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Smoking and cluster headache presentation and responsiveness to treatment

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Abstract

Background Though an association between cluster headache (CH) and smoking has been postulated, data from the Middle East region is scarce.

Aim of work To study the relationship between smoking and CH clinical characteristics and responsiveness to therapy in Egypt.

Methodology This was a prospective cohort hospital-based study conducted on patients with episodic and chronic CH in a tertiary headache clinic in Egypt during the period between 2019 and 2023. Patients were consecutively recruited at the time of their presentation and were followed up for two weeks after initiation of prophylactic treatment and steroids (as transitional therapy).

Results Of 172 patients with CH recruited, 144 (83.7%) were smokers. Twenty-eight patients (16.3%) had chronic CH. The mean age was 42.08 ± 10.93 (20–66) years, and 131 (76.2%) were males. Smokers had a significantly higher median number of cluster bouts in the past five years (3.0 (IQR2.0–4.0) versus 2.0 (IQR 1.0–2.0)) and worse HIT-6 scores [51.0 (44.0–59.75) versus 41.0 (38.0–41.75)] than non-smokers ($p < 0.001$). The number of cluster bouts in the past five years was positively correlated with the smoking index ($r = 0.249$ ($p = 0.006$) and the smoking duration (in years) ($r = 0.392$ ($p < 0.001$)). HIT-6 scores were significantly correlated with the age at smoking onset (r=-0.190, =0.023), smoking index ($r = 0.519$, $p < 0.001$), smoking duration ($r = 0.611$, $p < 0.001$), and number of cigarettes consumed per day ($r = 0.392$, $p < 0.001$).

Conclusion Smoking is significantly correlated with the daily frequency of CH attacks, the frequency of CH bouts in the past five years, and the HIT-6 scores among our cohort.

Keywords Cluster headache, Presentation, Responsiveness, Smoking

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Introduction

Cluster headache (CH) is one of the most excruciating pain syndromes that is characterized by severe agonizing strictly unilateral pain accompanied by various autonomic symptoms [1]. Based on the International Classification of Headache Disorders-3 (ICHD-3) [2], CH is diagnosed when a patient experiences at least five attacks of severe unilateral pain at the orbital, supraorbital, and or temporal regions that last for 15 min to three hours, and is accompanied by cranial autonomic symptoms (e.g., lacrimation, rhinorrhea, conjunctival injection, nasal congestion, … etc.) and/or agitation [2]. The typical frequency of the CH attacks ranges from every other day to eight attacks daily [2]. Two form of CH exists based on the yearly frequency of CH bouts i.e., episodic [3] and chronic CH [4]. Episodic CH is defined as experiencing at least two CH bouts (each lasting for seven days to one year) with at least three-month pain-free periods [3]. When pain-free periods are less than three months, the CH is defined as chronic [4]. Despite being a rare disease, occurring in about 0.1% of the population, CH is a burdensome disease [5]. It imposes a significant impact on the patient's quality of life, results in significant disability, causes economic and job-related burden, and increases the risk for suicide [6, 7]. Unhealthy lifestyle has been reported to be prevalent among patients with CH as delineated by a recent Danish cluster headache survey, where cluster headache patients were noted to have a higher prevalence of smoking, alcohol drinking and even body mass indices [8]. Nevertheless, over the years, the exact association between cluster headaches and smoking has been elusive [9–12].

Several studies in the literature noted an association between CH and smoking [13, 14]. It has also been reported that non-smokers who develop CH may have been exposed to secondary smoke during their childhood [14]. Accordingly, several hypotheses have been postulated for this notable association. Cadmium, a main constituent in cigarettes, was hypothesized to cause hypothalamic-pituitary-gonadal axis toxicity leading to the development of cluster headache [14]. More recently, several genetic loci have been identified implicating smoking as a potential causative risk factor to CH [15]. Another proposed mechanism is the negative effect of nicotine on trigeminal nociception [8]. Other hypotheses include the tobacco-induced estrogenization of the brain exacerbating CH and the toxic effect of nicotine and cadmium on the cerebral cortex [14].

To date, however, the studies comparing the clinical features of cluster headaches in smokers versus never smokers have shown contradicting results, further emphasizing the need for more descriptive data [16, 17]. Moreover, scarce data exists about the association between smoking and CH clinical features and the contribution of smoking to the responsiveness of cluster headaches to treatment, particularly in the Middle East region. Therefore, the aim of this study was to evaluate the relationship between smoking and CH presentation and responsiveness to treatment in a tertiary headache clinic in Egypt.

