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Research Article

Does Sneezing Play a Role in Multiple Sclerosis?

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Abstract

Objectives: The modern era of multiple sclerosis (MS) biomarkers has been ongoing for many years, with the periodical approval and renewing of MS criteria we are still facing many challenges. The new revision was recently approved, a few years after McDonald's Criteria, it was also followed by a promise to find new landmarks for the establishment of an MS diagnosis and its courses. An innate immunological clinical sign - which can better connect the suspected etiology and the disease is of major interest.

Data Sources: A literature search was performed using medical and health science search engines to find publications from January 1940 to December 2019.

Data Extraction: Data were extracted if any of the following keywords were mentioned in combination: sneezing, MS, stroke, biomarker, the nasal cavity. The search was expanded to the medical conditions included in this study.

Data Synthesis: Sneezing is a very clear sign and health reaction which has never been studied in MS and may potentially have a clinical impact. The sneeze function can, through other diseases and life events, teach us its importance and common understanding with MS. This review will focus on the sneeze in different medical conditions and use these comorbidities as a proxy to understand inflammation and their association with MS.

Conclusion: Sneezing is one of the common health reactions against pathogens, allergens, temperature changes, lightning, and cerebral injuries. This study has found a sign that sneezing has an untold role in MS and comorbidities such as a stroke. Measuring sneezes has the potential of becoming a clinical biomarker in MS.

Keywords: Sneezing; MS; Stroke; Biomarker; Nasal Cavity

Abbreviations

MS: Multiple Sclerosis; CNS: Central Nervous System; MRI: Magnetic Resonance Imaging; TGN: Trigeminal Nerve; TNC: The Nasal Cavity; NFL: Neurofilament Light; RRMS: Relapsing-Remitting MS; BT: Body Temperature

Introduction

Multiple sclerosis (MS) is an immune-mediated central nervous system (CNS) disorder characterized by neuroinflammation and neurodegeneration, the onset of which usually occurs in young adulthood, however, this has not been fully clarified etiologically.

Biomarkers, as a clinical sign of disease or investigational findings, have been periodically revised to define a more liberal and solid framework for the establishment of MS diagnosis as well as MS courses. Despite its innate immunity character with mechanical barriers and major brain defense reaction, sneezing is not mentioned in MS criteria [1]. There is also too little published about the role of sneezing as a potential sign or clinical biomarker of MS, or conversion from one MS course to another.

The association of sneezing in other medical conditions can support the impact of this most frequent reaction of the nasal cavity (TNC). A wide spectrum of diseases with viral (COVID-19) [2], immunological and genetic triggering mechanisms is associated with sneezing and it makes sneezing a candidate proxy to get insight into pathogens contributing to MS etiology. Sneezing refers to a primitive physiologic reflex, usually in response to the irritation of the respiratory epithelium lining of the inner nasal cavity to evacuate droplet nuclei or aerosol [3]. This irritation can be caused by an allergen, a simple involuntary hygiene practice, respiratory infections such as a cold or the flu or even spicy food. Furthermore, a sneeze can occur in response to trigeminal nerves (TGN) nasal cilia irritation in the conchae or autonomic stimulation. The 'sneeze center' is believed to be located in each rostral lateral medulla proximal to the interpolaris-caudalis area of the trigeminal spinal tract and nucleus [4]. The signal of nasal stimulation of small hairy unmyelinated afferent C-fiber of the ophthalmic nerve will arrive in the trigeminal ganglion and the transmitted information will travel to the CNS through the trigeminal dorsal horn in the lateral medulla and lead to sneezing. It's also said that many distal branches of the anterior ethmoidal and the maxillary nerve terminate in the nose, facial skin, and nasal mucosal epithelium in order to transmit tactile, pain and temperature sensations [5]. The nasal epithelium contains four major cell types including basal cells, ciliated cells, non-ciliated columnar cells and goblet cells [6]. The neurochemical signal transmission - involving peptides and tachykinins which depends on odds triggering substance P - is the most potent releasing factor of the sneezing response [7]. There are gender differences when analyzing the TGN's myelinated axons and nerve volume, as women present smaller values. Furthermore, the comparisons of the diameter of the cisternal portion of the TGN reveal significantly smaller left TGN volumes in women as compared to corresponding findings in men ($p < 0.0001$) [8], when using 3.0 Tesla (T) magnetic resonance imaging (MRI). Previous studies have pointed out, that even in general, the left-sided mean volume of TGN diameter is smaller: right nerves 0.093 cm^3 (0.055-0.147 cm^3) and left nerves 0.091 cm^3 (0.057-0.142 cm^3), when using MRI at 1.5 T [9]. This volume difference is probably associated with delayed sneezing from each nostril. Furthermore, heart rate alteration is described as being significantly different in genders, when the TGN is stimulated in women as compared to men. However, no study has yet been performed to analyze the TGN's function or sneezing with gender differences in MS.

