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Headache and Facial Pain Lasting Less Than Four Hours: Focus on Patients with Cranial Autonomic Features

Dört Saatten Kısa Süren Baş ve Yüz Ağrıları: Kraniyal Otonomik Bulguları Olan Hastalara Odaklanma

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Abstract

Objective: The aim of our research was to evaluate the demographic and clinical features, treatment characteristics, and responses of the patients who presented to the Ege University Neurology Headache Outpatient Clinic with headaches lasting less than 4 hours. Another primary goal was to compare the characteristics mentioned above of patients with and without cranial autonomic symptoms.

Materials and Methods: Our study was retrospective and cross-sectional. The findings were based on the data collected at our tertiary headache center. Headache disorder diagnoses were made in accordance with the International Classification of Headache Disorders-3 guideline. We reviewed the patients' charts and recorded the information on a standardized form. The patients' clinical features, and treatment responses were noted. The patients were divided into two groups as those with and without autonomic findings, and the above-mentioned features were compared. Treatment responses of patients with trigeminal autonomic cephalgia (TAC) and patients with trigeminal neuralgia (TN) were analyzed via logistic regression analysis. Values of $p<0.05$ were considered statistically significant.

Results: Sixty-eight patients were included. Twenty-five patients had TAC. Twenty-three patients had TN and 13 had tension type headache. Seven had other primary headaches. The patients' clinical features and treatment responses were different in the subgroups. In patients with TAC , having a triggering factor [Odds ratio (OR): 0.059, 95% confidence interval (CI): (0.005-0.645); p=0.02] reduced the risk of need of attack treatment. In patients with TN, having a brainstem lesion on cranial magnetic resonance imaging sequences [OR: 24.776, 95% CI: (1.033-60.613); p=0.049] increased the risk of long-term treatment failure with carbamazepine, whereas having headache attacks more than once a day [OR: 0.58, 95% CI: (0.04-0.832); p=0.036] decreased the risk.

Conclusion: The correct diagnosis of headache disorders is mainly based on the clinical features of the headache. For an effective treatment initiation, a correct diagnosis is mandatory, entirely dependent on adequate history taking.

Keywords: Headache, face, pain, shorter

Öz

Amaç: Araştırmamızın amacı Ege Üniversitesi Nöroloji Baş Ağrısı Polikliniği'ne 4 saatten kısa süren baş ağrısı ile başvuran hastaların demografik ve klinik özelliklerini, tedavi özelliklerini ve tedavi yanıtlarını değerlendirmektir. Bir diğer ana amaç ise kraniyal otonomik bulgulara sahip olan ve sahip olamayan hastaların yukarıda belirtilen özelliklerini karşılaştırmaktır.

Gereç ve Yöntem: Çalışmamız retrospektif ve kesitseldir. Bulgular, üçüncül baş ağrısı merkezimizde toplanan verilere dayanmaktadır. Baş ağrısı bozukluklarının tanıları International Classification of Headache Disorders-3 kılavuzuna göre konmuştur. Hastaların dosyaları incelenmiştir ve bilgileri standart bir olgu rapor formuna kaydedilmiştir. Hastaların demografik özellikleri, klinik özellikleri ve tedavi yanıtları not edilmiştir. Hastalar otonomik bulgulara sahip olan ve sahip olamayan hastalar olarak iki gruba ayrılmıştır ve yukarıda belirtilen özellikleri karşılaştırılmıştır. Trigeminal otonomik sefalji ve trigeminal nevralji (TN) hastalarının tedavi yanıtları lojistik regresyon analizi ile değerlendirilmiştir. $p<0,05$ değerleri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Altmış sekiz hasta dahil edildi. Yirmi beş hastada trigeminal otonomik sefalji vardı. Yirmi üç hastada TN, 13 hastada gerilim tipi baş ağrısı vardı. Yedi hastada başka birincil baş ağrısı vardı. Hastaların klinik özellikleri ve tedavi yanıtları alt gruplarda farklıydı. Trigeminal otonomik sefalji hastalarında tetikleyici faktör tarif etmenin atak tedavisi alma riskini düşürdüğü saptandı [Odds oranı (OR): 0,059, %95 güven aralığı (GA): (0,005-0,645); p=0,02]. TN hastalarında beyin sapı lezyonuna sahip olmak [OR: 24,776, %95 GA: (1,033-60,613); p=0,049] uzun dönemde karbamazepin tedavisinde başarısızlık riskini artırırken günde birden fazla nevralji atağı yaşamak [OR: 0,58, %95 GA: (0,04-0,832); p=0,036] azaltmaktaydı.

