Curr Treat Options Neurol (2018) 20: 10
DOI 10.1007/s11940-018-0495-4

Headache (JR Couch, Section Editor)

Headache and Its Management in Patients With Multiple Sclerosis

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Published online: 24 March 2018

This article is part of the Topical Collection on *Headache*

Keywords Prevalence · Pathogenesis · Multiple sclerosis · Headaches · Mimics · Treatment

Abbreviations *H/As* Headaches · *EM* Episodic migraine · *CM* Chronic migraine · *CDH* Chronic daily headaches · *HIT-6* Headache Impact Test · *MIDAS* Migraine Disability Assessment · *DMT* Disease-modifying therapy · *IFN-B* Interferon beta · *PRES* Posterior reversible encephalopathy syndrome · *CADASIL* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy · *CGRP* Calcitonin gene-related peptide · *CNSV* Central nervous system vasculitis · *NSAIDs* Non-steroidal anti-inflammatory drugs

Abstract

Purpose of review The purpose of this review was to discuss the prevalence, impact, pathophysiology, and treatment of headaches (H/As) in patients with multiple sclerosis (MS).

Recent findings Headaches and multiple sclerosis are more common in women than in men with the ratio of female to male being 3:1. It is not entirely clear if there is a correlation or an incidental comorbidity of two neurological conditions. A review of the literature shows a variable prevalence of H/As in MS patients. Using the International Classification of Headache Disorders (ICHD) criteria, the primary type of H/As, especially migraine, is the most common type seen in patients with MS. One of the theories of the pathophysiologic mechanisms of migraine in MS patients is inflammation leading to demyelinating lesions in the pain-producing centers in the midbrain. Secondary H/As due to MS medications such as interferons are also frequently present.

Summary H/As can be a cause for significant comorbidity in patients with MS. The treatment of H/As in patients with MS should be addressed in the same fashion as in the non-MS population, which is a combination of pharmacological and non-

pharmacological methods. Preventive medicines for the H/As should be carefully selected because of their side effect profiles. Acute attacks of migraines can be treated with medications such as triptans. Patients with MS who have migraine H/As should be educated about the phenomenon of overuse H/As, keeping headache journals, avoiding stress, and monitoring sleeping habits. The presence of depression in patients with MS and migraine affects quality of life (QOL) and should also be addressed for better outcomes.

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system and is frequently associated with comorbidities that affect the productive lives of patients and impact upon their quality of life. There are demographic similarities between MS and migraine because they both affect women more than men in a ratio of almost 3:1. MS typically occurs typically between 20 and 50 years with a peak around 30 and migraine prevalence is highest between 35 and 45 years [1].

The estimated number of people with MS is 2.3 million worldwide with a prevalence of 140 per 100,000 in North America and the women to men ratio is approximately 3:1 (www.msif.org/wp-contents/wp-contents/uploads/2014) [2, 3, 4•]. MS is classified as relapsing-remitting and progressive and is further stratified phenotypically as active or inactive [5]. The relapsing-remitting course of MS has been mainly observed to have a higher incidence of H/As [6•], and a prospective study of 72 patients from the Drexell College of Medicine MS program reported 85% of patients complaining of worsening headaches on questionnaires during MS exacerbations [7].

The global prevalence rate of H/As is around 50% with predominance of females in the migraine category [8] The American Migraine Study 11 using the International Headache Society (IHS) criteria reported that yearly prevalence of migraine is approximately 18% in women and 6% in men [1]. A Genetic Epidemiology of Migraine (GEM) Study comprising of 6491 subjects reported a lifetime prevalence of migraine in women as 33% and 1-year prevalence of 25% versus lifetime prevalence of 13.3% and 1-year prevalence of 7.5% in men [9]. Migraines may occur in episodic (EM) or chronic (CM) forms. In the general population, in addition to migraine headaches, the prevalence of tension type H/As is reported as 38% and of chronic H/As that last more than 15 days per month as 3% [10]. The burden of migraine H/As is considerable and the results of the American Migraine Prevalence and Prevention Study been reported by Buse et al. [11]. Amongst the 7169 respondents, 72.9% with CM and 42.3% with EM reported greater adverse scores on the Headache Impact Test-6 (HIT-6), a standard measuring tool to establish the severity and frequency of headaches on the ability to function at work, in school, at home, and in social situations [12]. Gender differences mentioned the presence of more frequent and long-lasting headaches in women and with more cumulative disability [13].