Methodology

Study design, setting, and participants

This was a prospective study conducted on patients with CH attending the headache outpatient clinic at Alexandria University Hospital in Egypt. The headache clinic at Alexandria University hospital is a tertiary public clinic that serves four big cities in Egypt with a population size of more than 16 million citizens. All adult patients (≥18 years old) fulfilling the ICHD-3 for episodic [3] or chronic cluster headache [4] attending at the clinic during the period between April 2019 to April 2023 were eligible for recruitment. Patients with mixed other types of headaches (e.g., migraine, tension-type headache, secondary headache syndromes … etc.) were excluded. The diagnosis was made by a headache consultant with a more than 15-year of experience in the field of headache.

Data collection and study procedure

Eligible patients were consecutively recruited when presented at the clinic during the study period. At the baseline visit, an interview was made with the patients (patient doctor interview) to collect their demographic, clinical data, and the impact of headache on quality of life using the headache impact test 6 (HIT-6) (Supplementary material) [18, 19]. The questions asked were the patient's gender, age, smoking index (number of cigarettes smoked per day divided by the number of years of smoking), smoking duration, average number of cigarettes consumed daily, age at onset of smoking, history of exposure to smoking during childhood, headache type (episodic versus clinic), number of CH attacks per day, bouts in the past five years, and associated autonomic symptoms. The questions were developed by an expert headache specialist based on data from the literature. The interview lasted for around 30 min. All patients were prescribed their medical treatment (steroids bridging therapy and prophylactic treatment) according to the best clinical practice, and they were prospectively followed up after two weeks to assess their treatment responses. The steroid therapy given to all patients was a single intramuscular injection of Betamethasone sodium phosphate 4 mg and Betamethasone Dipropionate 10 mg given once at the start of treatment. No oral steroids were administered or injected at the greater occipital nerve (GON) for any of the recruited cases.

The patients were asked to fill a headache diary through the two-weeks follow-up period, in which they were

asked to record each attack date, duration, and severity. In the follow-up visit, the responsiveness to treatment was categorized as adequate (i.e., defined as ≥50% reduction in the headache frequency, severity, and/or duration) and inadequate (i.e., defined as <50% reduction in the headache frequency, severity, and/or duration) compared to the previous month. It is to be noted that none of the recruited patients was on preventive therapy at the time of recruitment (while some used preventive medications during previous bouts). Patients were also prescribed abortive therapies, but this data was not collected because it was out of the scope of the aim of this study.

Statistical analysis

All data were fed into a laptop and analyzed using the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) software version 20.0. Qualitative data were summarized as frequencies and percentages. The normality of the distribution of the quantitative data was evaluated using the Shapiro-Wilk test. Normally distributed (parametric) quantitative data were summarized using minimum, maximum, mean and standard deviation (SD). Abnormally distributed (non-parametric) quantitative data were summarized using median and interquartile range (IQ). The Chi-square test was used to compare qualitative variables between smokers and non-smokers. The student t-test and Mann-Whitney test were used to compare parametric and non-parametric variables, respectively, between smokers and non-smokers. Univariate and multivariate regression analysis was conducted to study the factors affecting the number of cluster headache attacks per day, the number of cluster bouts in the past five years, and the HIT-6 score.

Ethical considerations

Ethical approval was obtained from the ethical committee (EC) of Alexandria University Faculty of Medicine (IRB no. 0012098 [Expires 6-10-2025]) which operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines [20]. The EC has a federal-wide assurance (FWA) [21] from 2010 (FWA no. 00018699 [expires 21-01-2026]). The EC approval serial number of this research is 0306009. An informed consent was obtained from the patients to use their anonymous data for research purposes.