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Sonuç: Baş ağrısı bozukluklarının doğru teşhisi, temel olarak baş ağrısının klinik özelliklerine dayanır. Etkili bir tedavi için doğru bir teşhis zorunludur, doğru teşhis tümüyle uygun öykü alınmasına dayanmaktadır.
Anahtar Kelimeler: Baş ağrısı, yüz, ağrı, kısa

Introduction

Headache disorders are among the most common neurologic ailments and often find themselves being addressed at a neurology outpatient clinic (1). The lifetime prevalence of headache disorders is up to 96% (1). Although headaches affect people in all regions of the world, the frequency of headache disorders is uneven (2). More than 90% of patients with headache have tension-type headache (TTH) or migraine (2). Although less common, other types of disorders can cause severe headache attacks and may be disguising a different neurological disease (3). Therefore, it is essential to diagnose and treat these less prevalent primary headache disorders properly.

The diagnosis of primary headache disorders is based on clinical features (4). One of the main criteria for the differential diagnosis of headache disorders is the duration of the headaches (4). Pain lasting more than 4 hours is a criterion for a migraine diagnosis; whereas most other types, such as trigeminal autonomic cephalgia (TAC), other primary headaches, and neuralgiform head and face pain disorders last less than 4 hours (4). These headache disorders differ in demographic, clinical, and treatment characteristics (2).

TAC is characterized by unilateral headache and generally parasympathetic cranial autonomic symptoms ipsilateral to the headache (5). Four main types of TAC are defined in the International Classification of Headache Disorders 3 (ICHD-3) guideline. Each type of TAC requires a specific clinical and treatment approach.

The aim of our research was to evaluate the demographic and clinical features, treatment characteristics, and responses of the patients who presented to the Ege University Neurology Headache Outpatient Clinic with headaches lasting less than 4 hours. Another primary goal was to compare the characteristics mentioned above of patients with and without cranial autonomic symptoms.

Materials and Methods

Our study was retrospective and cross-sectional. The findings were based on the data collected at our tertiary headache center. Headache disorder diagnoses were made in accordance with the ICHD-3 guideline (4). Patients who were followed-up between 01.01.2018 and 01.01.2021 were included in the study. We selected patients who met the following conditions: Being over 18 years of age, having a primary headache disorder, experiencing head or face pain lasting less than 4 hours, and having a follow-up at our clinic more than six months. Patients with severe general medical diseases such as severe cardiovascular diseases, pulmonary diseases, and malignancies were excluded.

We reviewed the patients' charts and recorded the information on a standardized form. The patients' age and sex were noted as demographic traits. The diagnosis of the exact headache disorder was recorded along with the age at onset, location, duration, quality, frequency, and level of severity. Accompanying symptoms, triggering factors, relieving factors, and prodromal symptoms were ascertained. Cranial magnetic resonance imaging (MRI) findings were also noted. Visual analogue scales were used to assess headache severity and headache diaries were used to assess headache frequency.

The patients were treated in line with the Turkish Neurological Society Headache Treatment Guidelines (6). Our tertiary center has three experienced headache experts and the patients had monthly or bi-monthly follow-ups depending on the nature of the disease. The number of drugs used for prevention and treatment, as well as other acute treatments were noted. Medications resulting in more than 50% reduction in headache frequency and/or headache severity were considered successful (6).