To explain why sneezing and MS are probably associated with each other, we need to consider the common site of data by searching in other comorbidities and pathophysiology, which is suggesting sharing commonality for both sneezing and MS.

Materials and Methods

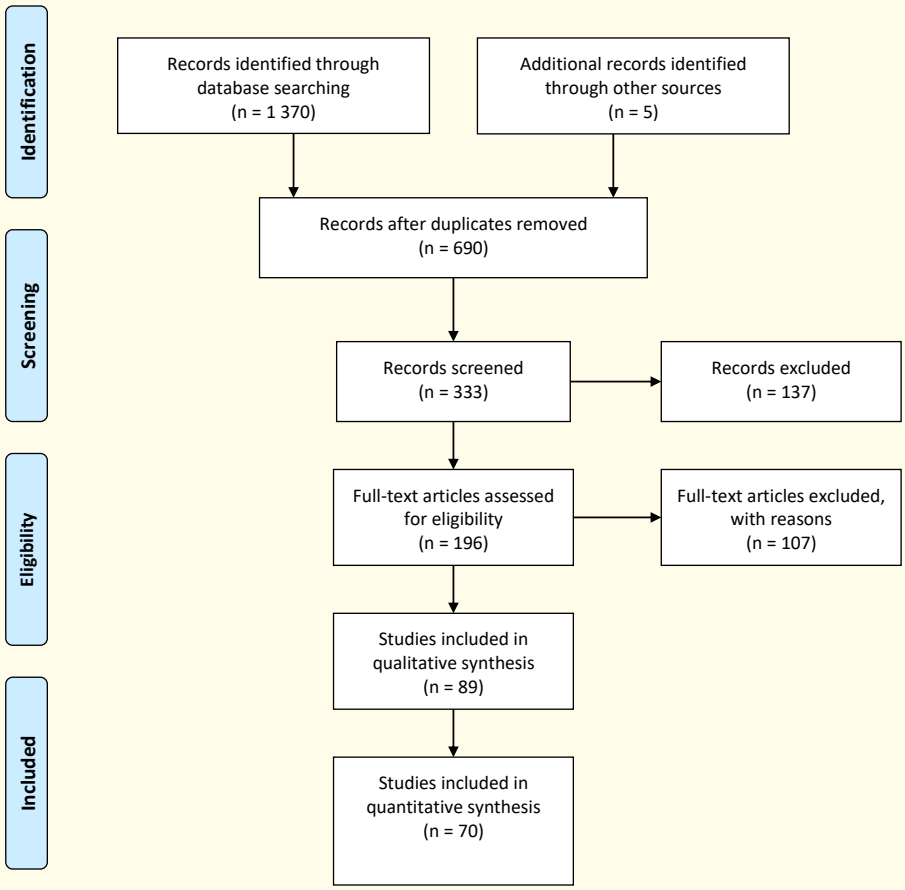
An interdisciplinary search following international medical guidelines for reviews was conducted, to incorporate the most up-to-date evidence the following data sources reached.

Data sources

The literature was reviewed using MEDLINE, Google Scholar, and any other online scientific library search of the following keywords: sneezing in combination with, TNC, TGN, stroke, psychogenic intractable, paroxysmal, autoimmune, respiratory disorders, gastrointestinal disorders, urinary tract, food allergy, habit, mast cells, spasticity and MS. The search was restricted to articles published from January 1940 to December 2019, although older references were cross-referenced if mentioned in recent publications. This review will focus on the factors that contribute to the sneeze, inflammation and association with MS and comorbidities.

