



The influence of lifestyle and gender on cluster headache

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Purpose of review

Cluster headache is by many regarded as a males' disorder that is often accompanied by an unhealthy lifestyle. We aimed to study the influence of sex and lifestyle factors on clinical presentation, the diagnostic process and management.

Recent findings

Overall, the clinical presentation of cluster headache in both sexes was similar; however, chronic cluster headache may occur more frequently in women than in men. Misdiagnosis was most prevalent in women and more women than men were not correctly diagnosed until seen in a highly specialized center. In relation to lifestyle, smoking prevalence remains very high and some studies suggest that obesity and use of illegal drugs may be pronounced as well. In contrast to previous beliefs, recent findings on alcohol consumption report a lower use in patients than in controls. Overall, men and to some extent chronic patients were more prone to some unhealthy lifestyle factors than women and episodic patients.

Summary

Despite an overall similar clinical presentation in men and women, the diagnostic process was more problematic for women in the form of more frequent misdiagnosis and failure to diagnose women in the primary and secondary sectors. Unhealthy lifestyle factors are prevalent in cluster headache and may ultimately have consequences for the management of the disease.

Keywords

clinical characteristics, cluster headache, lifestyle, misdiagnosis, sex

INTRODUCTION

Cluster headache is the most common of the trigeminal autonomic cephalalgias with a lifetime prevalence of 1/1200 [1]. The cluster headache attacks are of extreme severity with pain located in the periorbital, retroorbital, or temporal area of the head. Attacks are accompanied by ipsilateral cranial and/or systemic autonomic symptoms in the form of tearing, ptosis, redness of the eye, miosis, and restlessness. Attacks typically last 15–180 min and occur between once every other day and eight times a day when the disease is in its active phase. Most patients suffer from episodic cluster headache with attacks occurring in bouts (clusters), which typically last weeks to months, separated by attack-free periods, which typically last months to years. Around 10–20% of patients have a chronic variant with no meaningful attack-free periods (less than 3 months/year) [2].

Until recently, there has been reported a profound male preponderance ranging from 18–20:1 in the 1980s [3,4] to around 3.5:1 in later studies [5–7].

Yet, recent Danish and UK studies have reported a ratio as low as 2:1 [8,9[■]], leading to speculations on possible etiological factors explaining this decrease. As smoking is persistently identified to be highly prevalent in cluster headache patients, some have hypothesized women's lifestyle changes in an unhealthier direction to account for the increase of cluster headache in women [10,11].

The clinical presentation of cluster headache is very characteristic. Although some symptoms may overlap with migraine, the pain severity, the presence of autonomic symptoms, restlessness/agitation, the attack duration, and frequency are clear markers of cluster headache. Still, a thought

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KEY POINTS

- Both men and women have a typical clinical presentation, yet, women have been shown to be more frequently misdiagnosed and more often fail to be correctly diagnosed in the primary and secondary sectors.
- Smoking prevalence is high in cluster headache and may be related to a more severe clinical presentation.
- Overall, alcohol consumption is lower in patients compared with controls.
- Men and to some extent chronic patients were more prone to have an unhealthy lifestyle than women and episodic patients.
- Unhealthy lifestyle factors are risk factors for cerebro and cardiovascular diseases. Such diseases can limit treatment possibilities and may therefore have great consequences for cluster headache management.

provokingly long diagnostic delay of around 5–6 years exists and patients of both sexes are very frequently misdiagnosed [9[■],12]. Consequently, the patients will be insufficiently treated and unnecessarily burdened until a correct diagnosis is obtained. As cluster headache is most prevalent in men and as the presentation may be more atypical in women [13], there is a risk of the diagnostic process being even more prolonged in women.

This review aims to provide an updated overview on what is known about lifestyle factors and possible consequences of an unhealthy lifestyle in cluster headache patients as well as a thorough insight into whether male and female sex influences clinical presentation and the diagnostic process.