We classified the patients into two groups: Headache patients with cranial autonomic symptoms (patients with TAC) and headache patients without cranial autonomic symptoms (non-TAC patients). We compared the demographic, clinical and treatment characteristics of these two groups.

The Local Ethical Committee of Ege University Medical School approved the study (the approval code is: 21-8T/21).

Statistical Analysis

The data were analyzed using SPSS version 25. Numeric variables with a normal distribution were defined with means and standard deviations (SD), and those without a normal distribution were defined with median values. The Shapiro-Wilk test was used to test the normality of distribution. When comparing quantitative data to determine whether or not there was a difference between the groups, Student's t-test was used for data with a normal distribution and the Mann-Whitney U test for data without a normal distribution. To determine the differences between groups, the χ^2 and Fisher's Exact tests were used. The relationships between numerical variables were evaluated with Pearson correlation analysis for those with a normal distribution and Spearman's correlation analysis for those without.

Potential risk factors associated with a need for treatment in patients with TAC and long-term treatment failure in patients with trigeminal neuralgia (TN) were analyzed via univariate and multivariate logistic regression analyses. Univariate odds ratio (OR) and 95% confidence interval (CI) limits were calculated, and variables with $p<0.25$ were included in the logistic regression analysis as independent variables. Values of $p<0.05$ were considered statistically significant.

Results

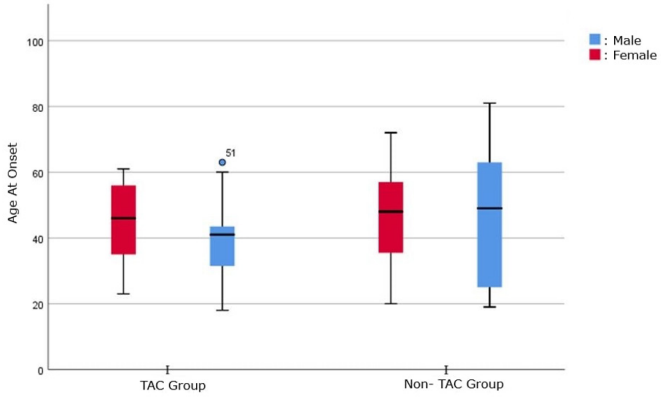
General Demographic and Diagnostic Findings

Sixty-eight patients were included in the study. Thirty seven (54.4%) patients were female, and 31 (45.6%) were male. The mean age was 47.25 years (SD: 15.16) and the mean age at symptom onset was 44.5 years (SD: 15.02) (Table 1). Comparison of the demographic features of the TAC and non-TAC groups are shown on Graph 1.

Among the participants, 25 patients had TAC. Twenty-three patients had TN and 13 had TTH. Seven had other primary headaches, three had hypnic headache, two had primary stabbing

Table 1. Demographic features of the patients				
	TAC group	Non-TAC group	Overall (n=68)	p
Gender				
Male	15	16	31 (46.6%)	0.08
Female	10	27	37 (54.4%)	
Age	43.68 (SD: 12.18)	49.33 (SD: 16.44)	47.25 (SD: 15.16)	0.14
Age				
<40 years	11	15	25 (36.7%)	0.6
>40 years	14	28	43 (63.2%)	

TAC: Trigeminal autonomic cephalgia, SD: Standard deviation



Graph 1. A boxplot graphic that shows the mean age at onset of the disease in TAC group and non TAC group
TAC: Trigeminal autonomic cephalgia

headache. Details of the clinical characteristics of the patients are provided in Table 2.

Trigeminal Autonomic Cephalgia

Of the studied population, TAC was the most common headache disorder. Twenty-five patients had TAC: 19 had cluster headache, 5 had paroxysmal hemicrania, and 1 had short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (Table 3).

Fifteen of 25 patients with TAC were male and 10 were female. Male gender preponderance was present in patients with cluster headache (p=0.01). The mean age at onset in the TAC group was 41.8 years (SD=12.3), while in the non-TAC group it was 46.05 years (SD=16.3). There was no significant difference in terms of mean age at onset between TAC and non-TAC groups (p=0.27). Although 56% of patients with TAC had a symptom onset after 40 years of age, late symptom onset was not associated with either of the groups (p=0.45).

