audience. By doing so, we hope to give more exposure to an effective and relatively safe headache treatment.

KEYWORDS: Headache, neural entrapment, treatment, surgery, botulinum toxin, nerve block

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Introduction

Two decades ago, three colleagues observed independently that patients reported the disappearance of frontal headaches after botulinum toxin type A (BoNT/A) injections and surgical forehead rejuvenation procedures.[1-3] This side effect was noted incidentally and was not anticipated, neither by patients nor by surgeons. Consequently, it was hypothesized that not all migraine headaches were triggered by a central nervous system disturbance but that some were provoked by peripheral circumstances.[3] Although increasing evidence indeed affirms a peripheral trigger point theory of migraine, from the traditional point of view, the trigger is of vascular origin.[4]

The treatment effect was supposedly due to the relief of 'sensory neural entrapment'. The entrapment was described as the result of hyperactivity of the glabellar musculature, especially the corrugator muscle strangling the supratrochlear and the supraorbital nerves, which run through it.[5-9]

Headache can also originate in the occipital and temporal areas in cases of migraine, tension-type headache (TTH), and temporal mandibular dysfunction (TMD). Since both the neck musculature and the temporalis muscle are forceful, and potentially able to compress nerves within their surrounding, entrapment neuropathies of the greater occipital and zygomaticotemporal nerves were hypothesized as other triggers of this headache-inducing mechanism.[10-13]

Ever since, many colleagues have been able to reproduce the effects of entrapment release both with BoNT/A and by surgical decompression.[14-17] To date, entrapment neuropathy and its treatment are not embraced by all colleagues yet. This narrative describes the most important facets in favour of this paradigm, distilled – non-systematically – from the extensive literature.

Headache epidemiology

Headache is a leading cause of disability, affecting more than 10% of the population. In the United States, it accounts for one in five outpatient visits to neurologists' offices.[18,19] It is estimated that approximately 4% of adults have primary headaches lasting more than 4 hours per day, for more than 15 days per month.[20,21] Chronic migraine (CM) and chronic tension-type headache (CTTH) comprise most of these chronic daily headache (CDH) disorders.[22]

Patients with headache are faced with restricted activity, decreased productivity, missed work days, and, most importantly, decreased quality of life.[19,22,23] In addition, over-the-counter and prescription medications can lead to significant adverse effects and may cause medication overuse headache (MOH). The economic burden of headache is substantial, with billions of dollars spent both in direct costs (utilization of healthcare resources) and indirect costs (reduced productivity).[19,24]

Classification

Headache is classified according to the International Classification of Headache Disorders (ICHD)-3 beta.[25] These headaches are further subclassified, but modified criteria have also been defined.[26] The ICHD has been criticized for the fact

that for primary headaches, it is symptom based and not based on the pathophysiology generating the headache.[27]

Especially for the long-term headaches, correct classification has proven difficult, and opinions can differ on the precise characteristics.[20] Chronic daily headache, although a well-known clinical entity, is not recognized in the classification.[20,23] In practice, a mixture of TTH and migraine is transformed migraine (TM), for which the diagnostic criteria apply to many patients.[20,23,26]Patients with TM have headaches that become more frequent, with associated symptoms of photophobia, phonophobia, and nausea becoming less severe.[28] Therefore, the clinical difference between migraine and TTH is getting less obvious. The diagnostic links to migraine are as follows: a prior history of migraine; a period of mounting headache frequency with decreasing severity of migrainous features; or superimposed attacks of headaches that meet the criteria for migraine. Transformed migraine often matures in patients who overuse medication.[23,28]

For occipitally located pain, a similar myriad of diagnoses exists. In unilateral cases, cervicogenic headache (CH) could be a diagnosis; for bilateral cases, TTH would seem more appropriate. Occipital neuralgia (ON) also constitutes a well-known entity. Another type of headache that frequently starts in the occipital area is 'persistent headache attributed to whiplash'.[25,29-33]

Pathophysiology

Headache is a heterogeneous condition that culminates in a wide range of disability within and among different patients.[18] The pathophysiological mechanisms underlying headaches are not completely understood. A number of hypotheses have been described regarding the central neural events causing the initiation of migraine. Some have stated that cortical neuronal hyper excitability, which has been found in different cortical and subcortical brain regions, is the culprit. Many think that both peripheral and central sensitization of the trigeminal system can culminate in migraine pain symptoms.