METHOD

PubMed was used to search for relevant articles published within the last 3 years using the search terms: ‘cluster headache’ in combination with ‘sex,’ ‘gender,’ ‘male,’ ‘men,’ ‘female,’ ‘women,’ ‘lifestyle,’ ‘smoking,’ ‘BMI,’ ‘alcohol,’ ‘illegal substances,’ and ‘drugs.’ However, as the number of articles was very limited, relevant references from the identified articles were also included. The searches were performed from October 2018 to November 2018.

The influence of sex on clinical presentation

It is debated whether the male preponderance of cluster headache is true or whether it could (at least partly) be explained by a more frequent misdiagnosis in women. Indeed, a recent Danish study of 351

cluster headache patients highlighted that women were more frequently misdiagnosed than men (61 vs. 46%, $P < 0.01$) and that women more often did not receive the correct diagnosis before seen at a tertiary headache center (39 vs. 21%, $P < 0.001$) [9[■]]. Several factors, and most likely a combination of these, could explain this finding.

In the primary and secondary health sectors, cluster headache might be perceived as a males’ disorder because of the high male preponderance previously observed. The male:female ratio was as high as 18–20:1 in the 1980s [3,14]; however, newer studies estimate it to be approximately 3.5:1 [5–7] or even as low as 2–2.5:1 [8,9[■]]. This is in clear opposition to migraine that has a female preponderance with a male:female ratio 1:2–3 [15]. Similar to the general population, more women than men with cluster headache suffer from migraine [9[■]]. This could result in more women potentially being perceived as having migraine and more men as having cluster headache.

It has previously been indicated that women could suffer from a more atypical presentation of cluster headache than men [5], but most of the existing literature has only identified minor differences in the presentation of cluster headache between the sexes [6,8,9[■],16[■],17,18]. Nevertheless, the findings regarding specific migraine-like features are diverging. In most studies, migraine-like features, as photo and phonophobia, have been frequently but equally reported by both sexes [9[■],19[■],20], also independently of co-existing migraine [9[■]]. Yet, a large internet-based study (not validating the cluster headache diagnosis) found that nausea and vomiting occurred more frequently in women than in men [13]; vomiting but no other migraine-like features occurred more frequently in women in a US study of 101 cluster headache patients [17]; and finally, Manzoni *et al.* [21] reported that nausea but not vomiting occurred more frequently in women. A large, prospective study of 500 cluster headache attacks found that migraine-like features were correlated with the duration of attacks and the pain intensity, but the study did not investigate whether the prevalence differed between the sexes [19[■]]. Taken together, more studies are needed to establish whether migraine-like features are more prevalent in women than in men. If they are, they may be confusing factors in the diagnostic process.

An already existing migraine disorder (which is more common in women) could potentially complicate the diagnostic process if physicians are more reluctant to give a second headache diagnosis, that is, both migraine and cluster headache.

Studies exploring genetic disposition have found that women may have a higher genetic

disposition to develop cluster headache than men. One study observed that women more often had a pediatric onset than men [22] and another showed that women had an earlier age of onset than men [13]. Another interesting observation is that chronic cluster headache has been observed to be more prevalent in women in two different studies [9^{••},22], suggesting basic pathophysiological differences between the sexes.

Smoking

A consistent finding when searching the literature is a disturbingly high prevalence of unhealthy lifestyle factors, especially smoking. Current smoking is reported in 48–68% of patients [6,8,12,23^{••},24,25] and former smoking in additionally 13–27% [6,12,23^{••},24,25]. In a Danish controlled study of 400 patients and 200 controls, smoking prevalence was significantly higher in patients compared with controls (48 vs. 9%, $P < 0.0001$), also when stratifying for sex (53 vs. 11%, $P < 0.0001$ and 30 vs. 6%, $P < 0.0001$ for men and women, respectively) [23^{••}]. Among patients, some studies have been able to identify specific subgroups more heavily burdened than others: men are more frequently reported to be smokers or former smokers than women [6,23^{••},25] and chronic patients are more frequently reported to be smokers or former smokers than episodic patients [23^{••}], although the latter is not a consistent finding [6].