Twelve patients with TAC had a hemicranial headache and 10 patients with TAC had a unilateral supraorbital/ retroorbital headache. Hemicranial headache was significantly more frequent in the TAC group than the non-TAC group (p=0.035).

Thirteen of 24 patients with TAC described their headache as throbbing, and five said they felt a pressure. The rest of the patients with TAC characterized their headache as stabbing, dull, and electric shock-like. Throbbing headache was seen more frequently in the TAC group than the non-TAC group (p=0.001). No particular type of pain was exclusive to a specific TAC

Table 2. Clinical characteristics of the patients				
	TAC group	Non-TAC group	Overall (n=68)	p
Headache location				
Hemicranial	15	2	17 (25%)	<0.001
Hemifacial	0	21	21 (30.8%)	
Unilateral retroorbital	10	2	12 (17.6%)	
Vertex	0	3	3 (2.9%)	
Bilateral frontal/ temporal	0	15	15 (22.1%)	
Headache quality				
Electric shock like	0	23	23 (33.8%)	<0.001
Throbbing	13	1	14 (20.6%)	
Pressing	5	14	19 (27.9%)	
Dull	7	3	10 (14.7%)	
Stabbing	0	2	2 (2.9%)	
Headache intensity				
Mild	0	1	1 (1.4%)	<0.001
Moderate	0	15	15 (22.1%)	
Severe	12	4	16 (36.5)	
Very severe	13	23	36 (52.9%)	
Triggering factor				
Yes	13	19	32 (47.1%)	0.61
No	12	24	36 (52.9%)	
Relieving factor				
Yes	5	10	15 (22.1%)	0.77
No	20	33	53 (77.9%)	

TAC: Trigeminal autonomic cephalgia

subgroup (p=0.93). Additionally, 7 patients with TAC described migrainous features during the headache attacks. Two patients had photophobia, 3 patients had phonophobia, and 5 patients had nausea or vomiting.

The level of pain was noted as severe in 12 of the patients with TAC and very severe in 13. There was no significant difference in terms of pain intensity between the TAC and the non-TAC groups (p=0.39).

The prevailing autonomic symptom in TACs is conjunctival injection and/or lacrimation, and 16 of our 25 patients with TAC had one or both. Other autonomic symptoms patients with TAC had, were nasal congestion, eyelid edema, facial sweating, and ptosis. No particular autonomic symptom was related to a specific TAC subgroup, and having conjunctival injection and/

or lacrimation did not affect the treatment response (p=0.57 and p=0.52, respectively).

Verapamil was the most frequently used prophylactic drug in patients with cluster headache. Indomethacin was used in patients with a paroxysmal hemicrania, hypnic headache, idiopathic stabbing headache or primary cough. The patient with SUNCT was treated with lamotrigine. In 4 (21%) of the 19 patients with cluster headache, verapamil was replaced with topiramate, as the former failed to reduce the headache frequency. Topiramate was the drug of choice in 4 patients with cluster headache with satisfying efficacy.

Thirteen patients with TAC needed attack treatment in spite of adequate prophylactic treatment. Ten of the patients had cluster headache and 3 had paroxysmal hemicrania. On univariate analysis, accompanying migrainous features [OR: 0.32, 95% CI: (0.049-2.108); p=0.23], having a triggering factor [OR: 0.016, 95% CI: (0.016-0.627); p=0.014], and/or having conjunctival tearing/lacrimation as cranial autonomic feature [OR: 0.300, 95% CI: (0.054-1.669); p=0.169] were evaluated in terms of need of attack treatment in spite of adequate prophylactic treatment. On multivariate analysis, having a triggering factor [OR: 0.059, 95% CI: (0.005-0.645); p=0.02] reduced the risk of need of attack treatment in spite of adequate prophylactic treatment (Table 4).