Results

During the study period, 193 patients fulfilling the ICHD-3 criteria of CH presented at the headache clinic. Of them, 172 accepted to be recruited. Of the 172 patients, 144 (83.7%) were smokers. The vast majority of smokers (n=121, 84%) were males. The clinical profile, demographic data, smoking parameters, and treatment responsiveness are summarized in Table 1. All non-smokers (n=28, 100%) reported exposure to passive smoking during childhood, whereas only three-fourths of smokers (n=108, 75%) were passively exposed to smoking during childhood (p=0.001). Of 144 smokers, 100 males (69.4%) had episodic CH and 21 (14.6%) had chronic CH. Among the 28 non-smokers, on the other hand, 8 males (28.6%) had episodic CH and 2 only (7.1%) had chronic CH. In general, 108 (82.44%) of 131 males had episodic CH and 23 (17.56%) had chronic CH. Of note, smokers had a significantly higher median number of cluster episodes in the past five years (3.0 [IQR2.0–4.0] versus 2.0 [IQR 1.0–2.0]) and worse HIT-6 scores (51.0 [IQR 44.0–59.75] versus 41.0 [IQR 38.0–41.7]) among non-smokers (p<0.001). There was no statistically significant difference between the smokers and non-smokers regarding the type of headache (episodic versus chronic), number of daily attacks during the past month, associated autonomic symptoms, and treatments prescribed (Table 1). It is to be noted all patients underwent initiation on transitional treatment with steroids (intramuscular injection of Betamethasone sodium phosphate 4 mg and Betamethasone Dipropionate 10 mg given once at the start of treatment) along with their prophylactic therapies detailed in Table 1. Of 172 recruited cases, 23 (13.4%) cases lost their follow-up. A detailed treatment response was depicted in Table 2. It is to be noted that smoking did not have a significant impact on any of the response to treatment parameters in CH (p>0.05) (Table 2).

Upon studying the relationship between smoking and clinical characteristics of cluster headache (Table 3), it was noted that the smoking index had a significant positive weak correlation with the number of clusters in the past five years (r=0.249, p=0.006) and a significant moderate positive correlation with the HIT-6 scores (r=0.519, p<0.001) (Fig. 1A and B). It is to be noted in these figures, that we have three outliers with very high smoking indices (i.e., 9600, 12,000, and 13,200, respectively). Two of them were males (44- and 53-year-old men) smoking approximately 400 cigarettes a day for 24 and 33 years respectively (i.e., smoking indices of 9600 and 13,200, respectively). Their CH was of episodic types, and the number of cluster headache episodes could be gathered during data collection. In contrast, the third outlier was a 50-year-old female who has been smoking 400 cigarettes a day for 30 years (i.e., a smoking index of 12,000). She had chronic CH, and therefore, she was omitted (as other cases of chronic CH) from Fig. 1A because the actual number of CH episodes could not be determined.

Similar to the smoking index, the duration of smoking (in years) showed a weak positive correlation with the number of headache clusters in the past 5 years (r=0.392, p<0.001) and a moderately strong positive correlation

Table 1 Demographic and clinical characteristics of the recruited patients ($n=172$)

	Smokers ($n=144$)	Non-smokers ($n=28$)	*P*-value
Gender (n, %)			
- Male	121	10	< 0.001*
- Female	23	18	
Age[#]	39.5 ± 10.09 (22–59)	42.58 ± 11.06 (20–66)	0.152
Smoking parameters			
- Smoking index[†]	540 (300–975)	0	-
- Smoking duration (years) [†]	20.0 (10.25–30)	0	-
- Average cigarettes/day[†]	30.0 (20.0–40.0)	0	-
- Age at onset of smoking	21.0 (18.25–25.0)	0	-
- History of exposure to smoking during childhood	108 (75.0%)	28 (100%)	0.001*
Headache type			
- Episodic	121 (84.0%)	23 (82.1%)	0.459
- Chronic	23 (16.0%)	5 (17.9%)	
- Episodic			
o Males	100 (69.4%)	8 (28.6%)	0.601
o Females	21 (14.6%)	15 (53.6%)	
- Chronic			
o Males	21 (14.6%)	2 (7.1%)	0.241
o Females	2 (1.4%)	3 (10.7%)	
Headache characteristics			
- Number of attacks per day[†]	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.676
- Bouts in the past 5 years[†]	3.0 (2.0–4.0)	2.0 (1.0–2.0)	< 0.001*
- Associated autonomic symptoms.	16 (11.1%)	2 (7.1%)	0.409
- Ptosis	17 (11.8%)	1 (3.6%)	0.168
- Lid oedema	143 (99.3%)	28 (100%)	0.837
- Lacrimation	133 (92.4%)	28 (100%)	0.133
- Conjunctival injection	91 (63.2%)	13 (46.4%)	0.075
- Nasal symptoms			
HIT-6[†]	51.0 (44.0–59.75)	41.0 (38.0–41.75)	< 0.001*
Treatment used [1]	$n=142$	$n=27$	
- Topiramate	38 (26.8%)	6 (22.2%)	-
- Verapamil	89 (62.7%)	17 (63.0%)	-
- Lithium	15 (10.6%)	4 (14.8%)	-
No. of follow-up cases	128	21	--

HIT-6: Headache impact test-6, n: number, *: Statistically significant, [†]: non-parametric data expressed as median and IQR, [#]: parametric data expressed as mean ± SD (minimum– maximum). [1] It is to be noted all patients underwent initiation on transitional treatment with steroids (intramuscular injection of Betamethasone sodium phosphate 4 mg and Betamethasone Dipropionate 10 mg given once at the start of treatment) along with their prophylactic therapies

with the HIT-6 scores ($p=0.611$, $p<0.001$) (Fig. 1C and D). No significant relation was noted between exposure to passive smoking during childhood and the headache presentation and responsiveness to treatment among the patients (Table 4).

