Clinical Characteristics and Burden of a Large Series with Cluster Headache From Turkey: A Cross-Sectional Study From Headache Centers

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Abstract

Background: Our purpose was to investigate the demographics, diagnosis patterns, clinical characteristics, triggers, treatment experiences, and personal burden of patients with Cluster headache (CH) in Turkey, a country located between Europe and Asia.

Methods: The study is a cross-sectional investigation based on data from eight headache centers in Turkey. All patients completed the semi-structured survey either face to face or by phone interview with a neurologist.

Results: A total of 209 individuals with a mean age of 39.8 (11.3) completed the survey (176 males; 188 episodic, 21 chronic). The mean age at disease onset was 28.6 (10.2) years. The diagnostic delay was 4.9 years and misdiagnosis before CH was 57.9%. Of participants, 9.1% reported a positive family history for CH. Male patients with CH showed higher rates for being current smokers in comparison to females (59.7% vs. 24.2%; $p<0.0001$) and they also had significantly more past history of smoking at the time of first diagnosis (60.8% vs. 21.2%; $p<0.0001$). Females with CH had a previous diagnosis of migraine more frequently (57.6% vs. 27.3; $p=0.001$). Attack duration without treatment was significantly longer in female patients with CH compared to males (112 min vs. 87 min; $p=0.029$). Female participants had more migrainous features (57.6 % vs. 36.9%; $p=0.033$) and nausea/vomiting (48.5% vs. 30.1%; $p=0.045$) during their attacks. Only 42.1% of all participants reported satisfying treatment experiences. Of the participants, 85.9 % reported that oxygen was efficient for abortive treatment of CH; however, only 22 % of them had an oxygen tube at home. Female participants, as well as chronic CH patients, reported a higher likelihood of preventive treatment experiences. In this study, 49.3% of all participants appeared to be disabled by their headaches. Over one-quarter percent of our cohort reported that CH caused job-related burden.

Conclusion: Remarkable diagnostic delay is an ongoing problem for CH and migraine was the most common misdiagnosis. Nearly half of the patients suffered from a burden of CH regardless of chronicity. Both past abortive and preventive treatment experiences of the participants highlight the insufficient efficacy of available choices and the necessity of more specific treatments for CH.

Introduction

Cluster headache (CH) is the most common form of the trigeminal autonomic cephalalgias and defined by short lasting attacks of excruciating unilateral headache associated with ipsilateral autonomic features and/or restlessness or agitation [1]. The diagnosis of CH is firmly based on clinical history because of the lack of a diagnostic marker. The prevalence of CH is estimated at 0.5-3/1000, with male predominance [2]. Even the prevalence of CH is fairly rare compared with migraine, more than 500.000 individuals are probably experiencing this “suicidal” primary headache syndrome, in the United States of America (USA) alone [3]. The neurobiological mechanism underlying CH remains incompletely understood, so far. Hypothalamic activation along with secondary activation of the trigeminal-autonomic reflex is the leading hypothesis in CH pathophysiology [4–7].

The investigation of burden is important to detect not only for ictal but also for interictal consequences of the headache disorders. Therefore, individual problems may be targeted selectively and then it is much easier to act against them. So far, studies on headache burden mostly focus on migraine. Unfortunately, the substantial

burden and consequences of living with CH have received less attention. Results of the Eurolight CH Project showed that the disease can have a huge and potentially irreversible impact on patients' lives even during interictal periods [8]. Considering the gender differences in the clinical presentation of CH, studies have reported that females with CH suffered from increased associated migrainous features, longer duration of untreated attacks, association with hormonal fluctuations and tended to have a positive family history of migraine [9–17]. It is well-known that headache disorders show geographic and ethnic differences between Asian and Western countries. Studies from Asian population disclosed that CH patients had a stronger male predominance, lower rates of clinical presentation with restlessness, extremely rare aura rate, a lower circadian rhythmicity, and lower headache attack and bout frequencies, and rare presentation with the chronic form [10, 18–23].

There is still no published study about CH from Turkey, which has a unique geographical location in the intersection of Asia and Europe. Therefore we aimed to investigate the demographics, diagnosis patterns, clinical characteristics, triggers, treatment experiences and personal burden of CH patients in Turkey. The second purpose was to search for gender differences in CH. Lastly, episodic CH (ECH) patients and chronic CH (CCH) patients were compared to elaborate similarities and disparities between two forms.

Material And Methods

Study population

The study is a cross-sectional investigation (performed between January and June 2020) based on data from eight headache centers in Turkey. Participants were recruited from the headache centers by two ways. First, patients diagnosed with CH were searched for retrospectively in the from records of the headache centers. Then, they were invited by phone to participate in the study. One-hundred-sixty-eight patients with CH volunteered to participate into the study. Second, newly diagnosed patients with CH were also enrolled from the outpatients or emergency clinics of these centers during the recruitment period. Forty-one participants with episodic CH were enrolled into the study in that way. Eleven individuals rejected to participate in the study. We did not reach out to 21 patients with CH by theirs phones or emails. All patients were evaluated by an experienced headache specialists and their diagnoses of CH were checked according to the International Classification of Headache Disorders-3 criteria [1].

