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Extracranial origin of headache

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Abstract

Purpose of review—To summarize recent clinical and pre-clinical studies on extracranial pathophysiologies in migraine. It challenges the opinion-based notion that the headache phase of migraine occurs without input from peripheral nociceptors or is caused solely by activation of intracranial nociceptors supplying dural and cerebral vasculature.

Recent findings—Data that support a scenario by which migraine can originate extracranially include (a) the perception of imploding headache that hurts outside the cranium, (b) the existence of a network of sensory fibers that bifurcate from parent axons of intracranial meningeal nociceptors and reach extracranial tissues such as periosteum and pericranial muscles by crossing the calvarial bones through the sutures, (c) the discovery of proinflammatory genes that are upregulated and anti-inflammatory genes that are down regulated in extracranial tissue of chronic migraine patients, and (d) evidence that administration of OnabotulinumtoxinA to peripheral tissues outside the calvaria reduces frequency of migraine headache.

Summary—These findings seek to shift clinical practice from prophylactically treating chronic migraine solely with medications that reduce neuronal excitability to treating irritated nociceptors or affected tissues. The findings also seek to shift current research from focusing solely on central nervous system alterations and activation of meningeal nociceptors as a prerequisite for studying migraine.

Keywords

Tension-type headache; chronic daily headache; inflammation; trigeminal; OnabotulinumtoxinA

Introduction

Pericranial muscle tenderness is common in both chronic migraine (CM) [1–4] and tension-type headache (TTH) [1, 2, 5]. Patients whose scalp, pericranial muscles and soft tissues are tender, may also perceive their headache as a tight vice around their head [6–8] and identify

the pain as originating outside, rather than inside, their cranium – a perception termed imploding headache [8]. When muscle tenderness is associated with TTH or with migraine attacks in which the muscle ache appears a few hours *before* onset of head pain, it is considered primary – postulated to originate in activation of pericranial nociceptors. In contrast, when muscle tenderness develops a few hours *after* onset of headache, it is considered secondary – postulated to be the result of pain referral by activated and sensitized second-order trigeminovascular neurons in the spinal trigeminal nucleus [9, 10]. Regardless of whether muscle tenderness is primary or secondary to the headache, the possibility that some migraine attacks and most TTHs originate outside the head depends on the identification of the causes of pericranial nociceptors activation. Historically, one can find clinical observations and philosophical remarks on the extracranial origin of migraine as early as the 2nd century AD, as in this quote from the essay “On the Affected Places” by Galen: “*Some believe that they are hit by a hammer, as it were. Others feel that the head is being pounded, or distended. It is not unreasonable that in some the meninges around the brain are affected, in others, the pericranium. Even among those who feel the pain in one half of the head, usually called hemicranics, some get the feeling that the pain is on the outside of the skull, and others, deep within the head*” [11]. Centuries later, Harold Wolff, suggested that the clinical presentation of extracranial hypersensitivities in migraineurs originate in hematomas, edema and tissue damage involving extracranial blood vessels [12]. Although Wolff’s observation was not found to be true, it directed attention into extracranial origin of hypersensitivity in migraine. This review summarizes recent anatomical, physiological and genetic evidence for extracranial pathophysiologies in CM patients.

The perception of imploding headache and its relief by extracranial administration of OnabotulinumtoxinA

There has been a novel distinction between migraine attacks in which the headache is perceived as exploding, as in a pressure buildup inside the head, and those in which the headache is perceived as imploding, like deformed, crushed or broken calvarial bones, with the pain often described as being inflicted from the outside (imploding headache) by a sharp knife or a more widely spread like a vise-like squeeze [8, 13]. This distinction gained mechanistic attention when it was demonstrated that extracranial administration of OnabotulinumtoxinA is effective in reducing the number of migraine days per month in patients who testified to having ‘imploding’, but not in those who testified to having ‘exploding’ headache (Figure 1) [8, 14]. It suggested that the pathophysiology of exploding and imploding headache differs to the extent that exploding headache is mediated by *intracranial* nociceptors innervating the meninges and sinuses of the dura, whereas imploding headache involves irritation of *extracranial* sensory fibers innervating scalp tissues such as muscles, fascia and periosteum, or perhaps the nerves themselves (due to compression, poor blood supply, or inflammation of the perineurium)