Due to the co-occurrence of migraine H/As in certain autoimmune diseases such as CNS vasculitis (CNSV), theories of a similar link between migraine and MS have been forwarded. Presence of localized inflammation and associated headaches in CNSV, especially at its onset, can pose diagnostic problems [14].

Epidemiology

Since H/As in patients with MS are frequently encountered, it is important to utilize the International Classification of Headache Disorders for

epidemiological studies. In the most recent International Headache Classification of Headache Disorders-3 beta, H/As are divided into primary and secondary (Table 1) [15]. The primary disorders are classified as migraine, cluster, tension-type headache, trigeminal autonomic cephalalgias, and other H/As. Migraines are recognized as without aura and with aura and can be episodic or chronic in nature. Chronic migraine (CM) is described as headaches occurring 15 days or more per month for more than 3 months with features of migraine on at least 8 days per month [16]. Chronic daily H/As, (CDH), which can be due to primary or secondary causes, are defined as H/As occurring > 15 days per month for greater than 3 months and include chronic tension type, transformed migraine, hemicrania continua, and new daily persistent H/As [17]. The ICHD-3 beta classification also includes trauma to head and neck,

Table 1. Primary and secondary headaches prefix-ICHD-3 classification

Primary headaches
1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.3 Chronic migraine
1.4 Complications of migraine
1.5 Probable migraine
1.6 Episodic syndromes that may be associated with migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
3.1 Cluster headache
3.2 Paroxysmal hemicrania
3.3 Short-lasting unilateral neuralgiform headache attacks
3.4 Hemicrania continua
3.5 Probable trigeminal autonomic cephalalgia
4. Other primary headaches
Secondary headaches
5. Headache attributed to trauma to head and neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to intracranial infection
10. Headache attributed to homeostasis
11. Headache or facial pain attributed to disorder of cranium, eyes, ears, nose, teeth, sinuses
12. Headache attributed to psychiatric disorder
13. Painful cranial neuropathies and other facial pain
14. Other headache syndromes

vascular disorders, non-vascular intracranial conditions, long-term use of non-headache medicines, use of substances and subsequent withdrawal, infections, disturbances in homeostasis, diseases in the cranium, neck, eyes, and ears, facial and cervical structure disorder, and psychiatric conditions as causes for secondary headaches.

Early studies mention the prevalence of primary H/As in patients with MS being 2% [18]. This was due to the lack of availability of uniform criteria for classification of headaches in the past. The more recent studies based on the International Classification of Headache Disorders (ICHD-2) have reported a higher prevalence of migraine varying from 35.5 to 61.8% [19].

A study from the NYU-MS Center showed the prevalence of H/As to be 64%, with 72% of those being of the migraine type, in a cohort of 204 patients [20•] The prevalence of tension type H/As in the MS population is reported to be between 21 and 48% H/As which is like the general population [21]. However, a higher number of older men reported tension type H/As in a study of 102 patients with MS [22].

Other types of primary H/As witnessed in the MS population are the cranial neuralgias, pain in the distribution of the trigeminal, occipital, and glossopharyngeal nerves. The prevalence of trigeminal neuralgia in the general population is 0.16–0.3% [23]. The lifetime prevalence of trigeminal neuralgia (TN) in patients with MS is reported as 4% and it increases with age as in the general population [24]. Since TN may have been underreported in previous studies, a large study was recently conducted, using the data from the North America Research Committee on MS (NARCOMS) registry [25]. The analysis from the study revealed TN in 9.5% of patients during the duration of MS. The diagnosis of TN preceded the diagnosis of MS in 15% of the patients. The facial pain is usually severe and distressing and has a negative effect on the quality of life for all affected patients. Glossopharyngeal neuralgia is a rare condition with an incidence of 0.8 per 1,000,000 people. The pain follows the sensory distribution of glossopharyngeal and vagus nerves and may be felt in the ear, throat, and base of the tongue. Glossopharyngeal neuralgia has been reported in rare cases of MS probably due to inflammatory lesions in the brainstem [26, 27].

