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Case Report

Switchman Hypothesis: A Novel Therapy Based on Trigeminal Nerve Stimulation by Sneezing for Management of Migraine Headache

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BACKGROUND: Several lines of evidence have shown that the trigeminal nerve plays a central role in pathogenesis of migraine headache. In the current study we are trying to provide an effective treatment for migraine headache based on switchman hypothesis of the trigeminal nerve. In this hypothesis, the trigeminal nerve is like train railways where a switchman is on the way; that is why it can only transfer one neural message at once.

CASE PRESENTATION: We hypothesized that trigeminal nerve stimulation will result in decreased number and severity of the migraine headache attacks. We share the experience of two patients with chronic migraine headache who used pepper to suppress their attacks. Patients experienced suppressed migraine headaches in 72% and 87% of the attacks and the intensity of the pain was extremely lower in the rest of the attacks.

CONCLUSION: The switchman hypothesis could be an effective and safe therapeutic basis for developing targeted therapies for migraine headache and attacks. Further clinical studies are required to shed light on the issue and evaluate the safety and efficacy of different modalities.

KEYWORDS: Management, Migraine headache, Pathophysiology, Switchman hypothesis, Trigeminal nerve.

INTRODUCTION

A large and growing body of literature has addressed the pathophysiology and mechanisms of the migraine headache, but the exact mechanisms of this type of headache remain elusive.[1] The brain is globally considered an insensitive organ; albeit, the meninges (dura and leptomeninges) and the bony structures are considered sensitive to the painful stimuli.[2] Small-caliber trigeminal axons are highly innervating the meninges, some of which bifurcate in proximity to small blood vessels branching from the middle cerebral (pial) and middle meningeal (dural) arteries.[3] The trigeminal axons contain densely packed granules of peptide neurotransmitters, especially the substance P, which modulates the nociception.[4] There are some testimonies in the literature of a trend that indicates that the trigeminal nerve plays a central role in the pathogenesis of the migraine headache.[5-9]

The sneeze reflex, regarded as a protective reaction belonging to the aerodigestive system, is generated by two main nociceptive afferent terminals of the trigeminal nerve (A delta fibers and C fibers) in the nasal mucosa.[10] Direct stimulation of trigeminal nerve complex or parasympathetic stimulation by a region located in the posterior hypothalamic zone triggers the sneezing.[11-13] Many conditions, including mechanical stimulation of the trigeminal nerve, satiation reflex, orgasm, sexual ideation, bladder fullness, light, pathology of central nervous system (CNS), or even using the local anesthesia in ocular operation have been considered as potential triggers of sneezing reflex.[10] Van Oosterhout and his co-workers coined a crucial paper in 2013 regarding a 28-year-old gentleman who suffered from 3 acute headache attacks after sneezing. They concluded that this patient's eye-catching stereotypical attacks were a "migraine without aura after sneezing." They postulated that sneezing might be a premonitory epiphenomenon rather than the trigger for the attack itself. Sneezing is a consequence of heightened brain sensitivity in the prodromal phase.[14] Back in 2019, the study of Sasayama et al. proposed the hypersensitivity of the trigeminal nerve as a mechanism for the photic sneeze syndrome (a condition in which sneezing occurs as the consequence of eyes exposed to sunlight), which could theoretically overlap with the pathophysiologic basis beyond migraine headache.[15]

With this, we propose our idea, the switchman hypothesis, considering the trigeminal nerve as the common executioner between sneezing and migraine headache.

The switchman hypothesis

The brain is traditionally known as an insensate organ, but the meninges are among the few pain-sensitive tissues within the cranium. Despite species differences in brain size and organizational complexity, trigeminal innervation appears remarkably similar in mammals

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such as the rat, cat, and human. It also contains the same constellation of peptide neurotransmitters.

There is an interesting behavior of the trigeminal nerve that can be used as novel management for migraine headaches. The trigeminal nerve has three main branches that we consider as train railways. The maxillary railway can transfer sneezing messages to the brain, and the mandibular railway can transfer the migraine headache massages. Different branches of the trigeminal nerve come together and are unified in a specific point that our "switchman" is standing steadily. Any of the nerve branches that are activated earlier would consequently reach the switchman sooner. When a train comes first it dominates the railway; the other must wait and not move on. In other words, if we stimulate the sneezing action at the beginning of the migraine aura, sneezing pathways would be activated, and migraine headaches do not initiate. Nevertheless, if we let the aura alone and the headache starts, then we cannot stop it until it ends; the point is that we cannot sneeze even if we stimulate it via stimulants such as pepper. One concrete evidence behind this scenario is the fact that if we observe a patient with migraine headache as an innocent bystander, they could not sneeze after the aura initiates, no matter how hard he/she tries to trigger it. We call this the switchman hypothesis, as if the trigeminal branches are like railways and a switchman is on the way to manage the trains carrying messages **(Fig. 1).**

CASE PRESENTATION

We want to share our own experience with two patients with chronic migraine headaches. They were evaluated during 100 consecutive migraine attacks for each. We observed the hypothesis that pepper inhalation would induce sneezing, which is the trigeminal nerve's motor response leading to the suppression of the migraine initiation and propagation. Patients reported a suppression rate of 72% and 87% of the attacks, whereas the headache intensity was significantly lower during the rest of the attacks when questioned based on the visual analog score. This hypothesis could be fundamental for developing management and therapeutic strategies for migraine headaches.