We used oxygen inhalation in the attack treatment of cluster headaches, and oxygen and triptans for the attack treatment of paroxysmal hemicrania.

Trigeminal Neuralgia

Twenty-three patients were diagnosed as having TN. Eighteen patients were female and 5 were male. Mean age at onset of the disease were 51.8 (SD: 12.8), while 78.3% of patients with TN were over 40 years of age at onset.

Twenty-one patients with TN had hemifacial pain (including nervus mandibularis and nervus maxillaris innervation zones), and only 2 patients with TN had pain located in the retroorbital/supraorbital regions. All patients with TN in the studied population delineated their facial pain as electric shock-like, likewise all patients with TN expressed the level of pain as very severe.

Eleven patients had abnormal findings on their cranial MRIs. Five of the 11 patients were patients with TN. Cranial MRI scans showed vascular compression on the trigeminal nerve in 4 patients and demyelinating plaque in the pons of another patient. Abnormal cranial MRI findings were more frequent in the patients with TN (p=0.02). Other 6 patients had non-specific T2-weighted hyperintense lesions.

Of the studied population, the most commonly used drug was carbamazepine. We also used oxcarbazepine and gabapentin for TN. All patients with TN benefited from carbamazepine at the beginning. However, a tolerance developed in 11 of the 23 (48%) patients. Carbamazepine was replaced with oxcarbazepine in 6 patients and with valproic acid in 4. Valproic acid was replaced with oxcarbazepine as it was unsuccessful in alleviating the pain.

Table 3. Summary of the TAC patients

	Cluster headache (n=19)	Paroxysmal hemicrania (n=5)	SUNCT (n=1)	TAC group (n=25)	p
Gender					
Male	14 (73.7%)	1 (20%)	0	15 (60%)	0.01
Female	5 (26.3%)	4 (80%)	1 (100%)	10 (40%)	
Age at onset					
<40 years	8 (42.1%)	3 (60%)	0	11 (44%)	0.79
>40 years	11 (57.9%)	2 (40%)	1 (100%)	14 (56%)	
Headache location					
Hemicranial	10 (52.6%)	5 (100%)	0	15 (60%)	0.37
Unilateral retroorbital	9 (47.4%)	0	1 (100%)	10 (40%)	
Headache quality					
Throbbing	9 (47.4%)	3 (60%)	1 (100%)	13 (52%)	
Pressing	4 (21.1%)	1 (20%)	0	5 (20%)	0.92
Dull	6 (31.5%)	1 (20%)	0	7 (28%)	
Headache intensity					
Mild	0	0	0	0	
Moderate	0	0	0	0	0.28
Severe	11 (57.9%)	5 (100%)	1 (100%)	17 (68%)	
Very severe	8 (42.1%)	0	0	8 (32%)	
Autonomic symptom					
Conjunctival injection	11 (68.7%)	4 (80%)	1 (100%)	16 (64%)	
Nasal congestion	2 (10.5%)	0	0	2 (8%)	
Eyelid oedema	1 (5.2%)	0	0	1 (4%)	0.057
Facial sweating	2 (10.5%)	0	0	2 (8%)	
Myosis/ptosis	2 (10.5%)	1 (20%)	0	3 (12%)	
Restlessness/agitation	1 (5.2%)	0	0	1 (4%)	

TAC: Trigeminal autonomic cephalgia, SUNCT: Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing

On univariate analysis; having headache attacks more than once a day [OR: 0.125, 95% CI: (0.019-0.805); p=0.029], and/or a brainstem lesion on cranial MRI sequences [OR: 9.167, 95% CI: (0.860-97.694); p=0.066], and having a triggering factor [OR: 4.167, 95% CI: (0.607-28.621); p=0.147] were found significant and they were selected for multivariate analysis since the p values were less than 0.25. On multivariate analysis, whilst having a brainstem lesion on cranial MRI sequences [OR: 24.776, 95% CI: (1.033-60.613); p=0.049] increased the risk of long-term treatment failure with carbamazepine, having headache attacks more than once a day [OR: 0.58, 95% CI: (0.04-0.832); p= 0.036] decreased the risk (Table 5).