On regression analysis, no significant association existed between the number of cluster headache attacks per day and any of the smoking parameters (Table 5). Multivariate regression analysis showed a significant independent impact of age (B=0.028, CI: -1.308:1.225, $p=0.026$), smoking (B=1.11, CI: 0.370: 1.853, $p=0.004$), and the number of headache attacks per day (B=0.605, CI: 0.136: 1.074, $p=0.012$) on the number of cluster episodes in the past five years (Table 6). Age (B=0.350, CI: 0.182: 0.519, $p<0.001$) and age at onset of smoking (B=-0.435, CI: -0.728: -0.142, $p=0.004$) had a significant independent impact on HIT-6 scores (Table 7).

Discussion

This study aimed to investigate the relationship between smoking and CH clinical presentation and responsiveness to treatment in Egypt. The main result of the study was the noted significant association between smoking and the previous five-year frequency of CH episodes and the impact of CH on the patient's quality of life assessed by the HIT-6 scores. To the best of our knowledge, this is the first study from Egypt to address this issue and one of few in the Middle East region.

Overall, we noted that the prevalence of smoking was notably high among our patients (83.7%) when compared to the data from the literature, closely similar to the prevalence reported in Western countries; and higher than that noted in Eastern countries or the Middle East region. For instance, the prevalence of CH was reported to be 72–88% in the United States (US) [17, 22], 85.4–92.5% in

Table 2 Treatment response to steroids along with prophylactic therapy among follow-up cases ($n=149$)

	Overall cases ($n=149$)	Smokers ($n=128$)	Non-smokers ($n=21$)	*P*-value [1]
Overall responsiveness to treatment [2]				
Adequate (≥ 50%)	41 (27.5%)	35 (27.3%)	6 (28.6%)	0.907
Inadequate (< 50%)	108 (72.5%)	93 (72.7%)	15 (71.4%)	
Categorized response to treatment [3]				
Improvement ≥ 50%	41 (27.5%)	35 (27.3%)	6 (28.6%)	0.787
Improvement 1–50%	98 (65.8%)	84 (65.6%)	14 (66.7%)	
No improvement	10 (6.7%)	9 (7.0%)	1 (4.8%)	
Improvement in CH severity of attacks over the two-week follow-up period				
Improvement ≥ 50%	22 (14.8%)	20 (15.6%)	2 (9.5%)	0.652
Improvement 1–50%	37 (24.8%)	31 (24.2%)	6 (28.6%)	
No improvement	90 (60.4%)	77 (60.2%)	13 (61.9%)	
Improvement in CH frequency of attacks over the two-week follow-up period				
Improvement ≥ 50%	28 (18.8%)	25 (19.5%)	3 (14.3%)	0.614
Improvement 1–50%	34 (22.8%)	29 (22.7%)	5 (23.8%)	
No improvement	87 (58.4%)	74 (57.8%)	13 (61.9%)	
Improvement in CH duration of attacks over the two-week follow-up period				
Improvement ≥ 50%	31 (20.8%)	28 (21.9%)	3 (14.3%)	0.685
Improvement 1–50%	33 (22.1%)	27 (21.1%)	6 (28.6%)	
No improvement	85 (57.0%)	73 (57.0%)	12 (57.1%)	

[1]The *p*-value is for the difference between smokers and non-smokers. [2]The overall response to treatment was defined as reduction in attacks severity, frequency, or duration either ≥ 50% of the baseline values (adequate) or less than 50% of the baseline values (inadequate). [3]The categorized response to treatment was defined as reduction in attacks severity, frequency, or duration either ≥ 50% of the baseline values (adequate), 1 to 50% of the baseline values, or no reduction at all

Table 3 Relation between smoking parameters and the headache presentation and responsiveness to treatment among the smokers' group ($n=144$)