Results

The result is displayed in PRISMA diagram. Sneezing, MS and stroke were searched for according to the description above. The same procedures were performed for each section and included in the search method and generated 1,375 hits. The hits containing a tumor, bleeding, or a publication without an abstract were excluded.



PRISMA diagram

Definition and epidemiological association

The innate immune response of sneezing depends on the number of aerosols expelled during a free forceful sneeze, which is estimated to be 40,000 blood droplets. The estimated velocity of the air coming up from the lungs during a sneeze varies between 150 km/h and 1,045 km/h, and it can reach nearly 85% of the velocity of the sound. This powerful innate immunological reaction cleans the major part of proximal airways of airborne debris pathogen bearing droplets are propelled much farther than if they were emitted in isolation without a turbulent puff cloud [3]. The daily sneezing frequency is age-dependent, and probably also due to environmental and genetic factors. In patients with MS (PwMS), we can only track associations when information has been mentioned in the published data. In other medical conditions, some studies have described sneezing as an outcome. These findings are given as the following.

Association of sneezing in MS

In a review of Lhermitte's sign in PwMS, radiation of the sensation was described as precipitating factors with sneezing, however, this was found only in one case out of 114 who reported sneezing and deteriorated sensation [10]. In some cases, sneezing was described as the provocation factor when the patient began to have severe pain along the branches of the TGN [11]. Another study was aimed at sneezing and its association with MS while focusing on high levels of sanitation in the environment. Sneezing was men-

tioned in the questionnaire, however, no data was presented about sneezing in MS patients [12]. In a similar study for measuring environmental sensitivities in autoimmune diseases (AID) 'inclusive MS', sneezing was given as the first symptom in approximately 90% of cases [13]. In some MS studies, occasional sneezing has been reported after exposure to therapies.

In an innovative phase I drug test in PwMS, the follow-up of cases showed some new attacks. Nine months after the study was conducted, one of the patients showed a relapse manifested by a painful pulling sensation in the left chest while sneezing. This was the only time sneezing was mentioned as an attack symptom and was not mentioned in other parts of data analysis [14]. In another study, sneezing as the first attack was associated with abnormal high-intensity lesions in the spinal cord at the cervical, where the trigeminus nucleus is located in the spinal cord [15]. The attention to sneezing is lowered, when a study did not find any association of airway diseases with MS, whereas respiratory tract allergies including allergic rhinitis and asthma decreased the lifetime risk of MS as well as allergies to food or drugs [16].

Autoimmune disease

There is a common site for all the autoimmune diseases (AID), including MS. A major part of AIDs have an unknown or not fully understood etiology and are, for the most part, more frequent in females. A literature review shows that AID implies separating into three groups, depending on how they are described with the frequency of sneezing: high, normal, lacking of sneezing frequency. Persistent sneezing is common in Wegener's granulomatosis which, by its inflammation, targets the nasal concha [18], arteries, veins and capillaries of the kidneys and the respiratory system and meninges. Another rare disease confined to frequent sneezing is Churg-Strauss syndrome (CSS). CSS is also a granulomas disorder that is characterized to affect multiple organ systems, especially the lungs and widespread vessels in the respiratory system. This disorder is defined by abnormal clustering of serum hypereosinophilia and vasculitis. 78% of individuals with CSS may suffer from peripheral or central neurological symptoms including polyneuropathies and fatigue [19]. It seems that the TGN's involvement is highly confined to sneezing.

Both AR and autoimmune thyroid disease (AITD) result from similar responses of the immune system and both conditions relate to one another with a high manifestation of daily sneezing [20].

In rarer cases of neuromyelitis optica spectrum disorder (NMOSD), significant lesions in the medulla oblongata have been associated with paroxysmal sneezing attacks [21].