What activates the peripheral trigeminal neurons, however, remains unknown. Some manuscripts state that activation of the trigeminovascular system might be of extracranial origin and have shown that headaches can be influenced by treatment targeted at the occipital nerves or the pterygopalatine ganglion.[34,35]

Moreover, since a headache diagnosis is based on a complex of symptoms (phenomenologically), it is possible that the pathophysiological trigger for a specific phenotype of headache differs within patient groups. Consequently, this would lead to suboptimal treatment effects for the total population if all patients with a specific diagnosis were treated in the same way, instead of with differentiated therapy based on the variety of triggers.

Current treatment options

Prophylactic treatment of migraine is primarily used not only to reduce the frequency of migraine episodes but also to diminish reliance on analgesic medications.[19] However, the available and/or approved pharmacological treatments are often associated with limited efficacy and intolerable side effects.[2,18,19,24] There is thus an unmet therapeutic need for effective, tolerable migraine prophylactic drug treatments.[19,24] This holds true for CDH as well; CDH sufferers are among the patients most dissatisfied with current treatment options. Specific goals in future research of pharmacological treatment were stated as identification of a population that would benefit from treatment and finding an efficacious dose without too much side effects.

But what about a totally different treatment concept?

Entrapment neuropathy

Entrapment neuropathy is traditionally a disorder of the extremities. It includes well-defined syndromes as carpal tunnel syndrome, suprascapular nerve compression, and meralgia paresthetica. Although muscles can cause neural entrapment, other structures such as blood vessels and fascia bands may compress nerves as well. Recent research has explored the concept of entrapment, compression, or irritation of the sensory nerves of the head and neck area as possible peripheral triggers for headache.[36,37] Given the fact that many migraine headaches are triggered by stress or light exposure and that many of these patients show significant hypertrophy of the corrugator muscles, the entrapment theory as a major factor becomes more compelling. In line with that, histopathology of the migraine patient's zygomaticotemporal branch indeed shows signs of compression as compared with healthy individuals.[38] This implies a new paradigm in headache pathogenesis.

Entrapment causes a localized neurogenic inflammatory response with release of different neuropeptides. This eventually leads to neural changes that make the nerve hypersensitive and which manifests behaviourally as hyperalgesia and allodynia.[39–41]

Phenotypes

Does nerve compression at a single site always trigger the same 'phenotype' of headache? We think not; we suggest that one trigger may be involved in different phenotypes. In our opinion, the actual phenotype depends on other factors such as genetics, hormonal status, obesity, stress, depression, and fatigue. Which phenotype of headache will develop is probably the result of the spectrum of these confounding factors.

Furthermore, compression does not indeed always provoke headache. Similarly, not all microvascular conflicts cause trigeminal neuralgia and, likewise, the incidence of patients with migraine headaches stemming from the auriculotemporal nerve trigger point is very low compared with the observed incidence of a potential conflict between an artery and the auriculotemporal nerve.[42] From these findings, one may conclude that other factors are extremely important in the actual development of headache symptoms.[43] In our opinion, all these factors combined contribute to a lower threshold among some patients for developing both peripheral and central sensitization processes which lead to chronification of pain.

Thus, the hypothesis most relevant to the concept of neural entrapment is that peripheral activation of the trigeminal or occipital nerves – entrapment of different nerve branches – may be involved in many different phenotypes of headache (classified as independent syndromes in the ICHD-3 beta). But to be perfectly clear, we are not suggesting that a form of neural entrapment is a sine qua non for all headache sufferers, not even within a specific phenotype of headache.