Inclusion and exclusion criteria

Inclusion criteria for the study were willing to participate in the study and being diagnosed with ECH or CCH by a headache expert. Exclusion criteria were diagnosis of secondary CH, unwillingness to participation, illiteracy, unstable medical and psychiatric condition. Informed consent was obtained from each participant following a detailed explanation of the aims of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki". The study was approved by the Acıbadem University Ethics Committee.

Assessments

All patients completed the semi-structured survey either face to face or by phone interview with a physician, due to the restrictions after the pandemic. The survey was composed of 85 questions which addressed sociodemographic characteristics as well as clinical features, delay of diagnosis, triggers for attacks,

treatment experiences and personal burden in CH (Appendix 1). Majority of the questions were adopted from the USA Cluster Headache Survey [14, 24].

Statistical Analysis

No statistical calculation of power was performed prior to the study. The sample size was based on available data. All analyses were planned by authors PYD, BB and ME. For missing data, the percentages were calculated from valid cases. Normality of data was evaluated by using Shapiro Wilks test. Data expressed as mean (Standard deviation (SD)) and percentages (%). Three groups analysis were done (all patients, females vs. males and episodic CH patients vs. chronic CH patients). For the comparison of categorical data, Chi-square (X2) test, Yates Continuity Correction and Fisher Exact test were used, where appropriate. For analyses of numerical data, Mann-Whitney U test was used for non-normally distributed two groups comparison and Kruskal Wallis test was used for non-normally distributed more than two variables. Post hoc pairwise comparisons were performed by using Bonferroni corrected Mann Whitney U test.

Statistical analysis was made using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY). $P < 0.05$ was considered significant.

Results

A total of 209 individuals with a mean age of 39.8 (11.3) (range: 18–71 years) completed the survey [176 males (84.2%) and 33 females (15.8%); 188 episodic (88.5 %), 21 chronic (11.5 %)] CH. The mean age at onset was 28.6 (10.2).

In this study, the participants were enrolled from 8 headache centers located in five different geographical regions in Turkey (Marmara, Aegean, Mid-Anatolian, Mediterranean, South-East Anatolian regions).

1. Demographics

Table 1 shows demographics, past and family history characteristics as well as, comorbidities and diagnostic issues of the main group as well as the subgroup comparisons in terms of gender and ECH vs CCH. In the main CH group, the mean age at first diagnosis was 33.5 (11.1) years and the diagnostic delay before the correct diagnosis was 4.9 (6.3) years.

Table 1
Demographics, family and smoking history and diagnostic issues of the patients with cluster headache.

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	39.8 (11.3)	39.6 (11.0)	41 (12.6)	0.555	40.1 (11.2)	37.7 (11.9)	0,350
Age of onset	28.6 (10.2)	28.8 (10.1)	27.1 (10.8)	0.399	28.6 (10.0)	28.3 (12.1)	0,923
Age at first diagnosis	33.5 (11.1)	33.4 (10.8)	33.9 (12.9)	0.848	33.7 (10.9)	31.6	0,438
Diagnostic delay (years)	4.9 (6.3)	4.6 (6.0)	6.8 (7.6)	0.123	5.2 (6.4)	3.3 (4.5)	0.073
	n, %	n, %	n, %		n, %	n, %	
Male sex	176 (84.2)	-	-	-	157 (84.9)	19 (79.2)	0.550
Head trauma before the diagnosis	21 (10)	20 (11.4)	1 (3.0)	0.210	18 (9.7)	3 (12.5)	0.716
Previous diagnosis with other conditions	121 (57.9)	98 (55.7)	23 (69.7)	0.179	108 (54.8)	13 (54.2)	0.827
Previous diagnosis with migraine	67 (32.1)	48 (27.3)	19 (57.6)	**0.001***	59 (31.9)	8 (33.3)	0.887
Current smoking	113 (54.1)	105 (59.7)	8 (24.2)	**< 0.0001***	99 (53.5)	14 (58.3)	0.828
Smoking at the diagnosis	114 (54.5)	107 (60.8)	7 (21.2)	**< 0.0001***	100 (54.1)	14 (58.3)	0.828
Parental smoke exposure during childhood	110 (52.6)	94 (53.4)	16 (48.5)	0.705	94 (50.8)	16 (66.7)	0.192
Alcohol consumption	89 (42.6)	74 (42)	15 (45.5)	0.848	81 (43.8)	8 (33.3)	0.385
Family history with CH	19 (9.1)	16 (9.1)	3 (9.1)	1.000	18 (9.7)	1 (4.2)	0.704
Family history with heart disease	70 (33.5)	64 (36.4)	6 (18.2)	**0.046***	60 (32.4)	10 (41.7)	0.367
Family history with headache	103 (49.3)	85 (48.3)	18 (54.5)	0.572	94 (50.8)	9 (37.5)	0.279

N: Number of subjects, SD: Standard deviation, CH: Cluster Headache, * = $p < 0.05$

Male patients with CH displayed higher rates for being current smokers in comparison to females (59.7% vs. 24.2%; $p < 0.0001$) and they also had significantly more past history of smoking at the time of first diagnosis (60.8% vs. 21.2%; $p < 0.0001$). Moreover, males had significantly more family history of heart diseases (36.4% vs. 18.2%; $p = 0.046$). On the other hand, females with CH had previous diagnosis with migraine more frequently (57.6% vs. 27.3; $p = 0.001$).