In contrast, in other AIDs such as Lupus, the sneezing is diminished and suppressed with ongoing breathing symptoms or pain and wounds in the nasal layer. Systemic Lupus Erythematosus (SLE) primarily affects women, with a gender bias of 9:1, which has been attributed in part to estrogen receptor 1. However, the presence of autoantibodies in patients - including anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm and anti-RNPs - suggests that a common mechanism is involved in the peripheral expansion of autoreactive B cells that has yet to be delineated fully. In AIDs with meningeal spreading, the sneezing rate is highest [19]. In PwMS, there is a striking spatial relationship between meningeal inflammation and grey matter lesions. The data from both human and mouse studies support the concept that meningeal inflammation is an unavoidable and perhaps necessary prelude to leukocyte infiltration into the CNS in PwMS [22], however, we are lacking information on sneeze symptoms in MS prior to diagnosis or after MS diagnosis.

Type I diabetes (T1D) is also accompanied by a decrease or lack in the frequency of sneezing, as the level of blood glucose is well controlled. The finding is revealed to be that rhinitis and T1D are associated negatively with smokers ($P < 0.001$), age ($P = 0.004$), leukocyte counts ($P = 0.013$), systolic blood pressure ($P = 0.034$), frequency of exercise ($P = 0.041$), and fasting plasma glucose ($P = 0.0478$) [23].

Stroke and transient ischemic attack (TIA)

There are some studies, which agree that MS and stroke are positively associated [24]. In stroke patients with localized infarction in the medulla, the sneezing reflex is declined in the opposite nasal tissue side as compared to the unaffected side [4]. In the transient ischemic attack (TIA), sneezing has been described as a protective warning and the first warning sign before the appearance of other well-known stroke signs [25]. Vertebral artery dissection has been responsible for many different health events, such as sneezing. Paroxysmal sneezing at the onset of the lateral medullary syndrome (LMS) or Wallenberg's syndrome, is usually interpreted as a cause of a vertebral artery dissection. There is also a case report which shows that due to the inactivity of the sneezing center in LMS, the ability to sneeze is lost [26].

Studies are suggesting that comorbidity of ischemic stroke for PwMS is likely valid and common symptoms can overlap in both conditions. Despite this report, there is also a report on sneezing in distinguishing subclass of stroke conditions [27], but we are lacking information about this symptom when studying MS and strokes.

Poststroke effects of sneezing

When a group of rats is forced to sneeze, the infarct volume and brain edema can be reduced, and some parts of neurological deficits improve as compared to the male rats subjected to middle cerebral artery occlusion. This achievement was most significant in the group which showed both ischemic and nonischemic brain edema. The highest protective effect was observed in the central region of the middle cerebral artery territory [28], however, this effect has not yet been studied in humans.

Body temperature (BT)

A change in temperature is one of the most common things that cause people to sneeze. Strong scientific evidence shows that sudden changes in temperature can trigger symptoms like those seen in the rhinitis group. In addition, both hot and cold temperatures were associated with a significant decrease in expiratory flow rates and regulated BT by the TGN [29].

In MS, both high and low outside temperatures prove to be uncomfortable as symptoms get worse and increase fatigue. An estimated 60 - 80% of MS patients experience a temporary worsening of clinical signs and neurological symptoms with heat exposure [30], further exacerbations of MS symptoms are most common in warmer months [31]. In 1800s Wilhelm Uhthoff described this phenomenon which occurred after a thermal activity in PwMS. Nowadays, the deterioration of optic neuritis symptoms is most commonly known as Uhthoff's phenomenon and is BT dependent. A single sneeze or several sneezes at once, without a known body temperature, has been said to worsen spasticity, however, there is no published study measuring these signs.

Migraine

Some reports suggest that sneezing is common with migraines or is predominant before the migraine attack [32]. Chronic sneezing has been confined with more chronic episodes of migraines and 70% of individuals with migraines meet the criteria for a case definition for rhinitis [33]. A migraine attack is suggested to be caused by the activation of peripheral or central trigeminal nociceptors or central sensory pathways, which lead to more frequent or severe attacks. Activation of the branches of the TGN leads to the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and some other neuropeptides that cause dilation and possibly neurogenic inflammation of dural blood vessels and engaging of nociceptive receptors in the TGN and then transmitting this pain to the receptors in brain-stem nuclei, thalamic nuclei, and the cortex [34]. The positron emission tomography (PET) brain imaging of ongoing migraine attacks illustrated an uptake of tracers at the dorsal midbrain, including the periaqueductal gray (PAG), and in the dorsal pons, near the locus coeruleus [35], roughly the same pathway was previously described for the sneezing reflex.