Migraine, migrainous or 'long-term headache'

Guyuron used the term 'migraine surgery', which could lead to a discussion on the question of whether or not his patients indeed suffered from migraine or would have had different headache types. However, a neurologist was part of his team in all studies to make the diagnosis.

The authors of this manuscript are calling for a headache classification that also relies on pathophysiological causes and not solely on a set of anamnestic criteria. We think that if a 'neural entrapment' exists, this should be addressed as such, irrespective of whether the pain it causes resembles criteria for migraine, CTTH, or CH.

If the 'primary headaches' were also (sub)classified on the basis of pathophysiological concepts, it might allow for better-focussed treatment options for subgroups of patients with primary headaches. In line with that, we consider it more logical to investigate decompression surgery for frontal headache in future studies only in patients with positive effects of both supratrochlear nerve blocks or BoNT/A injection in the corrugator, rather than to operate upon every patient with CDH and to observe improvement in only 50% of them, since other triggers for CDH were present in the remaining 50% of patients.

We believe that, as it is extremely difficult to classify patients with long-term headache, it would be better to focus on ameliorating the clinical selection criteria (and thereafter the treatment options) for patients with a definite pathophysiological cause who might benefit from a specific therapy – *in casu* surgical decompression – than on the overly strict (and unrealistic) adherence to nomenclature from an ambiguous research classification.

We therefore feel that it is necessary to classify headaches caused by compression or conflicts along certain nerves as 'entrapment neuropathy'. In terms of the ICDH-3 beta classification, however, this would mean that we are discussing 'secondary headache' types.[44]

Entrapment sites

In ear, nose, and throat (ENT) practice, a frequently occurring site of headache is the frontal region. Patients with frontal headache are usually referred because of a suspicion of long-term sinusitis; CT scanning, however, often reveals no sign indicative of an infection or other possible cause of sinus-related headache.[16] Another important region is the occipital region, where entrapment of all three occipital nerves (greater, lesser, and third) has been described.[37,45-47] In the past, the focus on headache and pain management concerned especially the greater occipital nerve, probably because this is the biggest and most well-known nerve in the area. In our ENT practice, however, we noticed that the lesser occipital nerve was more often found to be the culprit. As stimulation of the lesser occipital nerve may cause otalgia, some bias probably exists in the referral pattern. In the temporal region, compression of the zygomaticotemporal nerve by the temporalis muscle, causing supra-auricular pain, is the most frequently reported option.[48,49]

Since headaches are diagnosed by different medical specialities, there is a possibility that neuralgia/neuropathy of the major nerves (supraorbital and greater occipital nerves) is more easily diagnosed by general practitioners (GPs) and therefore referred to the neurologist. Therefore, selection bias might create different patient categories for different specialties, with consequently different treatment results.

Anaesthetic nerve blocks

For decades, peripheral nerve blocks (PNBs) of the trigeminal or occipital nerves have been performed with good treatment outcomes for different types of headache.[31,50,51] Use of diagnostic PNBs has been cited as the only means of establishing the diagnosis for CH.[29] Theoretically, a PNB proximal to the entrapment should provide relief of pain.

Depending on the pharmacological agent, the location of the block, and the headache 'phenotype', treatment outcomes of PNBs are described as having a large variance. Their analgesic effect typically lasts beyond the duration of anaesthesia caused by the blockade, providing some patients with pain relief for several weeks or even months.[50] Young et al hypothesized that the mechanism of action of PNBs may well be through changes in brain inhibitory nociceptive pathways based on the complexity of the migraine symptoms and the response time that exceeded the anaesthetic effect. They found a rapid onset of alleviation of symptoms (pain, allodynia, and photophobia) in migraine patients after occipital PNB.[52] PNBs are generally found to be safe, cost-effective, and well tolerated.[53]