2. Diagnosis issues

Majority of the patients with CH (97.1%) were diagnosed by a neurologist compared to a non-neurologist in Turkey. Diagnostic delay was 4.9 years for all CH patients. In the current study, 57.9% (n = 121) of the patients had initial different wrong diagnoses like migraine (n = 67; 32.1%), sinusitis (n = 57, 27.3%), others (n = 19, 9.1%), multiple diagnoses (n = 9, 4.3%), allergy (n = 7, 3.3 %), dental problems (n = 6, 2.9%).

3. Attack characteristics (Table 2)

Table 2
Clinical characteristics of the patients with Cluster Headache

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Attack duration without treatment (min)	91.75 (58.08)	87.93 (57.57)	112.81 (57.19)	**0.029***	88.95 (53.83)	106.30 (85.14)	0.377
Attack duration with treatment (min)	40.96 (31.58)	39.77 (30.27)	47.27 (37.75)	0.287	40.51 (31.47)	44.38 (32.98)	0.592
Attack duration with O2	25.12 (20.24)	23.50 (16.38)	34.35 (34.05)	0.147	24.43 (19.38)	29.75 (25.36)	0.377
NAS	8.73 (1.3)	8.68 (1.3)	8.97 (0.98)	0.152	8.71 (1.3)	8.83 (1.0)	0.601
Number of autonomic symptoms	2.5 (1.2)	2.5 (1.2)	2.5 (1.2)	0.837	2.5 (1.2)	2.8 (1.5)	0.272
Unilateral autonomic symptoms	N (%)	N (%)	N (%)		N (%)	N (%)	
Conjunctival injection	115 (55)	102 (58.0)	13 (39.4)	0.058	99 (53.5)	16 (66.7)	0.278
Lacrimation	167 (79.9)	140 (79.5)	27 (81.8)	1.000	149 (80.5)	18 (75)	0.588
Nasal congestion	115 (55)	98 (55.7)	17 (51.5)	0.705	103 (55.7)	12 (50)	0.665
Rhinorrhea	93 (44.5)	82 (46.6)	11 (33.3)	0.184	82 (44.3)	11 (45.8)	1.000
Unilateral eyelid oedema	105 (50.2)	85 (48.3)	20 (60.6)	0.255	91 (49.2)	14 (58.3)	0.516
Forehead sweating	56 (26.8)	52 (29.5)	4 (12.1)	0.052	48 (25.9)	8 (33.3)	0.466
Facial sweating	53 (25.4)	47 (26.7)	6 (18.2)	0.386	43 (23.2)	10 (41.7)	0.078
Myosis and/or ptosis	51 (24.5)	42 (24.0)	9 (27.3)	0.655	43 (23.4)	8 (33.3)	0.315
A sense of restlessness or agitation	115 (55)	98 (55.7)	17 (51.5)	0.705	101 (54.6)	14 (58.3)	0.829

N: Number of subjects, SD: Standard deviation, CH: Cluster Headache, NAS: Numeric Analogue Scale, min: minutes, O2: Oxygen, * = $p < 0.05$

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
Migrainous features	84 (40.2)	65 (36.9)	19 (57.6)	**0.033***	74 (40)	10 (41.7)	1.000
Aura	56 (26.8)	44 (25)	12 (36.4)	0.362	47 (25.4)	9 (37.5)	0.428
Nausea/vomiting	69 (33)	53 (30.1)	16 (48.5)	**0.045***	61 (33.0)	8 (33.3)	1.000
Photophobia/Phonophobia	29 (13.9)	22 (12.5)	7 (21.2)	0.180	24 (13.0)	5 (20.8)	0.343
Vertigo	15 (7.2)	14 (8.0)	1 (3.0)	0.475	14 (7.6)	1 (4.2)	1.000
N: Number of subjects, SD: Standard deviation, CH: Cluster Headache, NAS: Numeric Analogue Scale, min: minutes, O2: Oxygen, * = $p < 0.05$							

Attack duration without any treatment was significantly longer in female patients with CH compared to males (112 min vs. 87 min; p = 0.029). Moreover, female participants with CH had more migraineous features (57.6 % vs. 36.9%; p = 0.033) and nausea/vomiting (48.5% vs. 30.1%; p = 0.045) during their attacks.

In terms of the frequency of unilateral autonomic symptoms, there was no statistical difference between males and females and episodic vs. chronic courses.

3.1. Months of the year that cluster cycles would start

January (20.3%), December (13.5 %), July (10.8 %) October (10%) and November (10.8%) were the most commonly reported months which the “last” previous cluster headache cycles had started in ECH patients.

Change of the season as a trigger for a bout was reported by the majority of the ECH patients compared to CCH (85.2 % vs. 60.9 %; p = 0.008). The most cited period of time for a bout initiation was the turning point to a spring from a winter (26.9%) for those patients. Menstruation was reported as a trigger only by 3.3% of female patients with CH.

3.2. Number of the attacks per day for all participants was 2.5 (1.2). There was no statistical difference between females vs. males and episodic vs. chronic patients.

3.3. Time of the day for cluster attacks

In this study, 82.3% (n = 172) of the participants reported that their CH attacks had started exactly the same time of a day [nighttime: n = 120 (57.7%); daytime: 58 (27.9%); both: n = 30; 14.4%]. A total of 40 patients (% 19.1) had hurt themselves during CH attacks [33 males (18.8%) vs. 7 females (21.3%); p = 0.810].