Migraines are not classically included in clinical topographies of MS, although it is 2 to 3 times more common in PwMS than in the general population. There are also studies reporting rates up to 69% of the overlapping of migraines and MS [36]. Furthermore, in various animal models of TGN-associated disorders, the concentration of CGRP is increased in TGN. In most of these models, pathological changes in the trigeminal system are accompanied by inflammation within peripheral neuronal endings of the TGN, with a significant difference in CGRP expression in female mice. When analyzing age demographics, it seems that PwMS and migraine patients are predominantly younger females and have a shorter disease course than patients in a comparison group with neuropathic pain. There is also a higher overall frequency of any type of headache in MS patients compared with the non-MS population [37]. Despite this, migraines have a negative effect on the outcome of MS and they have some pathophysiologic commonality, however, there is no data about the sneezing frequency in MS patients with migraines.

Rhinitis

Sneezing is a common symptom of both allergic rhinitis and non-allergic rhinitis.

Allergic rhinitis (AR) is when an external factor is identified as a trigger for the nasal or other respiratory reactions, accompanied by frequent sneezing and triggers an immunoglobulin-E (IgE)-mediated immune response. AR is often diagnosed early in life and has a good response to allergen sanitation. Furthermore, in AR, immunologically triggered inflammation results in the recruitment and activation of both types of fiber that cause itching and sneez-

ing [38]. Genetic and phenotypic correlations of CD39 variants have been associated with allergic rhinitis and revealed a strong association with MS as well [39]. Some studies have explored the association between low serum vitamin and AR, which had a sneezing frequency of 95% [40]. The low level of vitamin D is also suggested as being a risk factor for MS [41]. Furthermore, treatment with mesenchymal stem cells possesses significant immunomodulatory effects in both AR [42] and MS [43]. Despite these findings, no data on sneezing has been registered for these conditions.

Non-allergic rhinitis (NAR) involves nasal hyperreactivity with chronic sneezing or a rhinorrhoea with no apparent exacerbation factor. It is more common after the age of 20. Triggering factors of NAR symptoms vary and can include certain odors or irritants in the air, changes in the weather, medications, certain foods, and chronic vasomotor rhinitis [44]. Demographical data have suggested that a history of rhinitis was observed in 37.5% of patients with MS [45]. Furthermore, some studies have reported no statistically significant association between MS and allergic diseases, allergic rhinitis, asthma, or eczema. However, there is no direct data about sneezing frequency in MS and NAR [46].

Sinusitis

The association of infection of the paranasal air sinuses and MS is being previously reported [47].

Sinusitis is often an isolated condition; however, it can follow a common cold or simple flu or show a chronic course depending on maxillary, frontal or ethmoidal sinus involvement. Chronic rhinosinusitis disease is usually bacterial rather than viral [48]. Sneezing is often infrequent if there is only bacterial rhinosinusitis with thick yellowish-green nasal secretion with nasal congestion, facial tenderness, headache, fatigue, and fever [49]. The common cold is simply overwhelming with prodromal sneezing compared to the flu which gives the patient less trouble with sneezing, however, both conditions may turn into sinusitis [50]. Acute sinusitis that follows an upper respiratory tract infection may cause facial pain [49]. It may be a sign of the engaging of the TGN terminal to mobilize immune response around the CNS.

Some studies found that the prevalence of radiologically diagnosed sinusitis in MS was 55% in both cases and controls [51]. The hypothesis that MS is spread by an infection in close proximity to the CNS [52] was tested by studying the MRI of 100 PwMS. The MRI was retrospective, blinded, substantiated, performed and compared to an age and demographically matched control group (n = 100). The study included an MRI of the mucosal pathology of the ethmoid and sphenoid sinuses. There was a 21% higher prevalence of sinusitis in the MS group, however, no significant association was confirmed, even though this study did not include maxillary sinusitis [23] or conchae nasalis.