Secondary headaches due to disease-modifying therapies (DMTs) for treatment of MS have been reported in several studies. Interferon-β (IFN-B) therapy worsened pre-existing headaches in 50% and triggered new headaches in 75% of cases [28••]. Headaches are recognized as part of infusion reactions with natalizumab [29]. Fingolimod may also produce headaches per prescribing information.

Proposed mechanisms of headaches in MS

Several hypotheses have been proposed to explain the presence of a higher incidence of migraine H/As in patients with MS. First, the H/As in patients with MS could be due to the presence of B cell follicles in the meninges and gyri on pathology as described by Magliozzi et al. [6, 30••]. Second, inflammation-mediated cortical demyelination that accelerates cortical spreading depression in rodent models may be the explanation for migraine in MS patients. [31, 32]. Third, another possible mechanism may be the location of the lesions. A retrospective study of 277 patients found the presence of active MS plaques in

the midbrain's periaqueductal gray on MRI with the presence of migraines [33]. This study reported that the presence of a MS plaque in the midbrain was associated with a higher likelihood of developing migraine; however, due to the retrospective nature of the study, it is difficult to ascertain if migraine would have occurred in the absence of a midbrain lesion.

Influence of co-existing factors on headaches and MS

There is a growing interest in the presence of comorbidities in chronic diseases. A systematic review of 249 articles comparing prevalence of comorbidities in MS showed that depression and anxiety were more common in the patients with MS [34] Psychiatric disorders including major depression, bipolar disorder, panic disorder, and social phobia have also been reported at a higher rate in patients with MS [35, 36••]. Amongst the psychiatric conditions in MS, depression is commonest and present in 50% of patients [37]. A recent review of psychiatric syndromes in MS mentions a lifetime prevalence of anxiety disorders in 36% of patients [38]. Several studies have shown the negative impact of life stressors have on primary headaches. A study of 267 patients with stressful events and chronic headaches, who answered questions on a standardized computerized questionnaire, showed worsening of chronic headaches in 44.9% and triggering of episodic H/As in 36.4% of cases by stressful life situations [39]. In the Eurolight project, questionnaires from 6624 participants, when analyzed, showed that migraine sufferers reported the presence of anxiety or depression or both in 19, 7, and 5% of cases as compared to 14.3, 5.6, and 3.8% in the general population [40]. Chronic migraine has been found to be more disabling than episodic migraine as recorded by the Migraine Disability Assessment (MIDAS) tool [41]. Presence of depression, anxiety, and migraine in conjunction with MS leads to loss of productivity with a substantial financial and social burden on the individual and society.

The cumulative effects of these comorbidities have been shown to affect the quality of life of individuals with MS as per a study using the health-related quality of life questionnaire (HLQOL) [42].

Influence of MS medications on headaches

Since the introduction of disease-modifying therapies (DMTs) in MS in 1993, adverse events, including headaches due to medications, are being recognized. The H/As with interferon beta (IFN-B) occur soon after the injections and are frequently accompanied by flu-like symptoms, which can be mitigated with non-steroidal anti-inflammatory drug (NSAID) premedication to help improve the compliance of the interferon use [43]. In the pivotal trial for IFN-B-1b in MS, H/A was not mentioned initially as an adverse event []. However, the incidence of headache was recorded as 67% in the treated compared to 57% in placebo group in the pivotal phase 3 trial of IFN-B-1a for MS [44]. In another study, 357 MS patients treated with IFN-β showed worsening of pre-existing headaches in 50% and the development of new headaches in 70% of cases [45]. In another prospective study at the MS Clinic at the C Besta Neurological Institute in Milan, 150 MS patients treated with different immune-modulating agents including interferons, glatiramer acetate, and azathioprine, when administered a

standardized questionnaire based upon the International Headache Society (IHS) criteria of 1988, reported pre-existing headaches in 38% of the IFN-treated group and 54% in the group treated by other agents. The study results showed the presence of new headaches was in 48% in the interferon-treated patients and an exacerbation of 41% in the existing H/As but the other group showed no significant change [46]. In another study of 167 patients treated with interferon-β or glatiramer acetate, 58% of patients in the IFN-β treated group experienced worsening of pre-existing headaches as compared to 11% treated with glatiramer acetate []. H/As were reported in 24% of patients receiving natalizumab versus 18% of placebo in a randomized, placebo-controlled clinical trial for relapsing MS [47]. In the AFFIRM trial, H/As occurred in 38% of patients treated with natalizumab compared to 33% in the placebo group [48]. However, the presence of H/As due to natalizumab infusion had a lesser impact on quality of life (QOL) of individuals with MS as compared to those receiving INF-β [49].