3.4. Average number of the bouts per year

Majority of ECH patients had more than one cycle per year (76.1%) followed by one cycle in two years (15.8%). Both males and females with CH reported more than one bout per year (74.3% vs. 66.7%) (p = 0.395), followed

by one bout in two years (14.9% vs. 24.2%) (p = 0.327).

3.5. Cluster headache features

In this study, 49.8% and 47.8% of the participants had right and left-sided attack, respectively. Only 3.3 % of the patients (n = 7) experienced side-changing attack during the same bout. However, 10% of the participants (n = 21) reported side-changing among different bouts of them.

Aura was reported by 26.8% of the participants and the most common reported aura type was visual (n = 19, 9.1%). Localizations of the pain during CH attack were behind the eye (n = 189, 90.4%), on the temple (n = 135, 64.6%), upper teeth pain (n = 58, 27.8%), jaw (n = 21, % 10), ear (n = 18, %8.6) and neck/shoulder areas (n = 32, %15.3). Pain in the temple (84.8% vs. 60.8%; p = 0.009) and an ear (18.2%; vs. 6.8%; p = 0.044) were more commonly reported pain locations in females compared to counterparts.

Triggers for CH attack were seasonal change (n = 104, 49.8%), stress (n = 49, 23.4%), alcohol (n = 40; 19.1%), sleep deprivation (n = 37, 17.7%), others (n = 33, 15.8%), multiple factors at the same time (n = 27, 12.9%) and menstruation (n = 7, 3.3%). As a trigger, sleep deprivation was cited higher in CCH patients (50% vs. 13.5%; p < 0.0001) compared to ECH patients; however, seasonal changing was mostly reported by episodic ones (52.4% vs. 29.2%; p = 0.049).

4. Neuro-radiological imaging

In the current study, all patients had brain magnetic resonance imaging (MRI) and 32.1% of them had at least more than one radiological imaging (3.6 ± 2, 2–16). Twenty-four patients (11.5%) had nonspecific findings in their brain MRIs regardless to their diagnoses.

5. Cluster headache treatment (Table 3)

Table 3
Treatment experiences of the patients with Cluster Headache

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Average duration for bout treatment (weeks)	4.5 (6.7)	4.3 (6.6)	5.5 (7.5)	0.423	3.9 (4.7)	11.2 (17.0)	0.121
Acute treatment	N (%)	N (%)	N (%)		N (%)	N (%)	
Triptans	104 (50.0)	82 (46.6)	22 (68.8)	**0.033***	94 (50.8)	10 (43.5)	0.659
Oxygen	153 (73.6)	135 (77.1)	25 (75.8)	0.825	139 (71.4)	21 (91.3)	**0.045***
Paracetamol	22 (10.6)	18 (10.2)	4 (12.5)	0.757	20 (10.8)	2 (8.7)	1.000
NSAI	99 (47.6)	84 (47.7)	15 (46.9)	1.000	88 (47.6)	11 (47.8)	1.000
Dihydroergotamine	14 (6.7)	13 (7.4)	1 (3.1)	0.700	12 (6.5)	2 (8.7)	0.657
Others	18 (12.8)	14 (11.5)	4 (21.1)	0.267	16 (13.1)	2 (10.5)	1.000
No treatment	18 (8.7)	17 (9.7)	1 (3.1)	0.319	16 (13.1)	2 (10.5)	1.000
Treatment experiences							
Acute treatment is efficient (yes)	88 (42.1)	70 (39.8)	18 (54.5)	0.127	80 (43.2)	8 (33.3)	0.389
Oxygen is efficient (yes)	140 (85.9)	121 (87.1)	19 (79.2)	0.340	122 (85.9)	18 (85.7)	1.000
Triptan is efficient (yes)	82 (39.2)	64 (36.4)	18 (54.5)	0.055	74 (40.0)	8 (33.3)	0.658
NSAI is efficient (yes)	55 (26.3)	51 (29.0)	4 (12.1)	0.052	47 (25.4)	8 (33.3)	0.461
Dihydroergotamine is efficient (yes)	4 (1.9)	4 (2.3)	0 (0.0)	1.000	3 (1.6)	1 (4.2)	0.388
Massage is efficient(yes)	11 (5.3)	9 (5.1)	2 (6.1)	0.686	9 (4.9)	2 (8.3)	0.367

N: number of subjects, SD: Standard deviation, CH: Cluster headache, min: minutes, ER: Emergency Room, NSAI: non-steroidal anti-inflammatory, *= $p < 0.05$

