Airborne Agents, TRP Channels, and Headache

Bolay and Rapoport\(^1\) depict a challenging overview on the well recognized, but still unresolved, relationship between changes in atmospheric pressure and migraine attacks.

In addressing the central question regarding the role of peripheral and central nociceptive systems in the generation of migraine attacks, Bolay and Rapoport cite articles on transient receptor potential (TRP) vanilloid 1 (TRPV1) and the ankyrin 1 (TRPA1) channels. Due to the specific expression on trigeminal sensory neurons, the research on TRP channels underscores the involvement of the peripheral component. Ethanol, recognized as a trigger of migraine attacks, lowers the threshold temperature for TRPV1 activation, and by this mechanism evokes neurogenic inflammatory responses, including meningeal vasodilation.\(^2\) In another report, a man with a history of cluster headache evidenced cluster-like attacks when exposed to the scent of *Umbellularia californica*. The observation that the attack was preceded by a sharp cold sensation in the nostril, ipsilateral to the pain, suggested a contributing role for cold-sensitive channels, TRPA1 or TRP melastatin 8 (TRPM8), the menthol receptor.\(^3\)

The ability of irritant chemicals, including ammonia, cigarette smoke, formaldehyde, chlorine, ammonium chloride,\(^4\)\(^5\)\(^6\)\(^7\) to trigger migraine attacks by targeting specific molecular targets on the trigeminal sensory nerve endings is supported by the observation that all these agents have been identified as TRPA1 agonists.\(^8\) Recently, we have found that umbellulone, an irritant volatile molecule contained in *U. californica*, as a potent TRPA1 agonist, causes meningeal vasodilation via a TRPA1- and calcitonin gene related peptide-dependent mechanism when applied intranasally.\(^9\) This finding supports the general hypothesis, first originated from the observation of a cluster headache provoked by ammonium chloride\(^5\) that, when inhaled, volatile molecules may hit specific trigeminovascular targets, thereby provoking headache attacks.

We are far from sorting out the dilemma between central or peripheral origin of migraine attacks. However, the extraordinary progress in the knowledge of ion channel localization and function in sensory nerve terminals\(^10\) offers remarkable support to the hypothesis, here expanded by Bolay and Rapoport,\(^1\) that airborne agents may cause migraine and cluster headache by targeting, via specific molecular mechanisms, the trigeminovascular system.

**REFERENCES**


Financial support: Authors declare no financial support for this manuscript.

Conflict of Interest: Authors declare no conflict of interest.


Harry Potter and Nummular Headache

In light of the recent culmination of the Harry Potter film series, we have recently reviewed the excellent differential diagnosis provided by Sheftell et al1 and augmented by others for Harry’s headache disorder, which includes probable migraine,1 symptomatic trigeminal neuralgia,2 scleroderma,3 and supraorbital neuralgia.4 With the addition of the final installment of J.K. Rowling’s series,5 we believe that Harry’s described headache history may be more consistent with an alternative diagnosis: nummular headache (NH).

Harry’s circumscribed headache location in the distribution of his lightning bolt scar would appear to fit the proposed criteria in the appendix of the International Classification of Headache Disorders, 2nd edition6 for NH. The criteria specify pain exclusively felt in a well-circumscribed region of 2 cm to 6 cm, round or elliptical in shape, either continuous or interrupted by spontaneous remissions lasting weeks to months. We understand through Rowling’s series on Harry’s teenage years that his headaches began in his 11th year, following a traumatic head injury in childhood surrounding the murder of his parents. His headaches were characterized by several months of spontaneous remissions, and as per the epilogue in the 7th book,5 were completely remitted by the age of 18. Rowling describes searing and burning pain along the finite region around Harry’s scar as the major feature of his headache, which is not inconsistent with the NH pain character. Depictions of the scar in the artwork on the book covers, as well as in the film series, show that the area of the scar (and thus, the area of the pain) is certainly confined to an area with a maximal diameter less than 6 cm. Although a frontal location of pain in NH is less common than other regions of the head, a sizeable minority of NH patients do experience pain in that location.7

Sheftell et al discussed the possibility of a secondary headache disorder, given the apparent causal relationship between Harry’s headaches with proximity to Voldemort. This hypothesis is supported by evidence that Harry’s headaches have remitted completely with the destruction of Voldemort, suggesting that perhaps Harry has suffered from secondary NH.

Secondary, or symptomatic, NH is not a well-described entity, but post-traumatic cases are now being reported. In Pareja’s 2 NH series, 5 of 27 (18.5%) of NH cases had head trauma preceding headache onset.8,9 In his second NH series, up to 9% of NH patients reported a history of remote head trauma,9 as did Harry Potter. Our center has recently reported a series of 35 NH patients, of whom 6 had post-traumatic NH and 2 had post-surgical NH (craniotomy),10 although all of these patients experienced NH onset immediately after cranial trauma. A frontal location of NH in this group was common, and 1 patient had NH onset at age 13.

Trophic skin changes have been described to occur in painful scalp regions of NH patients, although admittedly, none of these cutaneous lesions manifested in the shape of a lightning bolt. In a 3-year period where 59 NH patients were encountered at 1 center, 5 (8.5%) had trophic skin changes in the region of the pain, 2 of whom experienced the onset after head trauma or an insect bite.11

The major essence of Harry Potter’s headache disorder is that it is post-traumatic, severe, and well circumscribed, most consistent with NH. As a relatively recently described headache phenomenon, NH has mostly been described in an older patient population with a female predominance. However, larger series indicate that adolescents may experience NH.9,10,12 As its true prevalence and incidence are uncertain, its relative lack of reporting among this age group may be attributable to underrecognition rather than a true absence of NH in this demographic, underscoring the underrecognition of headache in the pediatric population in general, a major emphasis of Sheftell et al that we agree with wholeheartedly.
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