Tension Type Headache

Our study included 13 patients with TTH. Seven patients with TTH were female and 6 were male. Mean age at symptom onset was 36.08 (SD: 15.41). Of patients with TTH 69.2% were younger than 40 years at the onset of the disease.

Eleven (16.2%) patients complained of headache involving the bilateral frontal or temporal regions. Two patients with TTH had a headache located on the vertex. All described their headache as pressing, though none categorized their headache intensity as severe or very severe.

Seven patients with TTH were treated with amitriptyline and 6 were treated with venlafaxine. Three patients with TTH needed to switch between amitriptyline and venlafaxine. A pain-relieving maneuver was reported more frequently in patients with TTH (p=0.001). Six of the 13 patients with TTH identified sleep and physical compression to the head as pain-relieving modalities.

Other Primary Headache Disorders

Seven patients were diagnosed as having other primary headache disorders. Three had a cough headache, 2 had a primary stabbing headache, and 2 had hypnic headache (Table 6).

All patients with primary cough headache were male and older than 40 years of age. The exact location of the headache varied among patients. The vertex and bilateral frontal/temporal localizations were noted. Two patients with primary cough headache described the quality of the headache as dull and one described it as throbbing.

Two of the patients with primary stabbing headache were female. Ages at onset of patients with hypnic headache were 40 and 43. They had a hemicranial headache. One patient with primary stabbing headache depicted headache intensity as severe and the other classified it as moderate.

One patient with hypnic headache was male and the other was female. Ages at onset of hypnic headache patients were 27 and 53. They each had a bilateral frontal/temporal headache. The quality of the headache was described as dull and pressing. Characteristics of patients with other primary headache are summarized in the Table 6.

Table 4. Factors to predict need for attack treatment in TAC patients

	Univariable analysis		Multivariable analysis	
	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)
Migrainouse features	0.230	0.320 (0.049-2.108)	0.585	1.843 (0.206-16.511)
Trigger factor	0.014	0.016 (0.016-0.627)	0.02	0.059 (0.005-0.645)
Conjunctival tearing	0.169	0.300 (0.054-1.669)	0.105	7.737 (0.654-19.948)

TAC: Trigeminal autonomic cephalgia, CI: Confidence interval

Table 5. Factors to predict long term treatment failure with carbamazepine in patients with trigeminal neuralgia

	Univariable analysis		Multivariable analysis	
	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)
Brainstem lesion	0.66	9.167 (0.860-97.694)	0.049	24.776 (1.013-60.613)
Trigger factor	0.147	4.167 (0.607-28.621)	0.178	6.114 (0.440-85.035)
Attacks more frequent than once a day	0.029	0.125 (0.019-0.805)	0.036	0.58 (0.04-0.832)

TAC: Trigeminal autonomic cephalgia, CI: Confidence interval

Table 6. Characteristics of patients with other primary headache disorders

	Diagnosis	Gender	Age at onset	Headache location	Headache quality	Headache intensity	Treatment
Patient 1	Cough headache	Male	55	Bilateral temporal/frontal	Throbbing	Moderate	Indomethacin
Patient 2	Cough headache	Male	67	Bilateral temporal/frontal	Dull	Severe	Indomethacin
Patient 3	Cough headache	Male	81	Vertex	Dull	Severe	Indomethacin
Patient 4	Stabbing headache	Female	40	Hemicranial	Stabbing	Moderate	Indomethacin
Patient 5	Stabbing headache	Female	43	Hemicranial	Stabbing	Severe	Indomethacin
Patient 6	Hypnic headache	Male	27	Bilateral temporal/frontal	Pressing	Moderate	Indomethacin
Patient 7	Hypnic headache	Female	53	Bilateral temporal/frontal	Dull	Severe	Indomethacin

Discussion

General Demographic and Diagnostic Findings

The diagnosis of primary headache disorders is based on the clinical features of the headaches (4). Demographic features differ between particular headache disorders (7). While the incidence of TTH peaks in the fourth decade, the incidence of TACs peaks in the fifth decade (7). TN often affects women older than 40 years of age (8). Moreover, headache disorders vary with gender; TAC and TTH are ordinarily seen in women, and cluster headaches are more frequent in men (8). The demographic features of our study group are in line with the literature.

