

Clinical Speciality of 500 Headache Patients: Documentations of Headache Center

Beşyüz Başağrısı Hastasının Klinik Özellikleri: Bir Başağrısı Merkezinin Verileri

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ABSTRACT

Objective: Headache is a health problem which is a prevalent, disabling condition affecting people in all age groups. In this study, we evaluated headache characteristics and associated factors of patients in our headache center.

Method: In this study, we retrospectively investigated the file records of 500 patients followed up between 1994-1997 in our headache center. Demographical data and other information about headache of all patients were evaluated in the file records.

Results: Mean age was 33,5±10,1 years in patients. 47,4% of patients had migraine type headache. Other primary headache types were tension type headache, drug overuse headache and trigeminal autonomic cephalalgias, retrospectively. We investigated characteristics of pain, treatment schedules and their responses in all headache types.

Conclusion: Headache is one of the most frequent health problem in the general population and it may cause disability. Among patients submitted to the our headache center, half of them had migraine type headache. However, we found that some patients had a wrong diagnosis in their initial assessments. This results, suggest that special headache centers are required for headache patients.

Key Words: Headache, migraine, comorbidity.

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ÖZET

Amaç: Başağrısı, sık karşılaşılan, maluliyete sebep olan ve tüm yaş gruplarını etkileyen bir sağlık sorunudur. Biz bu çalışmada başağrısı polikliniğinde takip ettiğimiz hastaların başağrısı karakteristiklerini ve eşlik eden faktörleri değerlendirdik.

Yöntem: Çalışmamızda başağrısı polikliniğinde 1994-1997 yılları arasında takip edilen 500 hastanın retrospektif olarak dosyaları tarandı. Hastaların dosyada kayıtlı olan demografik özellikleri ve başağrısı tanısı ve takibi ile ilgili bilgileri incelendi.

Bulgular: Hastaların yaş ortalaması 33,5±10,1 idi. Hastaların %47,4'ünün migren tipi başağrısı mevcuttu. Diğer primer başağrısı tiplerimiz sırasıyla, gerilim tipi başağrısı, ilaç aşırı kullanım başağrısı ve otonomik bulgularla seyreden başağrısı idi. Çalışmamızda ağrı özellikleri ve tüm başağrısı için kullanılan tedaviler ve yanıtları da değerlendirildi.

Sonuç: Genel popülasyona bakıldığında başağrısı sık karşılaşılan işgücü kaybına da sebep olan genel sağlık sorunudur. Biz çalışmamızda kendi merkezimize başvuran hastalar içinde her iki hastadan birisinin migren başağrısı olduğunu saptadık. Bununla birlikte hastaların başağrısı nedeni ile farklı ve yanlış tanıları aldığını da tespit ettik. Sonuçta, başağrısı hastaları için başağrısı merkezi gibi özel ünitelere ihtiyaç olduğu anlaşılmaktadır.

Anahtar Sözcükler: Başağrısı, migren, eşlik eden hastalıklar.

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INTRODUCTION

Headache is a medical problem, which has been described as early as 3,000 BC (1). Headache is one of the ten most frequent reasons for referral to a physician (2). Headache is doubtlessly the most frequent pain, among all pains, affecting humans (3).

Since one-year prevalence of headache is 90 % and life-time prevalence is 99 %, it is an almost universal problem (4). In order to research, detect, describe with respect to types and the use the same things in epidemiological studies, International Headache Society (IHS) has made an international classification of headache disorders in 1988 (5). In 2004 this classification has been revised and published (6). According to IHS 1988 classification, all headaches have been categorized under 13 groups (Table 1). In this classification, groups 1 to 4 constitute primary headaches and groups 5 to 11 constitute secondary headaches. Cranial neuralgias, nerve root compression and deafferentation pains are grouped under group 12 (5).

There are very few studies in our country, containing demographic information for headaches, which are included among important public health problems due to high prevalence (7). Ankara Research and Training Hospital has one of the oldest headache center in Ankara. Therefore, in this study, we aimed to make a breakdown of demographic particulars of the patients, visiting our headache outpatient clinic.

After the forms are completed by the patient, the responses to the forms are individually assessed by a neurologist from headache clinic and the patient. During the assessment of the patients, who marked more than one choice in the form, the assessment, specified by the physician, was recorded.

The diagnoses of headaches were assessed in accordance with the diagnostic criteria of 1988 IHS (International Headache Society). The patients were followed up in 1994-1997. Instead of the IHS 2004 classification (6), the IHS 1988 classification was used. In the oldest classification of IHS, it does not include some type headache disorders for example sexual activity headache. Therefore, some types of headache disorders were not seen in this study. In data analysis, SPSS (Statistical Package for the Social Sciences) was used.