Anatomical substrate of extracranial headache

Attempting to understand better the pathophysiological meaning of these two headache perceptions, we noted that imploding headache could be preceded by several hours of neck

muscle tenderness but also by visual aura and that exploding headache could be preceded by visual aura but also by several hours of muscle tenderness. These observations have led us to postulate that the intracranial meninges and the extracranial periosteum and pericranial muscles are (somehow) connected anatomically. The search for such connections have led to the discovery of a network of sensory (peripherin-positive) and pain (CGRP- and TRPV1-positive) fibers that traverse the calvarial bones at random locations inside and outside the suture lines in young mice (Figure 2A–F) - which degenerate when the bone becomes fully calcified in the adult mice - but remain intact within the suture lines (Figure 2G–M) [15]. It was also found that many of the sensory/pain fibers that traverse the calvaria originate from dural nociceptor axons (parent axons) that bifurcated in 3 different directions - the first remained within the dura mater itself, the second crossed the subarachnoid space and reached the pia (Figure 2D), and the third followed the twisted path of suture between the inside and the outside of the calvaria to reach the extracranial periosteum (Figure 2G–I). Critical to these pre-clinical observations, similar findings were reported in human subjects where sensory/pain fibers of intracranial origin were traced between the intracranial dura, sutures, periosteum and pericranial muscles [15–17].

The identification of this network of sensory/pain fibers defined a novel anatomical substrate for conceptualizing how migraine headaches may be triggered by extracranial events such as mild trauma to the head or chronic muscle tenderness (Figure 3A). To be viable, this concept assumes that trigeminal sensory fibers are capable of conducting action potentials in both orthodromic and antidromic directions, and that pain signals originating in the periosteum, pericranial muscles, fascia surrounding nerves, or the nerves themselves, reach the spinal trigeminal nucleus through both, the above described pathway and the extracranial nerves that supply the head (dorsal, greater and lesser occipital nerves, posterior auricular, auriculotemporal and zygomaticotemporal, supraorbital and supratrochlear). (Figure 3B)

Upregulation of inflammatory genes in periosteum of chronic migraineurs: Evidence for localized extracranial pathophysiology

In an attempt to determine whether there are extracranial pathophysiologies in certain headaches, we first observed anatomically (Figure 4A) and then compared expression of gene transcripts (mRNA) that play roles in immune and inflammatory responses in the periosteum of CM patients and subjects with no history of headache[18] (Figure 5). We focused on inflammatory genes because anti-inflammatory drugs are effective in treating migraine [19, 20], and in mildly delaying the progression from episodic to chronic headaches [21, 22]. We focused on the calvarial periosteum because it is the tissue to which pericranial and neck muscles are inserted, because muscle aches can originate in their tendons [23, 24], and because it is commonly included in the perception of imploding headache (Figure 1A).

Remarkably, the targeted transcriptome analysis of periosteal biopsies revealed that patients attesting to chronic bilateral, occipital imploding headaches that are accompanied by chronic muscle tenderness have significantly increased expression of proinflammatory genes (e.g., CCL8, TLR2) and decreased expression of genes responsible for the suppression of

inflammation and immune cell differentiation (e.g., IL10RA, CSF1R) in the calvarial periosteum (Figure 5A–C). Because the up-regulated genes were linked to activation of mast cells, T cells and natural killer cells [25, 26], production of cytokines, cell adhesion, cell-cell signaling, glycoprotein production [27] and disruption of proper NF- κ B function [28, 29], whereas the down-regulated genes were linked to repression of TNF- α , IL-6, and macrophage activation [30, 31], the findings were interpreted as suggesting that the molecular environment in which periosteal pain fibers exist is inflamed and that this localized inflammation can activate, or lower the activation threshold of trigeminal nociceptors that reach the affected periosteum through suture branches of intracranial meningeal nociceptors [15] and somatic branches of the occipital nerve [32]. Further support to this scenario was provided by anatomical observation of somatic branches of the occipital nerve that appeared inflamed (white, ischemic) (Figure 4B).