It remains questionable how the close relation between cluster headache and smoking should be interpreted. So far, there are several indicators of an association between smoking and a more severe cluster headache phenotype. In a detailed study on smoking habits, Ferrari *et al.* [25] discovered that smokers had more bouts and a higher attack frequency than never-smoking patients. In accordance with this, a Danish study found that patients exposed to smoking (current and former smokers) had a longer average bout duration, higher attack frequency, and a higher pain severity than never-smoking patients, whereas treated attack duration was shorter, suggesting that treatment response was better in current and former smokers [23^{••}]. A large internet-based American study with 1134 participants also showed that exposed patients (current or former smokers, or patients exposed to parental smoking) present with a more severe phenotype than never-exposed patients [26[•]]. In addition to a more severe phenotype for exposed patients, the author suggests that smoking could be causally related to cluster headache development [26[•]]. Nicotine exposure has been shown to alter trigeminal pain processing in healthy people exposed to acute nicotine with inhibition at brainstem level and

facilitation at supraspinal level [27]. These findings indicate that it may be plausible for smoking to alter pain processing, also in cluster headache. Interestingly, the male:female ratio of cluster headache was 7:1 in a recent Korean study and the authors suggest that this could (partly) be because of the rarity of women being smokers in Asia [16[•]]. Nevertheless, studies investigating the effect of smoking cessation on cluster headache, report that most patients do not experience any changes in disease severity [8,25], blurring the picture. The observed relation between cluster headache and smoking could potentially also be explained by personality traits or certain behavioral patterns [28–30]. This hypothesis is supported by the simple facts that not all smokers develop cluster headache and not all cluster headache patients have been exposed to smoking. The cause of cluster headache is most likely multifactorial with smoking possibly contributing to the activation in already predisposed individuals. Nevertheless, there is an increasing evidence of smoking affecting disease severity. Further research is warranted before the relationship between cluster headache and smoking can be fully understood.

Alcohol

In the past, cluster headache patients were reported to have a very high alcohol consumption [6,31]. Yet, recent controlled studies suggest that alcohol consumption is actually lower in patients compared with controls (61 vs. 90%, $P < 0.0001$) [23^{••}] and with the general population (76 vs. 81%, $P < 0.001$) [32^{••}]. Subgroup analyses suggest that especially men [6,23^{••}] and chronic patients overuse alcohol [23^{••}], despite the fact that more episodic cluster headache patients are found to be regular consumers [6,23^{••}]. As alcohol is one of the most frequently reported trigger factors of cluster headache attacks [12,23^{••},33], the consumption in the active disease phase seems counterintuitive. Therefore, a clarifying observation is that alcohol is less often a trigger factor for those patients that do consume alcohol in the active disease periods compared with those that do report it as a trigger (23 vs. 39%, $P > 0.05$) [23^{••}]. Hypothetically, alcohol overuse could be explained by the higher prevalence of sleep problems in cluster headache patients [34] and alcohol being (wrongfully) perceived as an easily available hypnotic, or as for smoking because of certain personality traits and behavioral patterns of patients [28–30].

Obesity

To the author's knowledge, obesity has rarely been assessed in cluster headache cohorts. A Danish study

found that BMI was higher in patients than controls (BMI: 26.1 vs. 24.2, $P < 0.001$) [23²²]. This finding stayed highly significant when stratifying for sex (men: cluster headache patients 26.1 vs. controls 24.8 and women: cluster headache patients 26.2 vs. controls 22.9) [23²²]. In opposition, a recent Dutch study found no differences between patients and the general population, neither when stratifying for sex [32²²]. As with smoking and alcohol consumption men may represent a subgroup of cluster headache patients more prone to obesity but more studies are needed before conclusions can be drawn. A Korean study found normal BMI levels in both men and women with cluster headache, but identified significant differences between the sexes (24.1 vs. 21.4, $P = 0.002$) [16²¹]. However, in general, men are reported to have higher BMI levels than women [35] and comparisons between the sexes may possibly reflect this rather than a disease-related difference between them.