RESULTS

Five-hundred patients with headache were enrolled in our study. Average age of the patients was 33.5±10.1. Women constituted 85.4 % patients. The headache diagnosis rates of patients, are given in Figure 1.

The 47.4 % of the patients had migraine-type headache. The 77.6 % of the migraine patients (n: 184) had non-aura migraines. Women constituted the 88.6 % of non-aura migraine patients. While the average age was 33,5±8,8 (16-62), 52.1 % of non-aura migraine patient (n:96), had headaches few times a week, 43.4 % (n:80) few times a month.

Table 1: 1988 Headache diagnostic classification of International Headache Society

| | |
|--|---|
| <p>A. Primary headache disorders</p> <p>1. Migraines</p> <p>1.1. Non-aura Migraines</p> <p>1.2. Aura Migraines</p> <p>1.2.1. Migraines with typical aura</p> <p>1.2.2. Migraines with extended aura</p> <p>1.2.3. Familial hemiplegic migraines</p> <p>1.2.4. Basilar migraines</p> <p>1.2.5. Migraines aura without headache</p> <p>1.2.6. Migraines with acute onset with aura</p> <p>1.3. Ophthalmoplegic migraines</p> <p>1.4. Retinal Migraines</p> <p>1.5. Childhood periodical syndromes, which are precursors of migraines or accompanying migraines.</p> <p>1.5.1. Benign paroxysmal vertigo of childhood.</p> <p>1.3.2. Hemiplegia of childhood, switching sides</p> <p>1.6. Migraines complications</p> <p>1.6.1. Migraines status</p> <p>1.6.2. Migraine-related infarct</p> <p>1.7. Migraine-like headaches, which are not compliant with the above criteria</p> <p>2. Tension-type headache</p> <p>2.1. Episodic tension-type headache</p> <p>2.1.1. Episodic tension-type headache, accompanied by <u>precranial</u> sensitivity</p> <p>2.1.2. Episodic tension-type headache, not accompanied by <u>precranial</u> sensitivity</p> | <p>2.2. Chronic tension-type headache</p> <p>2.2.1. Chronic tension-type headache, accompanied by <u>precranial</u> sensitivity</p> <p>2.2.2. Chronic tension-type headache, not accompanied by <u>precranial</u> sensitivity</p> <p>2.3. Tension-type headache, which is not compliant with the criteria, given above</p> <p>3. Cluster headache and chronic paroxysmal <u>hemicrania</u></p> <p>3.1. Cluster headache</p> <p>3.1.1. Cluster headache with uncertain periodicity</p> <p>3.1.2. Episodic cluster headache</p> <p>3.1.3. Chronic cluster headache</p> <p>3.1.3.1. Which does not show remission since <u>beginning</u></p> <p>3.1.3.2. Developed from episodic cluster headache</p> <p>3.2. Chronic paroxysmal <u>hemicrania</u></p> <p>3.3. Cluster headache-like headaches, which are not compliant with the above criteria</p> <p>4. Various headaches, unrelated to structural lesions</p> <p>4.1. Idiopathic stabbing headache</p> <p>4.2. Headache, related to outer compression</p> <p>4.3. Cold-induced headache</p> <p>4.4. Benign cough headache</p> <p>4.5. Benign exercise headache</p> <p>4.6. Sexual activity related headache</p> |
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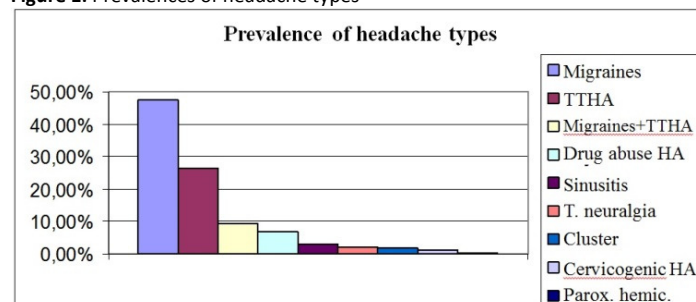
METHOD

In our study, the files of 500 patients, followed up between 1994-1997, in Ankara Training and Research Hospital Neurology Clinic Headache Outpatient Clinic, were retrospectively scanned. Ankara Research and Training Hospital has one of the oldest headache center in Ankara. The patients with deficient file information were excluded from the study. For our study, approval from the ethical board of our hospital, was obtained. The follow-up files in headache outpatient clinic, contained inquiry and follow-up information related to the diagnosis, treatment and control information of the patient.