With the availability of newer DMT agents to treat MS, physicians should be cognizant of their side effects including H/As to be able to confidently manage these patients. H/As are reported to a lesser extent with newer DMTs used to treat MS. In the FREEDOMS trial, the incidence of H/As in patients receiving fingolimod 1.25 and 0.5 mg daily was 26.6 and 25.2% respectively as compared to 23% in the placebo group [50]. Headaches in rare instances as complication of posterior reversible encephalopathy syndrome (PRES) have been reported as side effects with fingolimod in the prescribing information (package insert). Teriflunomide and dimethyl fumarate have not been reported to have major associated H/As [51, 52]. In the CAMMS223 study where alemtuzumab was compared to IFN-B-1a three times weekly, H/As were reported mainly as infusion reaction in 55% of alemtuzumab-treated versus 66% of interferon-treated patients [53]. The OPERA I and II and the DECIDE clinical trials with ocrelizumab [54] and daclizumab [55] infusion reported no major H/As.

Avoiding a misdiagnosis

Since MS and several other disorders have H/As as an associated or presenting feature along with abnormalities on MRI, a misdiagnosis is not uncommon. Migraine, either alone or in combination with other symptoms, is misdiagnosed as MS in almost 22% of patients. Amongst the causes for misdiagnosis are misapplication of MS diagnostic criteria to atypical presentations with an overreliance on MRI findings that may show non-specific white matter changes [56••]. Red flags like the presence of headaches with cognitive changes at the onset, with MRI changes suggestive of multiple subcortical infarcts, should raise the suspicion for other diagnoses like primary central nervous system vasculitis [57]. H/As are frequently reported in inflammatory and autoimmune conditions like Behcet's syndrome, Sjogren's syndrome, giant cell arteritis, Wegener's granulomatosis, neurosarcoidosis, aseptic (non-infectious) meningitis, and lymphocytic hypophysitis [58, 59]. A proposed hypothesis for H/As in the autoimmune conditions is secondary demyelination or ischemic changes of the trigeminal nucleus and tract caused by inflammation [57]. When the MRI shows discrete but non-specific white matter lesions, the autoimmune disorders may be mistaken for MS [53]. The prevalence of migraine in SLE has

been reported to range from 5.6 to 68% [60]. However, a prospective study of seventy-two SLE/control pairs found a similar prevalence of migraine between the SLE and other non-autoimmune disease control subjects. This study found no causative link between migraine and SLE [61]. Unlike other inflammatory conditions, migraine as a presenting symptom in patients with MS is less common. However, a case report describes the presence of status migrainosus as an initial presenting feature [62]. In another case report, worsening H/A preceded the typical symptoms of spinal cord involvement which eventually led to the diagnosis of MS [63]. A recent prospective, multicenter study of 50 patients with a diagnosis of clinically isolated syndrome (CIS) or MS with symptom onset in the last 6 months describes H/A prevalence in 78% of patients [64].

Presence of an abnormal MRI suggestive of a demyelinating disease during an evaluation for H/As raises the possibility of a radiologically isolated syndrome to be considered [65]. The clinical condition of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome can cause confusion in diagnosis but careful attention to the symptoms of H/As, mental status changes, hypertension, and the typical abnormal white matter lesions with preferential involvement of temporal lobes and lacunar infarcts on MRI will help in distinguishing MS from CADASIL [57].