	Age at onset of smoking (years)	Smoking index	Smoking duration (years)	Daily cigarettes consumption
Headache type (episodic/chronic)	$P=0.085$	$P=0.704$	$P=0.855$	$P=0.268$
Number of attacks per day	$r=0.017$ ($p=0.839$)	$r=0.162$ ($p=0.053$)	$r=0.27$ ($p=0.728$)	$r=0.215$* ($p=0.010$)
Cluster bouts in the past 5 years	$r=0.080$ ($p=0.384$)	$r=0.249$* ($p=0.006$)	$r=0.392$* ($p<0.001$)	$r=0.164$ ($p=0.071$)
Presence of autonomic symptoms				
Ptosis	$p=0.439$	$p=0.289$	$p=0.838$	$p=0.060$
Lid oedema	$p=0411$	$p=0.965$	$p=0.772$	$p=0.821$
Lacrimation	$p=0.931$	$p=0.806$	$p=0.889$	$p=0.958$
Conjunctival injection	$p=0.059$	$p=0.547$	$p=0.317$	$p=0.946$
Nasal symptoms	$p=0.182$	$p=0.931$	$p=0.907$	$p=0.590$
Responsiveness to treatment [1]	$P=0.542$	$P=0.290$	$P=0.508$	$P=0.568$
HIT-6	$r=$ -0.190* ($p=0.023$)	$r=0.519$* ($p<0.001$)	$r=0.611$* ($p<0.001$)	$r=0.392$* ($p<0.001$)

HIT-6: Headache impact test-6, n: number, r: Spearman co-efficient, *: Statistically significant, †: Median [1]. : Responsiveness to treatment was categorized as adequate (i.e., defined as ≥ 50% reduction in the headache frequency, severity, and/or duration) and inadequate (i.e., defined as < 50% reduction in the headache frequency, severity, and/or duration) compared to the previous month

Canada [23], 81% in Italy [24], 88–97% in Sweden [25, 26], 60.8% in Korea [13], 73% in Taiwan [27], 63% in Kuwait [28], and 56.9% in Turkey [29]. If previous second-hand exposure during childhood was also considered, then 100% of the patients in our cohort were exposed. Second-hand cigarette smoke exposure during childhood has been reported to be a probable causative or triggering factor for CH development [22, 30]. Female patients with CH were less likely to smoke in our cohort, which was similar to what has been reported in the US CH survey [31]. The prevalence of smoking among patients with CH, as noted in our study (87.7%), is also significantly higher than the prevalence of smoking among the general population in Egypt which is estimated to range from 19.7–30% [32]. Still to date, it is not adequately clear why many patients with CH smoke, whether this is an addictive behavior, a mechanism to relieve CH attacks, or there is a shared pathogenetic mechanism for both conditions. In a recent international genome-wide association meta-analysis study conducted on 4777 cases of CU from European and East Asian cohorts [15], a causal-effect relationship was noted where smoking was identified as a causal risk factor for CH. Smoking was noted to cause long-lasting changes in the expression of certain genes related to the development of CH such as the MERTK and CFTR genes [15]. This effect on genes was reported to last for decades [15].

In our cohort, smoking was significantly associated with the daily frequency of CH attacks, the previous five-year number of attacks, and the HIT-6 scores of the patient. No clear association could be identified