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
Sleeping is efficient (yes)	8 (3.8)	8 (4.5)	0 (0.0)	0.361	8 (4.3)	0 (0)	0.701
Concomitant usage of O2 and medication (yes)	76 (46.9)	62 (44.9)	14 (58.3)	0.271	67 (47.5)	9 (42.9)	0.816
O2 tube at home (yes)	40 (22)	33 (21.3)	7 (25.9)	0.617	32 (20.0)	8 (36.4)	0.100
Previous suggestion for having O2 tube (yes)	103 (57.2)	84 (54.9)	19 (70.4)	0.146	90 (57.0)	13 (59.1)	1.000
O2 treatment with facial mask (yes)	151 (72.2)	131 (74.4)	20 (60.6)	0.137	133 (71.9)	18 (75)	1.000
O2 treatment with nasal cannula (yes)	23 (11)	17 (9.7)	6 (18.2)	0.219	20 (10.8)	3 (12.5)	0.733
Knowing O2 treatment protocol (yes)*	105 (66.9)	87 (65.4)	18 (75.0)	0.481	88 (64.7)	17 (81)	0.212
Preventive treatment							
Past treatment (yes)	144 (69.2)	116 (66.3)	28 (84.8)	**0.040***	121 (65.8)	23 (95.8)	**0.002***
Verapamil	152 (72.7)	127 (72.2)	25 (75.8)	0.832	130 (70.3)	22 (91.7)	**0.028***
Lithium	24 (11.5)	20 (11.4)	4 (12.1)	1.000	19 (10.3)	5 (20.8)	0.165
Corticosteroids	76 (36.4)	65 (36.5)	11 (33.3)	0.844	62 (33.5)	14 (58.3)	**0.024***
Melatonin	21 (10.0)	15 (8.5)	6 (18.2)	0.112	19 (10.3)	2 (8.3)	1.000
Flunarizine	12 (5.7)	10 (5.7)	2 (6.1)	1.000	9 (4.9)	3 (12.5)	0.146
Topiramate	21 (10.0)	16 (9.1)	5 (15.2)	0.340	16 (8.6)	5 (20.8)	0.074
Sodium valproate	14 (6.7)	11 (6.3)	3 (9.1)	0.468	11 (5.9)	3 (12.5)	0.207
Botulinum toxin-A	7 (3.3)	6 (3.4)	1 (3.0)	1.000	5 (2.7)	2 (8.3)	0.186
Ganglion block	21 (10.0)	17 (9.7)	4 (12.1)	0.751	18 (9.7)	3 (12.5)	0.716

N: number of subjects, SD: Standard deviation, CH: Cluster headache, min: minutes, ER: Emergency Room, NSAI: non-steroidal anti-inflammatory, *= $p < 0.05$

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
Acupuncture	3 (1.4)	3 (1.7)	0 (0.0)	1.000	2 (1.1)	1 (4.2)	0.308
Others	7 (3.3)	5 (2.8)	2 (6.1)	0.305	5 (2.7)	2 (8.3)	0.186
Current treatment (yes)	50 (24.0)	36 (20.6)	14 (42.4)	**0.013***	41 (22.3)	9 (37.5)	0.126
Use of triptan or NSAI/ every day	22 (10.6)	21 (12.0)	1 (3.0)	0.213	16 (8.7)	6 (25)	**0.026**
ER utilization in past year	108 (52.2)	88 (50.6)	20 (60.6)	0.494	93 (50.5)	15 (62.5)	0.374

N: number of subjects, SD: Standard deviation, CH: Cluster headache, min: minutes, ER: Emergency Room, NSAI: non-steroidal anti-inflammatory, *= $p < 0.05$

5.1. Average duration of preventive treatment for ECH patients

Average duration of a bout treatment for ECH patients was mostly one month [one week (14.8%), 2 weeks (25.1%), 3 weeks (17.5%), 4 weeks (22.4 %), 6 weeks (8.2 %), 8 weeks (6.0 %), 12 weeks (2.7 %) and more than 12 weeks (3.3%)].

5.2. Acute treatment experiences

The most common choice for acute treatment was oxygen (73.6%), followed by triptans (50%) and non-steroidal anti-inflammatory drugs (NSAI) (47.6). Our study showed that female patients with CH had significantly higher use of triptans compared to male counterparts (68.8% vs. 46.6%; $p = 0.033$). Oxygen use was more often reported by CCH patients than episodic ones (91.3% vs. 71.4%; $p = 0.045$).

5.3. Preventive treatment experiences

Rates of past preventive treatment in male CH patients were lower than females (66.3% vs. 84.8%; $p = 0.040$). The participants with CCH reported more common past preventive treatments compared to episodic ones (95.8% vs. 65.8%; $p = 0.002$). In Turkey, verapamil was the most commonly used preventive treatment option and it was used with higher prevalence by CCH patients compared to episodic ones (91.7% vs. 70.3 %; $p = 0.028$). Rates of corticosteroid use in CCH patients was also higher than ECH patients (58.3% vs. 33.5%; $p = 0.024$).

5.4. Current treatment

At time of the study, females were more frequently under preventive treatment than males (42.4 % vs. 20.6%; $p = 0.013$) and 25% of CCH patients had been using triptan or NSAI drugs every day compared to episodic ones (25% vs. 8.7%; $p = 0.026$). More than half of all patients (52.2%) had a need for a visit of Emergency Room (ER) over the past year.