Headache form information consisted of information about age, gender, marital status, time of onset of pain, frequency, duration, daily and seasonal periodicity, localization, character of pain, its severity, accompanying or triggering findings, whether an aura is present or not and particulars of aura, the effect of pain on quality of life, the attack and prophylactic treatments, the type and amount of used analgesic, previous diagnoses and treatments, additional systemic diseases, childhood pain particulars, neurological examination of patient, neuroimaging and treatment responses of patient during follow-ups.

While the headache in 38.6 % of non-aura migraine patients (n:71) was always unilateral, in 43.5 % (n:80) it was seen sometimes on the right and sometimes on the left and in 13.6 % (n:25) the headache was bilateral. In the 87.5 % of patients, the particulars of non-aura migraines was in the form of throbbing. In aura migraines, pain peculiars had similar rates (86.8 %). In 47.2 % of non-aura migraine patients and in 38.6 % of aura migraine patients, menstruation triggered the headache.

Figure 1: Prevalences of headache types



Five (2.1 %) of total 237 migraines patients were in menopause and in non-aura migraines which had a rate of 2.2 %, and in aura migraines the rate was 1.9 %. Allodynia was prevalent at a rate of 23.9 % (n:44) in non-aura migraine patients. The rate was 13.2 % in aura migraine patients.

During headaches, the 91.9 % of migraine patients used analgesics and the 54.4 % used acetylsalicylic acid. The 26.1 % used nonsteroidal antiinflammatory drugs (NSAIDs).

The pharmaceutical treatments and rates, given to migraine patients, are given in Table 2. The 44 % of non-aura migraine patients have stated that they greatly benefited from the treatment. The 29.9 % have stated that they moderately benefited and the 4.9 % that they slightly benefited from the treatment. In aura migraine patients, these rates were 58.5% greatly, 20.8 % moderate, and 1.9 % slightly.

Table 2: Drugs, used by migraines patients

| | Non-aura Migraines % | Aura Migraines % |
|------------------------------|----------------------|------------------|
| Only attack treatment | %43 | %39,6 |
| Propranolol | %15,3 | %26,4 |
| Amitriptyline | %15,7 | %11,3 |
| Trazodone | %13,5 | %18,9 |
| SSRI | %9,4 | - |
| Valproate | %2 | %1,9 |
| Flunarizine | %1,1 | %1,9 |

The 26.6 % of all five hundred patients (n:133) had tension-type headache (TTHA), 20 % (n:100) had chronic tension-type headache and remaining 6.6 % was episodic type TTHA. Average age in episodic type TTHA was 31,6±8,4(18-50) and for chronic TTHA 32,9±10,1 (17-61). The 84 % of patients with chronic tension-type headache were women and the rate of women in episodic form was 84.8 %.

Drugs, used in the treatment of TTHA, have been given in Table 3. The initial treatment benefit rates of patients with episodic TTHA were 24.2 % greatly benefitting, 51.5 % moderately benefitting and 3 % slightly benefitting. These rates were 21 % greatly benefitting, 54 % moderately benefitting, and 3 % slightly benefitting among patients with chronic TTHA.

The 1.8 % (n:9) of all five hundred patients had cluster headache. All of the patients followed-up for cluster headaches were males. Mean age was 32,8±7,9 (24-51). In the 77.7 %, the pain was unilateral, and in 66.7 % of the patients, the pain was characterized as throbbing. The 66.7 % of the patients woke up from sleep due to pain. The 55.6 % of patients had nausea and the 88.9 % of patients had vomiting accompanying headache. The 33.3% of the patients stated that alcohol triggered headache. In the 88.9 % of the patients, the cluster headache was accompanied by redness in the eye and watering of the eye at the same rate, nasal discharge in the 77.8 % of the patients, nasal congestion in the 22.1 %, and edema at the same rate and sweating in the face at the same rate. All of the patients were recommended oxygen in case of an attack. As prophylactic treatment, the 88.9 % of the patients used 240 mg/day verapamil, the 11.1 % used lithium. It was stated that the 40 % of the patients using verapamil had moderate and the 40 % had great benefits and the patients using lithium had moderate benefits.