Finally, it is also important to be familiar with the difference between a migraine-related aura and a MS relapse. A migraine-related aura develops over minutes and usually lasts for 60 min while MS-related clinical relapse symptoms last more the than 24 h [66]. Thus, the application of accepted clinical and radiographic (McDonald) criteria is a must to improve the diagnostic certainty of MS and avoid the unnecessary exposure to potentially harmful medications [67]. The most recent revision of the McDonald criteria provides an updated version for more accurate diagnosis of MS for both clinical and research settings [68].

Headache management in MS

The treatment of H/As in patients with MS follows the same principles as in the general population. An accurate diagnosis followed by treatment with pharmacological and non-pharmacological modalities is the recommended approach. Pharmacological treatment includes acute symptomatic treatment for individual and daily preventive medications to decrease the frequency of occurrence of H/As. Guidelines for preventive medications are based upon expert consensus that have been defined by The American Migraine and Prevalence Study. Per expert consensus derived from the study, daily preventive treatment is recommended if there are at least 6 or more H/As per month with 4 or more days with some impairment, or 3 or more days with severe impairment requiring rest [69]. The goal of preventive treatment that includes non-pharmacological methods like cognitive behavioral and relaxation therapy as well as medications is to decrease the frequency and severity of migraine H/As that interfere with normal daily functioning at home and at work. The modern treatment is dependent upon understanding the pathophysiology of migraine that is believed to be due to hyperexcitability of neurons caused by a central generator with involvement of peripheral pain mechanisms in a genetically susceptible

individual. Some of the preventive medications inhibit the cortical spreading depression (CSD) and others have antiadrenergic serotonin (5-hydroxytryptamine (5-HT)) modulatory effects as well as inhibitory effects of gamma-aminobutyric acid [70••, 71]. The update on the evidence-based guidelines from the American Academy of Neurology and American Headache Society for preventive treatment of episodic migraine along with recommendations from other reviews provides important strategies for management of recurrent headaches [72, 73]. The most common migraine preventive agents are antiepileptic drugs, antidepressants, beta-adrenergic blockers, calcium channel antagonists, non-steroidal anti-inflammatory drugs, and angiotensin-enzyme converting inhibitors [74]. The exact mechanism of action of these agents is not known but the drugs that have been shown to be useful for migraine prevention are reviewed below [70••, 71, 73] Topiramate blocks voltage-gated sodium and calcium channels, and gabapentin blocks voltage-gated calcium channels and enhances GABA concentration. Valproate decreases inflammation by increasing brain GABA and tricyclic antidepressants inhibit norepinephrine and 5-HT high affinity uptake leads to reduced excitatory activity. Beta blockers reduce adrenergic tone by reducing norepinephrine release and synthesis, and the calcium blockers suppress CSD by inhibiting 5-HT release. The angiotensin-converting enzyme inhibitors and receptor blockers modulate calcium and potassium channel activities. Other treatment choices for chronic migraine include injection of neurotoxins (onabotulinum toxin A [BoNT-A]) into selected cranial muscles. A recent review discusses the mode of action of BoNT including the modulation of peripheral and central mechanisms involved in the production of pain and H/As. The authors mention that BoNT is taken up by peripheral sensory afferents, transmitted to central terminals, inhibits release of pain peptides, substance P, bradykinin, calcitonin gene-related peptide (CGRP), and glutamate from the dorsal root and trigeminal ganglia, and thus influences the production of trigeminal triggered pain [75]. Results from the Phase 3 Research Evaluating Migraine Prophylaxis Therapy Program (PREEMPT) showed beneficial effects of BoNT-A in the efficacy measures when headache frequency days were compared to the baseline [76]. The general principles for treatment of acute migraine attacks are early intervention and the use of non-specific or specific drugs. The non-specific treatment includes NSAIDs, neuroleptics, and antiemetics. Antiemetic agents (chlorpromazine, metoclopramide, prochlorperazine) given intravenously in the emergency department have demonstrated relief within 2 h in 24–67% of acute migraine cases. Specific agents for acute migraine attacks include triptans that act as selective activators of the 5-HT receptors and dihydroergotamine that is an agonist with serotonin and other receptors [77, 78•]. The benefit of steroids in acute attacks is unclear; however, a meta-analysis of randomized controlled trials found that recurrence of headaches was reduced for 72 h when parenteral dexamethasone was added to the accepted standard abortive drugs for migraines [79].