Botulinum toxin

Botulinum toxin type A blocks the release of neurotransmitters.[54] This specific biochemical interaction of BoNT/A is the basis of its therapeutic use in disorders associated with neuronal over-activity, both neuromuscular and autonomic.[24,55] In addition, BoNT/A's positive effect on pain was at first thought to be correlated with the reduced contraction of affected spastic muscles.[56] The antinociceptive effect of BoNT/A was reported in several non-muscular pain conditions, such as neuropathic pain, migraine, and arthritis, and this effect is mediated through sensory neurons.[57] Moreover, basic research suggests that BoNT/A blocks peripheral sensitization at injection sites and may also have a direct effect on the central nervous system by modulating central pain sensitization.[58-60]

Pericranially injected BoNT/A has been approved for the treatment of long-term migraine.[61] We suggest that BoNT/A, like surgical removal of the corrugator, eliminates the trigger point by paralysing the muscle that strangulates the supratrochlear nerve branches.

Interestingly, if CTTH patients also experience pericranial tenderness, this symptom can be regarded as a sign that the headache is peripherally triggered. In that case, the positive response to BoNT/A injection in this area was very high, whereas in CTTH patients without pericranial tenderness, BoNT/A had no effect.[22] In addition, in CTTH patients with temporomandibular disorders, the pain might be triggered by compression of the zygomaticotemporal branch of the trigeminal nerve. In these patients, the pain drastically improved in 46/46 patients after BoNT/A injections.[11]

With single-site BoNT/A injection in the corrugator supercilii, in the case of a frontally localized headache, Behmand et al[5] experienced improvement in 83% of patients (n = 29), while other authors have reported similar positive results.[16,62]

However, some studies with BoNT/A injection for headache resulted in less-positive treatment outcomes.[63-67] The negative results, in our opinion, were due to flaws in the rationale behind the treatment and inappropriate treatment expectations: injection in muscles that are not causing entrapment, not selecting patients based on possible trigger points, and too low a dose of BoNT/A.

To clarify: neural entrapment of the supratrochlear and supraorbital nerve is experienced as frontal headache, but the BoNT/A should be injected in the corrugator that compresses the nerve and not in the frontalis muscle located in the area of pain referral. A 'follow-the-pain' approach, without a convincing pathophysiological background, is more like random shooting that might incidentally also hit the bull's eye. Furthermore, BoNT/A should be administered in a high-enough dose in the corrugator; some studies used inappropriate doses that would not cause long-term beneficial effect. With less than 15 units in the corrugator, in our experience, the effect will not last for more than 10 weeks. With that in mind, follow-up time of 3 months or longer is an inadequate assessment with this dose.

In conclusion, BoNT/A is an effective therapeutic treatment for a subgroup of headache disorders caused by neural entrapment by excessive muscle contractions.[19,59] Its safety and tolerability are well established across multiple studies.[1,68]

Surgical treatment outcomes

Surgical decompression of peripheral sensory nerves at different trigger sites in the head and neck area has high success rates; it results in migraine elimination in 35% to 90% and pain reduction in 42% to 97%.[3,14,15,48,69] A study comparing surgical decompression to 'sham surgery' showed that complete relief of headache symptoms was obtained in 57% of patients undergoing actual decompression versus only 3% in the sham surgery control group. No effect of surgery was observed in 16% of the actual surgery group compared with 42% of the sham surgery control group.[36] If a screening algorithm (positive response to BoNT/A) was used to indicate good surgical candidates, 95% patients experienced improvement after surgery.[70]

A successful treatment outcome after decompression surgery therefore seems to depend on being able to correctly classify patients, on identifying the peripheral triggers, and on aiming the surgery at the right target.

Placebo

A relatively high treatment outcome in the placebo/sham surgery groups of headache studies is a well-known and intriguing effect. Headache trials with medication also showed this effect, but placebo injections and sham surgery seem to have an even more beneficial placebo effect.[36]

Even though these effects might be seen as pure placebo or psychological effects, there is a possibility that the needle itself creates an effect, or that incision and undermining of the tissues can alter neurosensory functions at least temporarily. Such an effect, neuro-modulation, has been the basis of several pain therapies, such as peripheral nerve electrical stimulation and magnetic field stimulation. Expanding further on this line of thought could be to question whether myofascial trigger site injection, acupuncture, and dry needling might harbour a similar sort of – as yet unknown – effect on tissues, causing a greater-than-expected improvement.