6. Personal Burden (Table 4)

Table 4
The personal burden in all patients with Cluster Headache and subgroup comparisons

Variables	All CH patients (n = 209)	Males (n = 176)	Females (n = 33)	p	Episodic CH (n = 185)	Chronic CH (n = 24)	p
	Yes (n, %)	Yes (n, %)	Yes (n, %)		Yes (n, %)	Yes (n, %)	
Personal burden	102 (49.3)	86 (49.1)	16 (50.0)	1.000	87 (47.3)	15 (62.5)	0.124
Loss in							
Education	23 (11.0)	18 (10.2)	5 (15.2)	0.375	17 (9.2)	6 (25)	**0.032**
Job	72 (34.4)	63 (35.8)	9 (27.3)	0.426	61 (33)	11 (45.8)	0.255
Economics	17 (8.1)	13 (7.4)	4 (12.1)	0.318	15 (8.1)	2 (8.3)	1.000
Relationship with partner	25 (12.0)	19 (10.8)	6 (18.2)	0.244	22 (11.9)	3 (12.5)	1.000
Relationship with friends	10 (4.8)	8 (4.5)	2 (6.1)	0.660	8 (4.3)	2 (8.3)	0.322
N: Number of subjects, CH: Cluster headache, * = $p < 0.05$							

In our study, 49.3% of all participants appeared to be disabled by their headaches. In addition, higher percentage of CCH patients (25%) had loss in education compared to ECH (9.2%) ($p = 0.032$).

Discussion

A large group of patients diagnosed with CH were systematically evaluated in terms of demographics, diagnosis patterns, clinical characteristics, triggers, gender issues, treatment experiences and personal burden by headache experts. There is still a remarkable diagnostic delay of 4.9 years for these patients experiencing severe and disabling headaches in Turkey. Our male CH patients showed higher rates of smoking, and family history of heart disease, whereas female CH patients had more commonly a previous diagnosis with migraine and past preventive treatment experiences of CH (Fig. 1). In addition to that, females reported more migrainous associated features, nausea/vomiting and triptan usage during their longer CH attacks. Moreover, CCH patients reported more frequent oxygen usage, past preventive treatment experiences, higher usage of verapamil and corticosteroid in-bout, and medication overuse headache compared to ECH patients, as expected. Furthermore, a higher percentage of CCH patients reported that their illness was negatively affected their education, probably reducing career opportunities later.

Demographics

In our hospital based cohort, the mean age at onset was 28.6 years, similar to the previous studies and male-to-female ratio was 5.3:1. The gender ratio was more compatible with Asian studies (5.1:1) compared to recent European/North American studies (2-3.1:1) [10, 18, 19, 21–23, 25–27]. Research about the mean time from CH onset to correct diagnosis reported various times in different countries (in the UK: 2.6 years, in Flanders: 3.6 years, in Spain: 4.9 years, in Italy and East European countries: 5.3±6.4 years, in Denmark: 6.2-9 years, in the USA: 6.6–8.5 years, in Japan: 7.3±6.9 years) [20, 28–35]. In our study, diagnostic delay was 4.9 years. In Greece and Flanders, neurologists missed the diagnosis in 40% and 80% of the patients [34, 36]. Even though a majority of our patients were diagnosed by a neurologist in Turkey, a correct initial diagnosis of CH occurred in 42.1% of them. Indeed, this rate was still higher than a previous large internet American survey (21%) [24]. Our finding was probably related to the fact that neurology was the mostly consulted specialty for headache disorders in Turkey because of the health care organization [37]. Our rate of family history for CH (9.1%) was higher than Eastern countries (0-6.7%) and more similar to Western countries (5–17%) [10, 18, 21, 24, 38–40].

It is well-known that the rates of being a previous or current smoker were high in patients with CH, as 73–81% [14, 26, 41]. Our male CH patients had statistically higher rates of past and current smoking compared to females in line with the USA study [24]. The percentage of active smokers in the male CH patients was higher than the average rate of overall active smokers (29.3 %) in Turkey (2018) [42]. Current smokers had higher numbers of attacks with longer bouts than patients with CH who report never having smoked [26, 41]. Although there is no strong evidence between quitting smoking and improvement of CH, smoking may enhance alcohol consumption and alcohol may trigger CH attack [41, 43]. Therefore, it might be wise to advice to quitting smoking for CH patients. But even clinicians gave advice about quitting smoking, our CH patients seemed not to follow it. Thus more strong suggestions might be necessary for those patients.

Gender comparisons

Females with CH had a longer mean duration of untreated attacks than males (112.8 min vs 87.9 min), this finding was compatible with previous studies [44, 45]. Migraine and CH have overlapping features that they share as different primary headache disorders. It was understandable but still interesting to note that females with CH are more frequently misdiagnosed as migraine [31]. Migraine was the leading misdiagnosis regardless of gender differences in Turkey, a pattern similar with the USA findings (32.1% vs. 34%). An important confusing factor in misdiagnosis is the accompanying symptoms during attacks. There is a need for increased awareness, since CH patients can also experience the same accompanying symptoms well-known in migraine, as also seen in Table 2. Migrainous features and nausea/vomiting were frequently reported by females with CH in this study compatible with previous reports [14, 15, 25, 44, 46], explaining the increased misdiagnosis rate in women along with the well-known male dominance of CH.

We observed that female patients were statistically more likely to experience pain in the temple and in the ear compared to men, for unclarified reasons.

Menstruation was cited as a trigger for CH attack in females similar to migraine, but with a low rate of 3.3% of females, in this study. Moreover, autonomic features can also occur in migraine, but usually bilaterally. Hence

the occurrence of either ipsilateral or bilateral autonomic features needs to be carefully questioned in headache patients.