Illicit drugs

In patients with a poor treatment response, self-medication with alternative and illicit drugs has been shown to be rather pronounced [36²¹]. A recently published large Dutch study focusing on lifetime use of illicit drugs, showed that patients were more likely to report a lifetime use than the general population (32 vs. 24%, $P < 0.01$) [32²²]. In this study, cannabis was the most frequently used drug (30%) followed by cocaine (9%) and 3,4-methylenedioxymetamphetamine (ecstasy) (9%). Further, as in the case of the other lifestyle factors, illicit drug use was significantly more prevalent in men than women (35 vs. 24%, $P < 0.008$). Two French studies found that as many as 26–32% of patients were regular cannabis consumers, being considerably higher than the 7% observed in the general French population [24,37]. A Danish study was unable to identify a higher use of illicit drugs among patients compared with controls, but in this case, the study design could have affected the findings (i.e., patients not being anonymous and most patients being in relatively close contact to the study team) [23²²]. However, the Danish findings are in line with a US study, in which only 10% of patients reported to have used cannabis occasionally or frequently [38].

Studies have suggested that illicit drugs can have therapeutic effects either as a preventive treatment [32²²,36²¹,39] or in the acute phase of the attacks [36²¹,39,40]. However, patients also report that illicit drugs, especially cannabis and γ -hydroxybutyrate, also known as GHB, can trigger attacks [32²²,41] and in the Dutch study, most users reported that illegal

drugs had no effect on their cluster headache at all [32²²]. As with smoking, the relation between illicit drugs and cluster headache remains speculative as the knowledge on possible pathophysiological overlaps between the two is limited. As most patients report to use illicit drugs without it influencing their cluster headache, the more frequent use may be attributed to other factors than a pain-relieving effect. Proposed factors are an increased use because of attention on social media and cluster headache blogs or perhaps a more addictive and risk-taking behavior among cluster headache patients [32²²]. Further, from clinical experience, cluster headache patients often report to have tried many different alternative therapies to achieve pain relief and this search may also include illegal drugs.

Consequences of a negative lifestyle

An unhealthy lifestyle increases the risk of cerebro and cardiovascular diseases like stroke, cardiac infarction, and atherosclerosis [42]. The Danish controlled study of 400 cluster headache patients and 200 controls, showed that a wide range of lifestyle-related diseases as hypertension, hypercholesterolemia, gastric ulcer, angina pectoris, and cerebral infarction, were more prevalent in cluster headache patients [23²²]. Surprisingly, diabetes was equally prevalent in patients and controls [23²²]. Diabetes also occurred less frequently in a recent US study; however, this study was unable to identify a higher prevalence of cerebro and cardiovascular diseases among 75 cluster headache patients compared with 152 controls [43]. The presence of certain lifestyle-related diseases can have significant consequences for the management of cluster headache, as some can restrict treatment possibilities of key medications in cluster headache: verapamil and triptans. Patients are hereafter left with less effective or more side-effect prone alternatives like lithium. Interestingly, the Danish study also showed an association between lifestyle-related diseases and cluster headache after controlling for potential confounders (age, sex, smoking, high alcohol intake, high BMI, and educational level), suggesting that unknown mechanisms in the disease itself increases risk of lifestyle-related diseases [23²²].

CONCLUSION

Cluster headache is a very characteristic primary headache disorder. The literature shows that both men and women overall have a typical clinical presentation. Some studies suggest that chronic cluster headache and migraine-like features may be more prevalent in women and these factors could

be confusing in the diagnostic process. Women have been shown to be more frequently misdiagnosed and more often fail to be correctly diagnosed in the primary and secondary sectors. Better education of medical doctors as well as public awareness on the different primary headache disorders are essential to minimize diagnostic delay, misdiagnosis, and mistreatment for both sexes.

Lifestyle factors have been investigated thoroughly in cluster headache patients and were historically very unhealthy. Recent studies support this in relation to smoking and to some extent in relation to obesity and use of illicit drugs. In opposition, alcohol consumption is lower in patients than in controls; yet, men and chronic patients have been identified as being more prone to alcohol overuse than women and episodic patients. Unhealthy lifestyle factors are risk factors for the development of comorbid cerebro and cardiovascular diseases. Such diseases can limit treatment possibilities for cluster headache patients and may therefore have great consequences for cluster headache management as triptans and verapamil can be complex to use in the presence of such diseases.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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