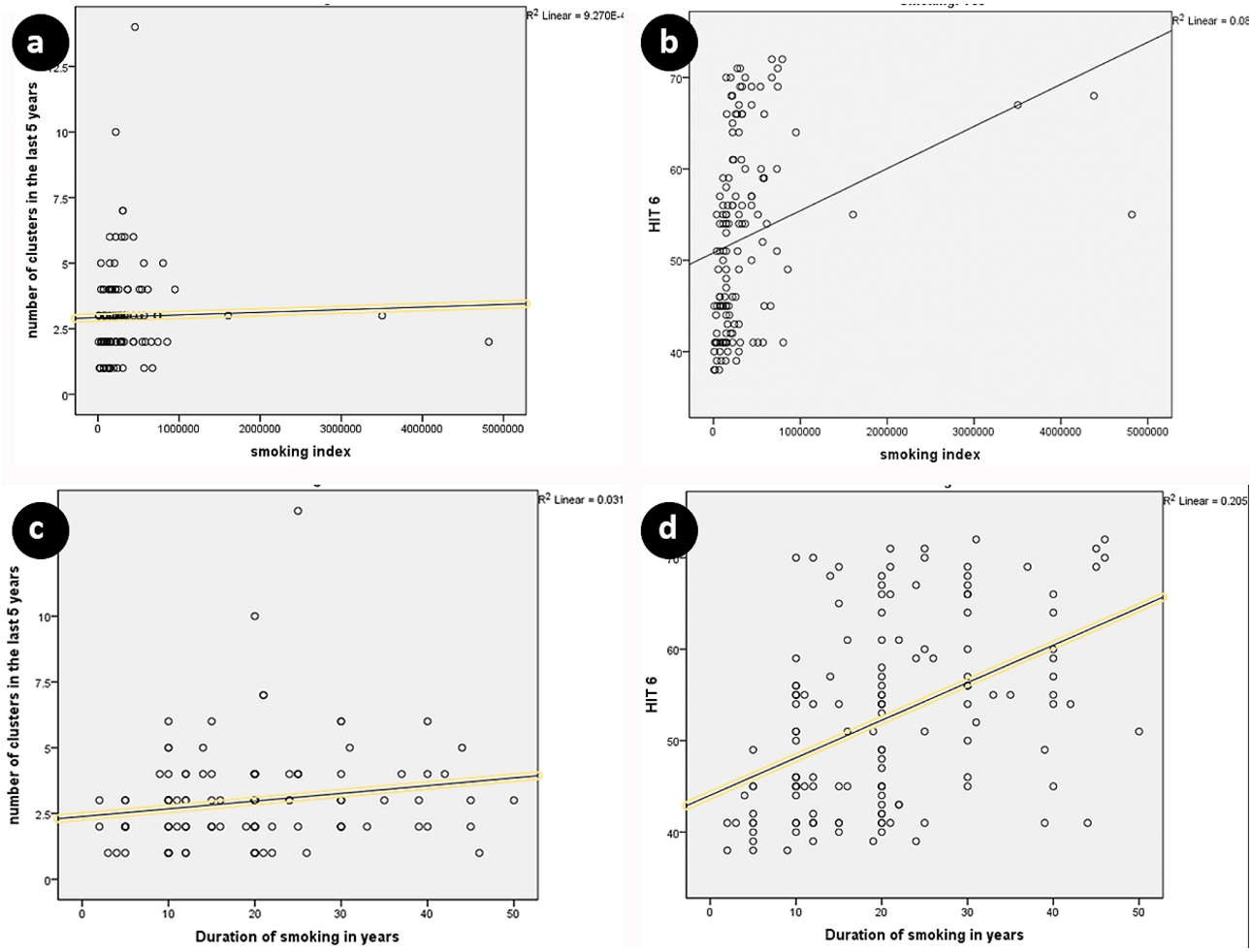

Fig. 1 Scatter plot of the correlation between smoking parameters and clinical characteristics of cluster headache ($n=144$): (**A**) Correlation between smoking index and the number of CH clusters during the previous five years, (**B**) Correlation between smoking index and the HIT-6 scores, (**C**) Correlation between smoking duration and the number of CH clusters during the previous five years, (**D**) Correlation between smoking duration and HIT-6 scores

between smoking and CH chronicity, autonomic symptoms, or responsiveness to preventive therapy. In Western countries, smoking was reported to be significantly correlated with different clinical parameters of CH [17]. Results from the US CH survey of 1134 patients showed that exposure to smoking was statistically associated with younger age at CH presentation, a transition from episodic to chronic CH ($p=0.02$), more autonomic symptoms, less cycles throughout the year ($p=0.02$), higher daily frequency of attacks, longer duration cycles, and higher rates of suicide, work-related disability, and lost home-days [17]. Similar data was reported by *Lund et al.* [33]. , in their Danish cluster headache survey of 400 cluster headache patients and 200 healthy controls, where the clinical presentation of cluster headache was more severe among smokers than non-smokers. Similar to our results, there was no association between smoking and response to preventive therapy [17]. In Canada, *Govare and Leroux* [23] reported, in their study of 166 cases of CH, that quitting smoking had no impact on improving CH. In Sweden, similar to our results, *Levi et al.* [26] reported no association between smoking and CH attack severity or frequency and, thus, suggested smoking as an addictive behaviour probably reflecting specific personality characteristics. In Italy, *Teraferri e al.* [24] studied 200 patients with CH from 2010 to 2012. In their results, they suggested that smoking was an aggravating factor for CH [24]. Smokers, among their cohorts, developed CH at a younger age ($p<0.01$) and had a longer active phase of the disease ($p<0.001$)) than non-smokers [24]. Chronic CH cases had also a higher prevalence of smoking and a high number of cigarette consumption per day ($p<0.01$), which is different from our cohort [14, 24]. This is not the case in our cohort, where there was no association between CH chronicity and smoking. Such difference might be attributed to the low number of chronic CH cases in our cohort. These association between smoking and cluster headache severity, noted in our study and