Clinical features

In our study, the most common cranial autonomic symptoms were lacrimation (79.9 %), followed by nasal congestion (55%), and agitation (55 %). In the USA study, lacrimation (91%) and nasal congestion (84%) were also the leading two autonomic symptoms reported in more frequent rates [24]. On the other hand, in Asian studies, lacrimation, conjunctival injection and rhinorrhea were the most common cranial autonomic symptoms [10, 18, 21, 22]. In the USA study, men experienced more frequently lacrimation (92% vs. 88%, p = 0.03), while woman were more likely to experience nausea (41% vs. 34%, p = 0.03). In the Italian study, ptosis and nasal congestion were more prevalent in females [46]. In contrast to aforementioned studies, we did not see any statistical difference between two genders in regard to occurrence of autonomic symptoms. Moreover, we did not see any difference of these symptoms between episodic and chronic CH patients in contrast to previous studies [38, 47].

It is worth to emphasize that the presence of aura is not particularly helpful in the differentiation between migraine and CH. Intriguingly, aura occurs in 14–23% of Western CH patients, but only <%1 of Asian patients [10, 14, 18, 21, 22, 25, 38, 39, 48]. Our finding of 26.8% with aura was pretty similar with the Western cohort studies. Agitation is also the most striking difference between migraine and CH, it was reported up to 93% of patients in the USA population. More than half of our participants (55%) reported a sense of restlessness or agitation during their attacks, remarkably.

January and February were the most frequently reported months of the year that cluster bouts would start in Turkey. Seasonal propensity has been reported partly discordant in studies, this might be related to geographical location of countries [10, 22, 24]. Seasonal changing, stress and alcohol were the most common triggers for attacks in our study. Sleep deprivation was more likely to be reported by chronic CH patients. The chronobiological features of CH have been extensively studied [13, 49]. Higher risk was reported at 21.41, 02.02 and 06.23 [49]. However, the highest peak was during the afternoon in an Italian population [13]. In our cohort, 82.3% of the participants reported that they had the exact same time of the day for CH attacks and an increased risk peak was found at the night (57.7%). Many factors might be related to this timing like light exposition in different altitudes and different sociocultural habits [13]. In Western, Japan and Korean studies, nocturnal CH attacks were frequent (58–73%), whereas CH patients (65%) had both diurnal and nocturnal attacks in some Asian studies [10, 20, 22, 24, 38, 40, 47].

Treatment experiences

We noted that triptans were more widely preferred by our female patients with CH, partly explained by longer attack durations. In regard to the effectiveness of abortive treatment, only 42.1% of all participants reported satisfying treatment experience. CCH patients (33.3%) gave lower scores about effectiveness of acute therapies, as expected. But still the rates of oxygen use for attacks were statistically higher in CCH patients compared to episodic ones. Oxygen has been well-known as an acute treatment of CH since 1985 [50]. Studies have shown that oxygen therapy frequently was found to be effective by more than 75% of patients in both Western and Asian countries [19, 21, 51–54]. In the current study, 85.9 % of all participants reported that oxygen was efficient for an abortive treatment of CH; however only 22 % of them had oxygen tube in their

home. In our hospital-based population, only 57.2% of all participants remembered that they had a previous advice for having an oxygen tube at home. Moreover 11% of all participants had been using a nasal cannula instead of a non-breather mask during oxygen treatment and 33.1% of our cohort did not know about an exact oxygen treatment protocol for CH attacks [55]. These findings may be related to insufficient patient education, difficulty to obtain durable medical equipment of home oxygen because of insurers and unreluctance of patients to have this equipment in spite of enough suggestion and encouragement from clinicians. Subcutaneous sumatriptan 6 mg has been shown to be effective as an abortive treatment of CH [55]. Zolmitriptan and sumatriptan spray can both be used as an alternative treatment of CH attacks, but they are not available in Turkey [55]. In the current study, efficacy of triptan treatment was reported by 39.2% of the participants. Indeed, females had statistically more frequently used triptans in their attacks and also reported to effectiveness of triptans more superior compared to males (54.4% vs. 36.4%; NS). In the USA study, females were significantly more likely to respond to sumatriptan than males (injectable sumatriptan 72% vs. 86%, p = 0.003; nasal spray 35% vs. 47%, p = 0.02). The response rates to triptan in Asian studies have been reported as 80-97.3% of the CH patients [19, 21, 52, 54]. Our response rates to triptan treatment seems to be lower than other studies. This finding might be related to genetic differences, wrong timing of usage or unavailability of some active drugs in Turkey.

Corticosteroids are commonly used as bridging therapy of CH [56, 57]. In our cohort, 36.4% of the participants had past experiences with steroid therapy. Another bridging therapy is suboccipitical nerve block injections with steroids [55]. In our study, only 10% of the participants were treated with nerve block injections.

In this study, 69.2% of the participants had been treated with preventive medicines. As expected, female participants as well as CCH patients reported higher likelihood of preventive treatment experiences. The average duration of bout treatment was 4.5 weeks in this study. Past experiences with other preventive treatment agents were lower (around 10% for lithium, melatonin, topiramate) in Turkey and verapamil (72.7%) was obviously many clinicians' first choice in our country.

During the study enrollment, 24% of all participants were under treatment for CH, and female gender showed statistical significance compared to males (42.4% vs. 20.6%; p = 0.013). Medication overuse headache is another important, yet controversial topic in CH [58–60]. Ten percent of the participants and 25% of CCH patients reported usage of triptan or NSAI drugs every day. Despite the treatment efforts in the headache centers, in our study, at least 50% of the participants reported ER admission in the previous year, a finding indicating the need for more efforts in acute treatment of CH.