At the molecular level, the most notable innate and adaptive immune response pathways activated in the periosteum of the CM patients were IL6, TLR and NF- κ B signaling (Figure 6A). To produce pathophysiology, however, it is essential that members from different pathways cross-talk to an extent that creates a biological network (Figure 6B). Of all identified members of the biological network we associated with extracranial pathophysiology of CM (Fig. 3 system boil), IL6 was most interactive, rendering this molecule most critical in ‘creating’ the headache state (Figure 6C). IL-6 signaling is a key part of the adaptive immune pathways inducing cellular and intracellular signaling cascades and producing inflammatory cytokines in response to trauma and tissue damage [33, 34]. Toll-like receptors 2 (TLR2) upregulation was also observed in the periosteal biopsies of CM patients (Figure 6D). When activated in neurons, TLR2 facilitates the production of proinflammatory cytokines in an NF- κ B dependent manner, which leads to the development and maintenance of inflammatory and neuropathic pain [35–37]. In the context of headache, activation of TLR2 has been linked to meningeal inflammation, influx of leukocytes into the meninges, increased blood flow and intracranial hypertension [38] – all capable of triggering headaches of intracranial origin. As for suppression of the NF- κ B pathway, a pathway of immense importance in the suppression of inflammation [39–42], our transcriptome data showed that it was driven by a significant upregulation of the NF- κ B inhibitor gene (NF- κ BIA) in the periosteum. We interpreted these findings as suggesting that suppression of NF- κ B activation is critically involved in the pathophysiology of the studied CM patients. Collectively, the findings point to a dual mechanism in the chronification of chronic occipital headache: the first is activation of proinflammatory pathways and the second is suppression of pathways involved in resolving the inflammation.

Other proinflammatory pathways activated in the periosteum include the granulocytes and agranulocyte adhesion and diapedesis pathways (Figure 6A). These pathways regulate the process through which neutrophils, eosinophils, basophils, mast cells, B cells, T cells and natural killer cells - which normally circulate in the blood unattached - adhere to the surface of the endothelium (diapedesis) and pass between neighboring endothelial cells (transmigration) to reach infected/irritated tissues [43–45]. In the context of CM, the invasion of extracranial tissues by these white blood cells is likely to contribute to the formation of an inflamed environment in tissues where the pain fibers exist.

This genetic study raises the idea that suppression of normal anti-inflammatory processes may be common to the pathophysiology of certain chronic, bilateral, occipital headaches. Consequently, the identified localized extracranial pathophysiology could be considered as evidence that migraine attacks can originate in pain-sensitive extracranial tissues. Although not included in that study, the findings may also be relevant to patients fulfilling diagnostic criteria for TTH as they share features such as bilateral occipital pain, muscle tenderness, perception of imploding headache, and aggravation of headache when bending the head down and stretching muscles of the neck [3, 46–48].

Therapeutic implications for chronic migraine

The identification of extracranial pathophysiologies in CM patients whose headaches are most commonly perceived as imploding [18], and the finding that imploding migraine patients are those who benefit most from prophylactic treatment with OnabotulinumtoxinA [8], gave rise to the notion that these migraines may be most responsive to therapeutic approaches that target extracranial tissues. Because this hypothesis was never tested in a randomized controlled trial, it is difficult to state with certainty whether or not such approaches are in fact beneficial. With proper caution, however, one can view the multiple reports on the reduction in the number of migraine days per month following a variety of nerve decompression surgeries [49–51], occipital nerve stimulation [52], and nerve blocks [53–55] as a reasonable assurance that extracranial pathophysiology may actually play a role in certain headaches/migraines. In fact, the biopsies analyzed in the genetic study [18] were taken from tissues discarded during occipital nerve decompression surgeries for the alleviation of chronic occipital headaches fulfilling migraine criteria. Although unblinded, the clinical outcome of these surgeries was highly encouraging – showing marked reduction in migraine frequency and marked improvement in quality of life.