Since studies have shown higher prevalence of depression in migraine and MS, it is important to screen for this comorbidity and address it appropriately. Interventions that include antidepressants and cognitive behavioral therapy have a role for a favorable outcome. However, a recent review reports lack of clinical trials that could offer the best treatment guidelines of treating patients with MS who have migraine H/As and depression. It is recommended that further research work needs to be done in this field [80]. A comprehensive management strategy

for migraines should include a discussion about avoiding triggers like alcohol, smoking, and other food targets as well as following a plan for sleep hygiene.

Lastly, when treating migraine H/As in patients with MS, caution is required since there is an increased risk of possible side effects associated with multiple medication interactions. Preventive headache medicines in the category of antiepileptic drugs like topiramate and valproic acid in the female population in the childbearing age should be used with caution because of their potential teratogenic side effects [81]. Valproate is contraindicated in pregnancy and should be avoided in women, who wish to be pregnant, because of the possibility of neural tube defects, while topiramate is classified as category D because of possible oral cleft developmental abnormalities [77].

Future directions

Better understanding of the pathophysiology of migraine and the role of CGRP in the trigeminal system has led to the development of monoclonal antibodies that have shown efficacy in a phase 2 trial as preventive treatment for migraines [82]. In a recent phase 3 trial, fremanezumab, a monoclonal antibody against calcitonin gene-related peptide (CGRP), used as a preventive agent in chronic migraine showed a reduction of at least 50% in the number of headache days in 38% in the quarterly treated group and 41% in the monthly treated group compared to 18% in the placebo group [83••]. Release of monoclonal antibodies against CGRP awaits FDA approval in 2018. Since there is no information currently available about interactions of the CGRP agents with the DMTs, the role of the monoclonal CGRP antibodies in patients with migraine and MS requires further investigations.

Of the non-pharmacological strategies, mindfulness-based interventions and acupuncture hold promise for the future. Mindfulness, introduced by Jon Kabat-Zinn, is described as a practice to "pay attention to the moment" [84]. The technique of mindfulness has been explored in the treatment of headaches; however, this technique is in its early stages of evaluation [85]. A systemic review based on three studies on the use of mindfulness-based interventions in symptoms of anxiety, depression, fatigue, and pain in patients with MS showed improvement which was sustained at 6-month follow-up as measured by health-related quality of life (HRQOL) questionnaires. Interventions labeled as "Mindfulness in Motion" that use techniques of yoga, mindfulness meditation, and music therapy were studied in 22 MS patients, and the results in a recent publication report favorable outcomes in physical functioning, vitality, and mental health as measured by Mental Health Inventory, 36-item Short Form Health Status Survey, Modified Fatigue Impact Scale, and Five Facet Mindfulness Questionnaire [86]. Acupuncture has also been explored as a treatment of migraine H/As. A randomized controlled trial of 401 patients with chronic H/As were divided into two groups: one, allocated to receive 12 acupuncture treatments in addition to standard treatments over 3 months and a control group that received only the standard treatments for migraine [87]. The results showed persistent improvement over 12 months in measures of quality of life, use of medications, and absenteeism from work. In another randomized 24-week clinical trial, 249 H/A patients were assigned to three groups: one receiving true acupuncture, another sham acupuncture, and the third was a

control group, waiting for treatment [88]. The results showed a significant reduction in the number of headaches in the true acupuncture versus sham-treated groups ($p = .002$) and in the true acupuncture-treated versus the waiting for treatment groups ($p < .001$). The difference was not statistically significant between the sham-treated and waiting for treatment groups ($p = .07$). The role of mindfulness and acupuncture for migraine H/As in patients with MS as standard treatments is worth exploring.

Finally, our personal experience is that recognition of the presence of co-morbidities such as H/As but also depression is important and a comprehensive approach serves as the best model to improve the quality of life in these patients with MS.

Compliance with Ethical Standards

Conflict of Interest

Farhat Husain and Meheroz Rabadi declare no conflict of interest.

Gabriel Pardo is a consultant for Bayer and is a consultant and on speaker's bureau for Biogen, Genentech, Genzyme, Novartis, Serono, and Teva.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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