The disease burden of cluster headache

The burden of a disease has many dimensions such as symptom burden, disability burden, lost-productivity burden, interictal burden, cumulative burden and financial burden. Personal burden related to CH was reported by 49.3% of the patients in our study. CCH patients appeared to be more disabled by their headaches in terms of loss in their education (25% vs. 9.2%). Over one-quarter percent of our cohort reported job related burden. As expected, it was higher in CCH patients (45.8 vs. 33%). A consequence of lost school-time and/or recurring inability to work may reduce the probability of promotion and decreased career opportunities for those patients. Furthermore, these cumulative effects might be resulted in difficulties on relationships, love life and family dynamics.

Limitations and strengths

Several limitations were present in this study. Firstly, our cohort was hospital-based. For that reason, our findings and conclusions may not generalize to community-based patients. Secondly, we collected data retrospectively from patients' files and from interviews. Hence, recall bias may obscure our results [61, 62]. Thirdly, it is possible that coexisting migraine diagnosis in our cohort may create problems. This comorbid condition might blur some our results such as the presence of aura, associated symptoms, and triggers. But investigation of the files and the interviews were realized by headache experts and we tried to isolate CH findings from migraine as far as we can. Fourth, it might be hard to precise conclusions regarding treatment experiences retrospectively without any established guide or previous consensus among the centers. Nevertheless, the study has some obvious strengths. This is the first large-sized multicenter study about CH from Turkey and our findings were gathered on face-to-face or detailed phone interviews due to pandemic by experienced headache specialists. Moreover, we compared results of two genders and two forms of CH to get more detailed picture of this ominous disease.

In conclusion, remarkable diagnostic delay is an ongoing problem for CH and migraine was the most common misdiagnosis, especially for females with CH due to longer attacks and higher rates of associated symptoms. Therefore females who have confounding features about a diagnosis of CH need to be examined in detail. In the treatment part, even though higher oxygen efficacy for attack treatment, only 22% of patients had oxygen tube in their homes. We think that the availability of oxygen tube may reduce ER utilization of the patients for abortive treatment. Finally, nearly half of the patients suffered from a personal burden of CH and at least one-third of them had job related burden in our country. Past treatment experiences of the patients underscore insufficient efficacy of available choices and need for more specific abortive and preventive treatment options.

Declarations

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Figures

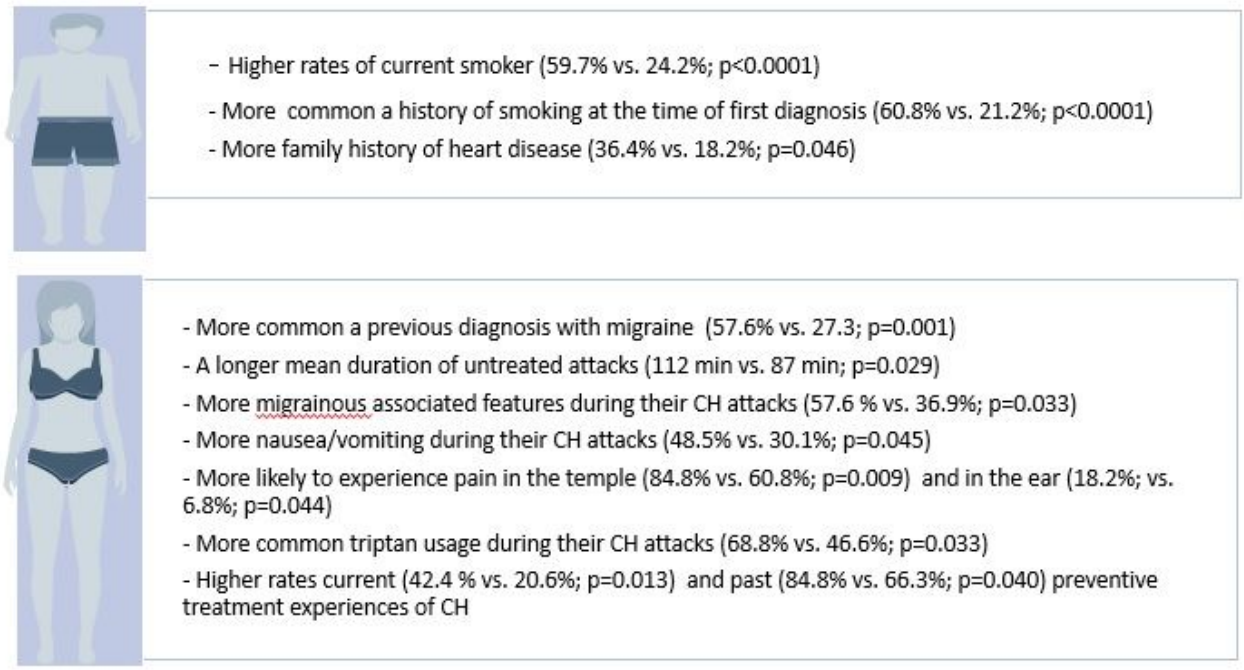

Figure 1

Comparison of male and female patients with Cluster Headache

Supplementary Files

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- ClusterHeadacheQuestionnaire.doc