Table 4 Relation between exposure to passive smoking during childhood and the headache presentation and responsiveness to treatment among the patients ($n=172$)

	History of passive smoking during childhood		*P*-value
	Yes	No	
Headache type (n, %)			
- Episodic	111	33	0.205
- Chronic	25	3	
Number of attacks per day†	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.068
Cluster bouts in the past 5 years†	2.0 (2.0–4.0)	2.0 (2.0–3.0)	0.834
Presence of autonomic symptoms (n, %)			
- Ptosis	13	5	0.314
- Lid oedema	13	5	0.314
- Lacrimation	135	36	0.791
- Conjunctival injection	127	34	0.586
- Nasal symptoms	86	18	0.108
Responsiveness to treatment (n, %)			
- Poor	9	1	0.979
- Fair	33	8	0.451
- Good	73	25	0.412
HIT-6†	46.0 (46.0–57.0)	48.0 (42.25–59.75)	0.575

HIT-6: Headache impact test-6, n: number, †: median and IQR, *: Statistically significant

Table 5 Regression analysis (univariate) of the factors affecting the number of cluster headache attacks per day ($n=172$)

	Univariate regression		
	B	CI 95% (LL: UL)	*p*-value
Age	0.003	-0.005: 0.011	0.508
Gender	0.140	-0.065: 0.345	0.180
Smoking (No/Yes)	0.009	-0.229: 0.247	0.941
Smoking index	6.379	0.000: 0.000	0.820
Number of cigarettes per day	0.017	-0.001: 0.002	0.843
Age at onset of smoking	6.724	-0.016: 0.016	0.993
History of passive exposure to smoking during childhood	0.165	-0.050: 0.380	0.131
Headache type (episodic versus chronic)	0.119	-0.119: 0.357	0.324
Cluster bouts in the last 5 years	0.072	0.018: 0.125	0.009*
Preventive treatment used			
- Topiramate	-0.195	-0.396: 0.007	0.059
- Verapamil	0.049	-0.136:0.234	0.603
- Lithium	0.261	-0.019: 0.541	0.068

CI: Confidence interval, HIT-6: Headache impact test-6, B: Unstandardized co-efficient, LL: Lower limit, UL: Upper limit, *: Statistically significant, #: Smoking index was considered zero among non-smokers

in the previous literature studies, represent a potential speculation, because the increase tobacco use might have resulted from the frequent attacks and not vice versa. Still, the data reported by *Winsvold et al.* [15], in their meta-analysis, are suggestive of smoking being the cause of exacerbated CH severity and not vice versa.

Studies from the Far East showed results similar to ours. On looking at 250 patients with CH from the Korean cluster headache registry, *Pil-Wook Chung et al.* [13]. reported that there was no association between smoking and different clinical features of CH including frequency and autonomic symptoms. They noted an association between triptan responsiveness and smoking ($p=0.001$) [13]. We did not study the response to triptans in our cohort, but we found no association between smoking and responsiveness to preventive therapy. Similarly, *K-H Lin et al.* [27], in their study of 104 patients with CH, reported that smoking did not exacerbate or trigger CH episodes (only 8% compared to 24% with alcohol consumption). The proportion of our patients on different preventive therapies particularly topiramate and lithium was quite high, this was based on the best clinical practice in our country.

Few studies in the Middle East region have addressed the relationship between smoking and CH [28]. In Kuwait, *Jasem Al-Hashel et al.* [28]. reported, in their hospital-based cross-sectional study of 63 patients with CH, that smoking was significantly correlated to chronic

Table 6 Regression analysis (univariate and multivariate) of the factors affecting the number of cluster bouts in the past five years ($n=172$)

	Univariate regression			Multivariate regression		
	B	**CI 95% (LL: UL)**	***p*-value**	**B**	**CI 95% (LL: UL)**	***p*-value**
Age	0.034	0.008: 0.060	0.010*	0.028	-1.308: 1.225	0.026*
Gender	-0.575	-1.236: 0.086	0.088			
Smoking (No/Yes)	1.220	0.456: 1.984	0.002*	1.111	0.370: 1.853	0.004*
Smoking index	0.00	0.00: 0.00	0.305			
Age at onset of smoking	-0.003	-0.058: 0.051	0.909			
History of passive exposure to smoking during childhood	-0.147	-0.835: 0.541	0.674			
Headache type	1.243	-2.238: 4.724	0.481			
Number of attacks per day	0.659	0.169: 1.148	0.009*	0.605	0.136: 1.074	0.012*
Preventive therapy used						
- Topiramate	-0.106	-0.757: 0.545	0.748			
- Verapamil	0.106	-0.545: 0.757	0.748			