Conclusion

The presented evidence for extracranial pathophysiology in migraine (and potentially other chronic headaches) bears the potential to replace the view that all migraine attacks originate in the brain and that the accompanying headaches depends solely on activation of intracranial meningeal nociceptors with a view in which these headaches can originate in the extracranial nerves themselves or in tissues they innervate (e.g., calvarial bone and periosteum, pericranial muscles, and fascia surrounding nerves) that contain abnormally high levels of pro-inflammatory agents (cells, proteins, genes) and abnormally low levels of agents that resolve inflammatory processes. The identification of inflammatory molecules and immune cells that are involved in the pathophysiology of migraine, tension-type headache (and potentially other poorly defined daily headaches) has the potential to lead to the identification of new target for future drug development. The presented data, especially those pointing to the role of novel inflammatory pathways in extracranial pathologies, bear the potential to shift clinical research on migraine prophylaxis from focusing solely on medications that act centrally to reduce neuronal excitability to medications and/or interventions that treat the irritated extracranial nociceptors or the affected extracranial tissues.

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Key points

- Not all migraine attacks originate in the brain.
- Migraine attacks associated with imploding headache and chronic muscle tenderness can originate in abnormal inflammatory processes affecting the calvarial periosteum at locations in which neck muscles are inserted.
- Muscle tenderness and periosteal inflammation may be secondary to ischemic compression of extracranial nerves.
- The ‘suture pathway’ of headache – consists of dural pain fibers that issue collateral branches to the intracranial pia and extracranial periosteum - establishes an anatomical bi-directional highway for communication between somatic and visceral tissues.
- Irritation of extracranial nociceptors by events such as mild trauma to the head, irritation of peripheral nerves, and chronic muscle tenderness can lead to activation of intracranial nociceptors and the perception of exploding headache.
- NF- κ B, IL6 and TLR2 seem to play central role in the extracranial pathophysiology of CM and TTH.

Figure 1.

Illustrations of exploding and imploding headache perception (A) and their different responses to prophylactic treatment with OnabotulinumtoxinA (B). Histograms show mean $\pm$ SEM number of migraine days per month before (gray) and after (black) treatment. Source: All panels adapted with permission from Jakubowski et al., Pain 2006; 125:286–295.

Figure 2.

Intracranial origin of pain fibers that innervate extracranial tissues such as the periosteum and neck muscles. (A–F) Nerve fibers traversing the calvarial bones in young mice. (A–B) Peripherin-labeled fibers crossing the diploë of the parietal bone. (C) CGRP nerve fibers crossing the diploë of the calvarial bones. (D) CGRP nerve fibers traversing the subarachnoid space between the dura and the pia in the calvarial leptomeninges. (E) Camera lucida reconstruction of peripherin nerve fibers in the parietal bone reconstructed from coronal sections of the head. (F) Camera lucida reconstruction of peripherin nerve fibers in the frontal, parietal, and interparietal bones reconstructed from horizontal sections of the head. (G–M) Nerve fibers in the sagittal, coronal and lambdoid sutures of the adult calvaria. (G–H) Peripherin-labeled fibers in the coronal suture (coronal view). (I) CGRP-labeled nerve fiber entering the coronal suture from the dura (horizontal view). (J–L) In vivo 2-photon imaging of TRPV1-positive axons (red) in the sagittal and coronal sutures. (J) View from inside the head. (K) View from within the bone. (L) View from outside the head. tdTomato red fluorescent protein is activated by TRPV1-cre expression. Calvarial bones and sutures appear blue because of second harmonic generation. (M) Camera lucida reconstruction of CGRP-labelled fibers in the sagittal, coronal, and lambdoid sutures of the adult calvaria (horizontal views). At this level, labelled fibers appear to concentrate

distinctly in the sutures but are absent from the diploë. Arrows point to labeled fibers. Blue areas depict bone marrow.