Trigeminal Autonomic Cephalgias

The TACs are comparatively uncommon disorders (5). In the literature, the episodic cluster headache is the most prevalent TAC, as in our study population (5). In a descriptive study, cluster headaches were more frequent in men, with the median age at onset being over 40 years of age (9).

Unilateral headache and cranial autonomic features are characteristic for TACs (10). Quality of pain varies among the TACs (11). The quality of headache can be throbbing, burning or stabbing (11). In our study, throbbing and hemicranial headaches were significantly more frequent in the TAC group than the non-TAC group (p=0.001 and p=0.035, respectively). Additionally, 7 patients with TAC described migrainous features during the headache attacks. These included photophobia, phonophobia and nausea/vomiting, and they could be seen in up to 56% of patients with TAC (11,12). Moreover, cranial autonomic symptoms were shown in patients with migraine (13). Lacrimation, conjunctival tearing and facial swelling can be seen in patients with migraine (13). Headaches provoked by starvation and history of abdominal pain raise the risk of having cranial autonomic features in patients with migraine (13).

Lacrimation and conjunctival injection are autonomic symptoms described in up to 90% of patients with TACs, especially in patients with cluster headaches (9,10,11). No autonomic symptom is related to a specific TAC subtype or has prognostic implications (10). Of our patients with TAC, 50% had lacrimation and/or conjunctival injection as autonomic symptoms. In line with the literature, the type of autonomic symptom did not affect the demographic or clinical features of patients with TAC nor did it affect treatment response.

Verapamil is considered the first-choice preventive therapy for cluster headaches (14). It may reduce headache attack frequency in 69-94% of patients (14). Although evidence is scarce regarding topiramate in preventive therapy of cluster headache, we treated 5 of our patients with cluster headache with topiramate (as they had not responded to verapamil) and observed a satisfactory response (14). The patient with SUNCT was treated with lamotrigine, and headache frequency and severity were reduced by more than 50%. Patients with paroxysmal hemicrania were treated with indomethacin and their headache attacks improved as expected.

The logistic regression analysis indicated that having a triggering factor reduced the risk of needing an attack treatment in patients with TAC [OR: 0.059, 95% CI: (0.005-0.645); p=0.02]. Steinberg et al. (15) proposed a scale for cluster headache severity which included attack frequency, attack duration, and bout duration. It was also emphasized that patients with cluster headache with a triggering factor had lower severity scores than the patients without a triggering factor (especially alcohol use). Higher age at the disease onset was also suggested as a risk factor for maximum cluster headache severity (15). However, our study did not have the same result.

Trigeminal Neuralgias

TN is characterized by sudden and intense pain in the region of one or more divisions in the trigeminal nerve (16). The female predominance is one of the differences between the TN and TACs, especially cluster headaches and SUNCT (17). In our study, merely 2 (8.6%) of the patients with TN had pain in the region of the ophthalmic nerve. Localization of the pain can be a distinguishing factor in TN and TAC (17).

Specific brainstem lesions may cause TN (16). Neurovascular compression and multiple sclerosis plaques are well-known causes of TN (16). These disorders are named "classical TN" and "TN attributed to multiple sclerosis", respectively (4). We had 4 patients with classical TN and 1 patient with TN attributed to multiple sclerosis.

Carbamazepine is the gold standard in preventive therapy of TN (18). Carbamazepine was replaced with oxcarbazepine in case of treatment failure. Oxcarbazepine is also considered effective in TN treatment (18). Treating TN with valproic acid failed in 1 patient. An early publication suggested that valproic acid might be beneficial in treating TN, but valproic acid was not recommended in the European Academy of Neurology guideline on TN (18,19). None of our patients with TN underwent neurovascular decompression surgery due to due to unavailability in our university in our university.