CI: Confidence interval, HIT-6: Headache impact test-6, B: Unstandardized co-efficient, LL: Lower limit, UL: Upper limit, *: Statistically significant, #: Smoking index was considered zero among non-smokers

Lithium was not analyzed, due to few cells

Table 7 Regression analysis (univariate and multivariate) of the factors affecting the HIT-6 score ($n=172$)

	Univariate regression			Multivariate regression		
	B	**CI 95% (LL: UL)**	***p*-value**	**B**	**CI 95% (LL: UL)**	***p*-value**
Age	0.307	0.172: 0.442	< 0.001*	0.350	0.182: 0.519	< 0.001*
Gender	-4.881	-8.446: -1.315	0.008*	1.853	0.182: 0.519	0.406
Smoking (No/Yes)	11.573	7.753: 15.394	< 0.001*			
Smoking index	0.002	0.001: 0.003	< 0.001*	0.001	-0.001: 0.002	0.090
Age at onset of smoking	-0.335	-0.598: -0.073	0.013*	-0.435	-0.728: -0.142	0.004*
History of passive exposure to smoking during childhood	-0.855	-4.666: 2.957	0.659			
Headache type	1.736	-2.459: 5.931	0.415			
Number of attacks per day	0.009	-2.662: 2.680	0.007*	-0.417	-3.235: 2.400	0.770
Cluster bouts in the past 5 years	1.401	0.488: 2.314	0.003*	0.594	-0.327: 1.515	0.204
Preventive therapy used						
- Topiramate	3.140	-0.413: 6.693	0.083			
- Verapamil	-3.077	-6.297: 0.142	0.061			
- Lithium	1.152	-3.826: 6.129	0.648			

CI: Confidence interval, HIT-6: Headache impact test-6, B: Unstandardized co-efficient, LL: Lower limit, UL: Upper limit, *: Statistically significant, #: Smoking index was considered zero among non-smokers

CH ($p=0.036$). They noted smoking in 100% of their patients with chronic CH compared to 56.4% among episodic CH patients [28]. This is different from our cohort where smoking was seen in 82% and 84% of chronic and episodic CH cases, respectively. *Jasem Al-Hashel et al.* [28]. did not investigate the detailed relationship between smoking and CH in their study. In Turkey, *Dikmen et al.* [29]. studied 209 patients with CH. They noted a significant association between smoking and a phenotype of CH who are older at age, have less evident autonomic symptoms and are poorly responsive to triptans [29].

The strength points of our study are its prospective nature, along with being one of few studies in the Middle East region and the first – to the best of our knowledge – in Egypt to address the criteria and association of CH with smoking among a population with different ethnicity and race. The main limitations, however, are short follow-up period, the lack of studying some parameters such as smoking cravings, the reciprocal relationship between the attacks and immediate smoking effect, the attack duration, responsiveness to acute therapy (including triptans and oxygen), the impact of smoking quitting on treatment response, and the long-term effect on treatment response. These variables, however, could not be collected in an accurate way to allow their analysis and publication. The sample size is relatively small and may not be representative of the general population of patients with cluster headaches in Egypt or the Middle East region. The study did not collect data on some important variables such as smoking cravings, the reciprocal relationship between the attacks and the immediate smoking effect, the seasonal rhythmicity, the attack duration, responsiveness to acute therapy, the impact of smoking quitting on treatment response, and the

long-term effect on treatment response. The study relied on self-reported data on smoking history and exposure, which may be subject to recall bias and social desirability bias. A power analysis was not also performed, which is another limitation for the current study.

Conclusion

In our cohort, smoking was prevalent among patients with CH. There was a significant relationship between smoking and the CH attacks daily frequency, the previous five-year number of attacks, and the impact of attacks on the quality of life assessed by the HIT-6 scores. However, no clear association was noted between chronic CH and smoking. Smoking had also nothing to do with the responsiveness to preventive therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03706-z.

Supplementary Material 1

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None to declare.

Author contributions
MMH: Research idea, conducting research, and writing; NN: Writing, data collection; EH: Writing, revision, and correspondence.

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Data availability
The data will be available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the ethical committee (EC) of Alexandria University Faculty of Medicine (IRB no. 0012098 [Expires 6-10-2025]) which operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines [20]. The EC has a federal-wide assurance (FWA) [21] from 2010 (FWA no. 00018699 [expires 21-01-2026]). The EC approval serial number of this research is 0306009. An informed consent was obtained from the patients to use their anonymous data for research purposes.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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