Common cold

The common cold confined with massive sneezing in humans and is caused by a specific viral agent which is an unsolved puzzle in MS etiology [31]. Studies with mice infected with influenza A showed that they develop symptoms similar to those seen in PwMS. The upper respiratory symptoms are common in MS and can - in 27% to 42% - increase the risk of relapse within the first week. Besides, some reports suggest that relapses occurring around the time of infection are associated with sustained deterioration. The pathogen explanation behind influenza A virus's role in MS comes through activated trafficking immune cells from the peripheral blood to the brain [53]. The experimental results also showed that the respiratory infection by influenza A virus can create potentiating immune cells by CXCL5 which is defined as a mast cell signaling pathway to the CNS [53]. Even though the common cold is confined with sneezing, similar symptoms have not yet been reported for MS.

Coronavirus

The COVID-19 in majority attaches to proximal and nasal respiratory airway [3] and it should come to the MS focus with results from that study which discussed the association with TGN biopsy and coronavirus. T cell clones from patients with MS have been shown to react with both HCoV229E antigens and myelin basic protein, suggesting molecular mimicry as a basis of pathogenesis [54]. The PwMS may be of more harm by COVID-19 as some 36% of investigated COVID-19 cases are presenting some central or peripheral nerve system affected signs [55].

Pregnancy

Pregnancy in PwMS remains an unsolved puzzle. There is a general consideration that women sneeze more during later gestational weeks. This condition is called pregnancy rhinitis and can be found in 39% of pregnancies. Pregnancy rhinitis is described as sneezing, a runny nose, and stuffiness, even with no known allergic

cause or delivery [56]. These symptoms are correlated to increasing levels of serum sexual hormones where blood flow to the mucous membranes increases and, accordingly, the membranes swell and sneezing is triggered. The condition is self-limited and revealed immediately within 2 weeks after partum [57]. In MS, some sensory symptoms improve during pregnancy. However, other symptoms may worsen, such as fatigue, balance and bladder symptoms, particularly in the later stages of pregnancy. Bell's palsy and entrapment neuropathies, for example, carpal tunnel syndrome and meralgia paraesthetica, are more common in late pregnancy and may cause new symptoms and not count as an MS relapse [58]. Postpartum risk of relapse increases 2 weeks after delivery [59], and no data on sneezing in pregnant MS patients have been published yet.

Epilepsy

Like the protective nature of a sneeze there have been rare reports of peri-ictal sneezing. In a couple of cases from older epilepsy literature, sneezing was described as epileptic post-ictal, however, there are sporadic case reports of patients with clusters of sneezes after a left temporal seizure [60].

In MS, partial seizures - with or without secondary generalization - appear to be more common [61], however, no information on sneezing has been registered, or if it has a shared signal between MS and epilepsy, it has not yet been published.

Photic sneeze

In 1875, Watson described the first cases of photic sneeze reflex (PSR) that were associated with mechanisms correlated to the sensitivity of the TGN. In recent years, genetic studies have suggested that sneezing caused by light or the sun could be autosomal compelling helio-ophthalmic outburst (ACHOO syndrome) [62]. PSR is used for a more global form of PSR. This condition can be triggered in response to other stimuli as well, such as looking at bright lights or periocular (surrounding the eyeball) injections. The frequency of affected people is high, 18 - 35% of the population in the United States, predominantly female with other family members with the same clinical character. The majority of this population (90.7%), three times or fewer, sneezes following light exposure [63]. We lack data about this issue in MS, however, an indirect interpretation of data can send us the message that PwMS are suffering from vitamin D insufficiency. It could indicate an association between less sunlight exposure and the risk of developing MS, given the immunological effects of sunlight exposure, either through UV radiation or vitamin D, the metabolism is affected, probably in association with PSR.

Psychogenic

Psychogenic sneezing is also recognized in both intractable and pure psychogenic form. In majority, the intractable form is associated with a stereotypic situation and an external substance, whereas sneezing is usually refractory to various medications and has an otherwise unremarkable extensive check-up [64]. In a rarer condition, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), sneezing is an almost predominant symptom [65]. The association of these conditions in MS has not yet been studied.