Source: All panels adapted with permission from Kosaras, et al. *J Comp Neurol* 2009; 515: 331–348.

Figure 3.

Peripheral innervation of extracranial structures relevant to migraine. (B) Schematic illustration of peripheral nerves that carry sensory/nociceptive information from pericranial muscles, fascia and periosteum through the greater occipital nerve (blue) and from the intracranial dura and pia and extracranial periosteum through meningeal nociceptors that travel along intracranial nerves (red, such as the tentorial nerve). (A) Possible scenario of extracranial origin of intracranial pain. In this scenario, action potentials generated at extracranial collaterals of meningeal pain fibers (1) spread antidromically to collaterals that terminate inside the cranium, resulting in local release of proinflammatory neuropeptides and activation of neighboring meningeal nociceptors (2). Asterisk marks original site of activation. Red dots represent local release of inflammatory neuropeptides. C2, second cervical dorsal root ganglion; SpV, spinal trigeminal nucleus; SSS, superior sagittal sinus; TG, trigeminal ganglion.

Source: Panel (A) adapted with permission from Kosaras, et al. *J Comp Neurol* 2009; 515: 331–348. Panel (B) was adapted from Burststein et al., *Cephalalgia* 2014 34(11) 853–869

Figure 4.

Anatomical characteristics of extracranial pathophysiology. **A.** Periosteal image of an area identified by a patient as the area where the head hurts. **B–C.** Visual appearance of symptomatic (top) and asymptomatic (bottom) branches of the occipital nerve and their surrounding fascia.

Figure 5.

Targeted transcriptome analysis showing that the occipital periosteum of chronic migraine patients whose headaches involve the back of the head and are accompanied by chronic muscle tenderness contain more genes that promote inflammation and less genes that suppress inflammation. (A) Unsupervised clustering of transcriptome data from CM patients and controls showing how dissimilar the samples from the 2 groups are. (B) Heat map of 36 significantly differentially expressed genes identified in the periosteum of CM patients compared to control subjects using supervised analysis. Rows depict differentially expressed genes; columns depict individual control subjects and CM patients. The relative expression level of genes is indicated using a pseudocolor scale from -3 to $+3$ (green represents down regulation and red represents up regulation). (C) Principle component analysis of gene expression profiling data of periosteum tissue of CM and control subjects. This analysis shows clusters for controls (green), and CM subjects (red). Note the clear separation along principle component 1.

Source: Adapted with permission from Perry et al., *Annals of Neurology* 2016; 79(6):1000–1013

Figure 6.

Functional, pathway and system biology analyses depict inflammatory pathways and genes that are central players in extracranial pathophysiology of chronic migraine. (A) Pathway enrichment analysis showing that the significance of the effect chronic migraine have on inflammation-related pathways such as IL10, IL6, NF- κ B and glucocorticoid receptor signaling. (B) Interactive network-based system biology analysis showing a very cohesive interaction ($p=e10^{-30}$) between all the molecules that are dysregulated in the CM patients. In this network, each node represents a gene and each arrow represents an interaction between genes. The red and green colors depict up and down regulation of genes, respectively. (C–D) Interactive network of IL6 and TLR2, the two top activated key regulators found to be significantly upregulated in CM patients compared to controls. In each of these networks, the central molecule is a key regulator (orange=activated, blue=inhibited).

Source: Adapted with permission from Perry et al., *Annals of Neurology* 2016; 79(6):1000–1013