Blinding for the effect of BoNT/A in the corrugator or for the removal of that muscle as suggested by opponents is impossible. We do not have a medication that works in a similar manner. However, if a medication did have the same paralysing effect, it is logical that it might have the same effect on headache as well.

We therefore believe that rate ratios are a better way of describing the treatment effects and gathering evidence.[71] We think that if the reported treatment outcomes are that high, then they are indicative of genuine treatment effects.

Most importantly, surgical placebo effects may lead to improvement in up to 58% of patients, whereas the effects of decompression surgery in carefully selected groups are higher than 85%.[72] We must therefore be careful not to disregard studies because a placebo effect also occurs; therapies with specific results showing higher efficacy rates than those of the sham control groups will otherwise be withheld from patients even though they are far more effective than standard treatments.[72]

Contra

Certainly not everyone is convinced that decompression surgery and BoNT/A injections constitute an effective headache therapy.[73-79] Even the American Headache Society is rather sceptical.[80] During the last decade, the neural entrapment theory and its treatment options have therefore been the topic of constant debate. The study methodology, the blinding of patients and the open-label design were given as just some of the possible flaws

leading to biased results. Similarly, studies performed for types of headache that in theory are not likely to be caused by neural entrapment were referenced.[19] However, the overall non-effectiveness of BoNT/A for episodic migraine patients cannot be turned around as an argument against the entrapment theory in other types of more long-term headache or better-specified patients.

Authors of studies and reviews with negative outcomes ignored the entrapment theory completely or did not use the rationale for the effectiveness of treatment therapy as the most important factor in their work.

In our opinion, they searched for the evidence of BoNT/A, decompression surgery, and the neural entrapment theory as 'in the manner of the fabled drunkard who searched under the street lamp for his door key because that is where the light was, even though he had dropped the key somewhere else'.[81]

A scientific discussion on a paradigm shift is possible only if we truly debate and focus on the same topic and respect other points of view.

Future of decompression surgery

If a specific genotype makes the patient susceptible to headache triggered by neural entrapment of one nerve, it will probably make this patient susceptible to entrapment of other nerves as well. For assessment of treatment efficacy, this implies that if only one trigger is surgically treated, only the pain relief in that specific area or arising only from that specific nerve can be measured; for a reduction of all headaches, it will still be necessary to treat all trigger sites. The aims of studies therefore need to be optimized to allow a comparison between the effects of surgical therapy and those of medication.

Moreover, since great success has been achieved in many but not all patients after decompression surgery, there is a possibility that, in the case of failure, the surgery was anatomically 'incomplete'. This belief has instigated further research into the anatomy of the lesser and third occipital nerves, and the anatomy of multiple potential compression points along the length of nerves.[1] It is possible that even more trigger points – both different nerves and different compression points along the same nerves – will be identified in the future. Additional nerves at risk are, for example, the zygomaticofacial nerve and the auriculotemporal nerve.[42] The diagnostic criteria will be further improved with, for example, the use of Doppler. Furthermore, different surgical techniques should be assessed and compared to define which technique is the most adequate with the least side effects.

Conclusion

Decompression surgery for entrapment neuropathy may be a viable treatment option for patients with different types of headache. Especially long-term types of headache with a positive response to an anaesthetic nerve block and/or treatment with BoNT/A will benefit.

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Author Contributions

AdR was the initiator of the project and wrote the first draft of the manuscript. BF, JL, and EvdV performed thorough analysis of the manuscript and did extensive editing of the manuscript. PL was the senior author who was co-initiator of the project, contributed to the scientific discussion on the topic and helped in the final editing of the manuscript.

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