Gastrointestinal

Snatiation is a combination of the words 'sneeze' and 'satiation'. The stretching of the stomach causes people to sneeze uncontrollably after excessive nutrition [66]. This reflex refers to an autosomal dominant inheritance pattern [67]. Furthermore, many spicy or cold foods can also trigger a series of sneezes. The mechanism is described as neurogenic gustatory rhinitis and various types of gustatory rhinitis are described, including age-related, posttraumatic, and postsurgical and associated with cranial nerve neuropathy. The neurogenesis specific nerve induction is not fully understood, however, it could be associated with a parasympathetic reflex and activation of cholinergic muscarinic receptors which are sensitive to atropine [68]. Recent data are displaying that food allergies are more common in relapsing-remitting MS (RRMS) and have a 1.38 times higher rate for the cumulative number of attacks compared with the unknown allergies group (P = 0.0062). This difference remained significant in the adjusted analysis and shows a still higher relapse risk of 1.27 (P = 0.0305) [69]. Despite data demonstrating a high prevalence of food allergies, dysphagia and defecation disorders in PwMS, these studies only include coughing or other symptoms of allergies (hives, itching, nasal congestion, rashes, watery/red eyes, tingling or itching in the mouth, swelling (tongue, lips, face, throat or other parts of the body), and trouble breathing, abdominal pain, diarrhea, nausea, vomiting, dizziness or anaphylaxis), however, sneezing is lacking in the study designs [69].

Stress urinary incontinence and sneezing

Despite the quality of life which was aimed to be measured with the impact of sneezing in MS [115], a few studies have shown

that stress urinary incontinence (SUI) is common in MS and up to 55.9% have reported that physical stress, coughing, and sneezing is involved in SUI, however, no separate result for sneezing has been reported [70].

Habit and sneezing

There are many different ways to stop or release a sneeze. The most common form in the majority of western countries, especially Scandinavian countries, is to hold the sneeze in. However, most non-western countries do "free sneeze". Because of long maintained aristocratic politeness, some people put a finger under their nose and push up, others press their tongue against the back of their teeth to hold in the sneeze. Still in many schools in European countries, children are told not to sneeze rather than to release it. Though in the last couple of years, a new piece of medical advice recommends to not stop a sneeze, however, it was mostly based on a life-threatening case report [71]. Furthermore, the latest study of pandemic health disaster shows that amount of COVID-19 in each sneeze has a major consequence for spreading of infection [3].

Common immunology

When we talk about sneezing, the mast cell's role is not to be ignored. In various studies, tissue mast cells have invariably shown ultrastructural evidence of activation even in normal healthy conditions, suggesting that these cells are constantly providing information to the nervous system. Mast cells (MCs) contribute to IgE-mediated immunological reactions. The IgE antibodies stick to the surface of mast cells within tissues and act as remote sensors within the environment. Mast cells are like 'land-mines' and contain 'bean bags' filled with irritant chemicals including histamine. When IgE antibodies attach, mast cells are triggered to dump their contents into the tissues. When these are released in small amounts, they cause local itching and irritation. In much larger amounts, the result can be much more serious. Symptoms may include sneezing and itching or hay fever, coughing and wheezing or asthma, or the devastating head to toe rash, severe difficulty breathing and a vascular collapse of anaphylaxis [72].

The mast cell activation in MS is discussed in many studies. Mast cells have been previously identified in MS lesions, are activated by myelin basic protein and can participate in the regulation of blood-brain barrier permeability, as well as in myelin destruction. There is evidence of activation of mast cells by proteolytic enzyme tryptase which was significantly elevated in cerebrospinal fluid (CSF) of MS cases, suggesting that mast cell activation may be involved in the pathophysiology of MS [73]. In agreeing with cell response, the mucosal gamma delta T cells are intensively described in AR and MS indicating that a peripheral pathogen is transmitting a signal to activate Th17 cells in CNS [74]. In the same line as AR pathophysiology, a Swedish study, involving healthy subjects as well as patients with AR, has shown that TNFα produces plasma exudation when applied topically onto the nasal mucosa. This response is associated with pro-inflammatory cytokine production (IL-8) and increased granulocyte activity. The observations are of interest in the context of viewing TNFα as a mediator of potential importance to nasal airway defense as well as to the pathophysiology of TNC [75], further of interest as TNFα inhibition has given rise to the risk of triggering MS.