DISCUSSION

The primary trigeminal nerve afferents connect to nucleus caudalis or so-called spinal trigeminal nucleus and meningeal vasculatures via the trigeminal ganglions. A rich amount of Calcitonin gene-related peptide (CGRP) exists in the ganglion mentioned above, and it is released from either central nerve terminals or from peripheral neural structures in addition to the trigeminal ganglion. CGRP neuropeptide's secretion leads to the incremented sensitization of the trigeminal fibers and nitrous oxide (NO) synthesis from the peripheral terminals. The released CGRP also impacts proximate neurons

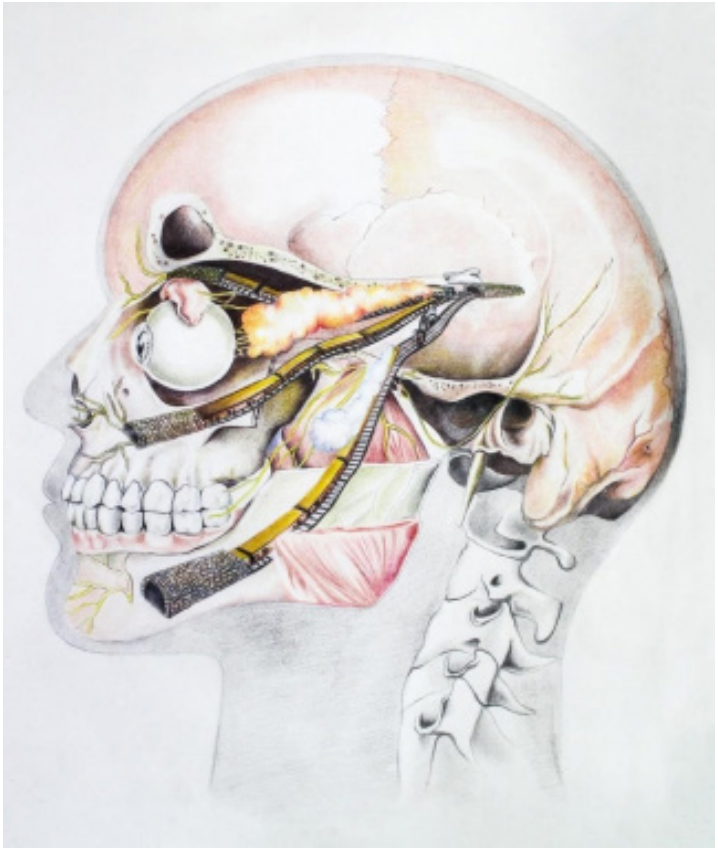

Fig 1: Switchman hypothesis; Trigeminal nerve tracks as train rails. There is a switcher on the way. If the migraine train starts moving, then the sneezing one cannot move; however, if we push the sneezing train to move forward, the migraine's way will block.

comprising amphicytes (satellite glial cells) and second-order neurons, including the last-longing peripheral/central sensitization of these neurons. A movement resulted from action-dependent to action-dependent central sensitization might suggest that how chronic migraine can result from episodic migraine.[16]

Almost 15-20% of the public present with migraine headaches, a chronic neurologic abnormality accompanied by severe episodic attacks, aura, nasal senilities, photosensitivity, and nausea. According to the World Health Organization (WHO) reports, it also affects sleep disturbance, stress emotions, and other disabling chronic disorders such as dementia, quadriplegia, and psychosis.[5,16,17]

Bhutta and his colleagues stated that the parasympathetic nervous system plays a crucial role in inducing sneeze in situations like the fullness of the stomach, orgasm, photic sneezing, or even bladder fullness.[11-13,18-20] Following the trigeminal nerve or parasympathetic nervous system's stimulation, exciting the posterior hypothalamus has been claimed to trigger sneezing.[21] Afferent neural stimuli transmit to the trigeminal ganglion via anterior ethmoidal, posterior nasal, infraorbital, and ophthalmic branches of the trigeminal nerve. Through the trigeminal ganglion, the stimuli reach the sneezing center in the lateral medulla.[22] In explaining the pathophysiology of sneezing, Maniyar conceded that the hypothalamus provokes the parasympathetic or trigeminal nerve. Sneezing can also be triggered via deep brain stimulation of the posterior hypothalamic zone for conquering cluster headaches. The hypothalamus is responsible for a partial latency within migraine headache and sneezing by direct stimulation of trigeminal fibers, unrelating to the peripheral provocations.[19-21] Although the trigeminal nerve is responsible for developing migraine headaches by innervating the meninges, the underlying mechanism is incompletely understood and still is regarded as controversial.[5]

Nowadays, current available pharmacologic therapeutic options (e.g., nonsteroidal anti-inflammatory drugs (NSAID) or analgesics) are not satisfying anymore, mainly due to several side effects, headache chronification by excessive consumption of acute migraine medications, incomplete efficacy, and portending unfavorable outcomes. Furthermore, traditional migraine medications might lead to therapeutic resistance, especially in those who suffer from chronic migraines. Consequently, these limitations demand more attempts to find a non-pharmacological target therapy for those suffering acute migraine headache.[16,23-27] In a recent open-pilot trial, it was mentioned that effective impacts accompany external trigeminal nerve stimulation (e-TNS) and consequently could be used as a reliable therapeutic approach for acute pain-relieving and prohibiting the episodic migraine during migraine attacks.[23,28,29]

CONCLUSION

In the present study, we tried to establish a significant association between snuffing-induced sneezing and migraine headache with aura by showing that the trigeminal nerve serves as a "switchman" who determines which mechanism should be triggered whereby we can prevent the migraine attacks by triggering the sneezing pathway.

Nevertheless, the current hypothesis is still raw and demands reliable confirming, open-label trial and double-blinded trial to become a theory.

List of abbreviations

CGRP: Calcitonin gene-related peptide.
CNS: Central nervous system.
e-TNS: External trigeminal nerve stimulation.
NO: Nitrous oxide.
NSAID : Nonsteroidal anti-inflammatory drugs.
WHO: World Health Organization.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this paper.

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