The logistic regression analysis showed that having a brainstem lesion increased the risk of treatment failure with carbamazepine in the long term [OR: 24.776, 95% CI: (1.033-60.613); p=0.049]. In contrast, having pain attacks more than once a day at onset of the disease decreased the risk of the treatment failure in the long term [OR: 0.58, 95% CI: (0.04-0.832); p=0.036]. It was emphasized in the European Academy of Neurology that patients with secondary TN responded to treatment less favorably (18). Carbamazepine increases the refractory period of neurons (19). Therefore; it is the most effective treatment for high frequency discharged neurons (19).

Tension Type Headache

As traditionally understood, TTH is usually located bilaterally and is characterized by mild to moderate pain intensity (20). Pressing quality of the headache is typical for TTH (20). Venlafaxine and amitriptyline are recommended drugs for TTH treatment (20). We believe that patients with TTH in our study showed typical features of TTH.

Relieving factors in migraine and TTH are described in the literature (21). The presence of a relieving factor was significantly associated with TTH in our group (p=0.001). Similarly, the most frequently expressed relaxing modality in TTH is sleep (21). Triggering factors are described for multiple headache disorders (11,17,21). The presence of a trigger such as emotional stress, sleeplessness, alcohol, and noise did not differ significantly between the groups included in our study (p=0.35).

Our center is a tertiary referral center, which might result in a patient selection bias and a low number of patients with TTH.

In addition, the study was conducted during the coronavirus disease-2019 (COVID-19) pandemic, which reduced the number of patients that presented to our center. Moreover, due to our patient selection criteria, we excluded patients with TTH with headache attacks lasting longer than four hours.

Other Primary Headache Disorders

Although the other primary headaches were rarely seen, we had 7 patients with other primary headache disorders. Incidence of other primary headache disorders has not been elucidated yet (22).

Primary cough headache generally effects people over 40 years of age (22). Although usually more common in women, all our patients with primary cough headache were male (22). Clinical features of primary cough headache involve a pain with sudden onset and bilateral location as in our patients (22). Primary cough headache typically lasts seconds to minutes (22). Besides the cough, sneezing, blowing one's nose and laughter can also precipitate the pain (22).

Primary stabbing headache is also more common in women after adolescence (22). It may change location in each individual patient (22), though it has the shortest duration among the primary headache disorders (22).

Hypnic headache also has female predominance (22). It often affects people around 50 years of age, but it can occur in the younger population as well (22). Patients with hypnic headache complain of bilateral and mild to moderate pain (22).

Study Limitations

Our study has limitations, foremost among them was our reduced number of patients due to the COVID-19 pandemic. The retrospective nature of the study could also affect the quality of the data. Our center is a tertiary referral center, which might result in a patient selection bias. Due to low number of patients, logistic regression analysis of risk factors for long term prophylactic treatment failure in patients with TAC could not be performed.

Conclusion

In conclusion, the correct diagnosis of headache disorders is mainly based on the clinical features of the headache. Patients with headache lasting less than four hours should be questioned for cranial autonomic features. Demographic features, clinical characteristics, and drug responses differ among different headache disorders.

Ethics

Ethics Committee Approval: The Local Ethical Committee of Ege University Medical School approved the study (the approval code is: 21-8T/21).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D., A.O., G.N.B., H.Ş., N.Ç., F.G., Concept: H.N.Ö., B.D., A.O., G.N.B., M.M.D., Design: H.N.Ö., B.D., A.O., G.N.B., M.M.D., Data Collection or Processing: B.D., A.O., G.N.B., M.M.D., Analysis or Interpretation: H.N.Ö., H.Ş., N.Ç., F.G., Literature Search: H.N.Ö., B.D., A.O., G.N.B., M.M.D., Writing: H.N.Ö., H.Ş., N.Ç., F.G.

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