The anterograde axonal transport along the nerve fiber has suggested that toxins are spread back to the CNS. There is also a potential sign that in MS tissue the staphylococcal toxin can probably be identified. One could suggest sinusitis as a potential focus for bacterial migration to CNS, however, the bacterial sinusitis is seldom followed by sneezing. In case the bacterial focus in the nasopharyngeal region is found then it's estimated that staphylococcal toxin could degrade the mast cells, then it's probably expected to reduce the frequency of sneezing and this suggestion can be trusted, when studying recurrent optic perineuritis in intranasal cocaine abuse.

Discussion

To the best of our knowledge, this is the first review of sneezing in medical conditions inclusive to MS. Sneezing and its potential role in MS have not been studied in previously published papers. In the absence of a reliable and specific laboratory test for MS, sneezing can present an unstudied potential role to clarify early signs of MS. Today the MS diagnosis is primarily established by clinical criteria, which have recently been revised. Recent advances in immunology, neurophysiology, and neuroimaging have provided techniques to improve diagnostic confidence, particularly in early or atypical cases of MS. We are still facing annual or periodic revisions of diagnostic criteria of MS. The nasoepithelial cavity, as a trigger organ for sneezing, and as an important site involved in the initiation and exacerbation of MS has not got the deserved recognition. Even lately, some biomarkers show association with the TNC nerve branches and new ways for nasal MS therapy administration

are gaining attention, but we lack enough knowledge of the same information on TGNs role in MS [76]. We learned through other diseases that sneezing has major information that should be recognized and explored in proper international MS studies to clarify its feature as a biomarker. Symptoms triggered by temporary or chronic sneezing may obtain a higher rating on EDSS scoring, and cause studies which did not pay attention to this impactful factor to be challenged in the near future. Although, the potential for nasal epithelial cells for wound healing can be of interest for future MS therapies as well.

Additionally, sneezing could - as a common sign for MS and other health conditions - guide us to an etiology that is more reliable for MS. If the animal model proved to shorten the stroke progression and symptoms when they were forced to sneeze, this could be a simple task to test on humans who suffered an acute stroke [28]. This will help us to understand if MS and stroke communality can share sneezing as a trigger for improvement.

At least one common belief is that sneezing is deteriorating the spasticity in MS and many chronic TGN pain conditions, such as trigeminal neuralgia, migraine and temporomandibular disorders, the pathogenesis of which is still not clear. One of the proposed biochemical mechanisms involves CGRP, which is considered as the most important neuropeptide in the trigeminal system when fibers display a wide innervation in CNS. The CGRP and connected TGN get thoughts set in motion that TGN via CGRP is impacting the spasticity in MS and all other neurological disorders while showing some effects on migraines and spasticity when patients are treated with botulinum toxin.

Furthermore, with no focus on TGN, a new study on another cranial nerve in TNC has recently displayed an association between the olfactory function with serum neurofilament light (NFL) in patients with RRMS. This finding has not yet been studied in association with sneezing. The measuring serum NFL in the combination of scaling the sneeze in PwMS can be new guidance for coming biomarkers.

Limitations

A limitation of this review is that the paper is mostly focused on the results of publications that have mentioned any information on sneezing in that specific medical condition; however, there are a few studies that included population-based data or consecutive patient admission. We cannot rule out the possibility of bias because few were truly a population or hospital-based study of MS, stroke or other conditions included in this study, which shows incidence and prognosis. Simultaneously investigated effects of sneezing in each disorder with adjustments for confounders *e.g.* hot or cold temperature is needed to be considered in coming studies.

Conclusion

A triad of sneezing, nerve branches in the TNC and transaxonal transmission of agents are of major impact in untold association with MS and other neurological disorders such as stroke. We believe that there are outstanding issues that should be considered for planning strategies for MS and rehabilitation post-stroke when sneezing is forced in the early phases of the disease.

Conflict of Interest

None.

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