Table 3: Drugs used in TTHA treatment and rates

| | Episodic TTHA, % | Chronic TTHA, % |
|----------------------|------------------|-----------------|
| Amitriptyline | %63,6 | %51 |
| SSRI | %18,2 | %15 |
| Trazodone | %18,2 | %34 |

In our study, 1 % (n:5) of rare headaches was cervicogenic headaches, the 0.6 % (n:3) was hemicrania continua, the 0.4 % (n:2) paroxysmal hemicrania, the 0.4 % (n:2) temporal arteritis, the 0.4 % (n:2) hypertensive headache and the 0.2 (n:1) idiopathic stabbing headache.

While trigeminal neuralgia was present in 2 % (n:10) of all patients, 60 % of the patients were women. Mean age was 54.8±7.9 (27-80). Pain character was described as "just like stabbing" by 70 % of patients. In 10 % of trigeminal neuralgia, there was tinnitus, and in 10 %, jaw pain. Due to pain, 90 % of patients with trigeminal neuralgia took analgesics. The 50 % of these consisted of NSAIDs and 40 % acetylsalicylic acid. The 80 % of patients with trigeminal neuralgia used carbamazepine. The 25 % of patients using carbamazepine stated that they moderately benefited from the treatment, the 75 % that they greatly benefited from treatment; and, the patients, who took amitriptyline had moderate benefits.

The 6.8 % (n: 34) of patients had excessive drug use headaches. Women constituted the 88.2 % of these patients. Mean age was 34.8±7.8 (22-53). The 47.1 % excessively used drugs which consisted of non-steroidal antiinflammatory drugs. The 25.6 % used acetylsalicylic acid; and, the 17.6 % ergotamine compounds. The 50 % of the excessive users of drug stated that they benefited from the treatment.

DISCUSSION

Headache is one of the ten most frequent reasons for referral to a physician (2). With a prevalence of 86.9 % it is more frequently seen in women than men and with a prevalence rate of 54.8 %, headache is most frequently seen between the ages of 31 to 45 (8). In compliance with literature, the rate of females among headache patients was 85.4 %; and, the 50.2 % of patients were between 31 and 45 years of age.

The prevalence of migraines in our headache outpatient clinic was 47.4 %. We thought that this could be the result of referrals of specific headaches to our headache clinic. In a study, conducted by Manzoni et al., the prevalence of non-aura migraines has been reported to be 37.1 % (8). In our study, the prevalence for non-aura migraines was at a high rate of 36.8 %.

In the literature, the 88.5 % of migraine patients are women (9). In our study, in compliance with literature, the migraine headache was observed in female patients at a rate of 88.1 %. It was determined that 73.2 % of women with migraines had non-aura migraines and 26.8 % had aura migraines (9). In our study, 77.9 % of women with migraines had non-aura migraines.

One of the most important points in headache description is the characterization of pain. Throbbing headache is seen at a rate of 88.8 % in migraines (10). In 87.3 % of migraine patients, throbbing headache was observed.

In a study, conducted by Inan et al., the prevalence of phonophobia, accompanying migraines has been reported to be 86 % (11). In our study, it was observed that phonophobia accompanied migraines at a rate of 83.7 %. In migraine attacks, nausea or vomiting is generally seen. In the literature, it has been reported that in 93 % of migraine patients, nausea, and in 61 %, vomiting was observed (12). Our study, with rates of 96.6 % for nausea and 59 % for vomiting, was in line with the literature. In migraines, the pain was unilateral in 74 % of the patients (13).

The most frequently seen aura in aura migraine patients, was reported to be visual aura. This rate has been reported to be 82.3 % in a study (14). In our study, close to that of the literature, we have determined this rate to be 77.4 %.

Menstruation-related migraines cover both the patients having migraine attacks during menstruation or outside of menstruation (4). In the literature, menstruation related migraine rate was 49 % (15). In our study, we found menstruation-related migraines rate to be 47 %, which is in line with the literature.

In the literature, migraine prevalence is lower in menopausal women as compared to premenopausal women (16). In postmenopausal women, migraine prevalence has been reported to be 11 % (13). In our study, migraine prevalence in postmenopausal women has been observed to be 2.1 %, a lower rate. We thought that the difference of this rate could be caused by the lack of an additional question in the questionnaire form and the failure of a group of patients to specify this.

Beta-blockers are used in prophylactic treatment of migraines. In a study, conducted by Johansson et al., 44 % of patients receiving propranolol had benefit from the treatment (17). In our migraine patients, 46.7 % of patients, taking propranolol had benefits.

In the prophylaxis of migraines, the effective dose of amitriptyline varies greatly. In a study, a decrease in headache was observed with a low dose (25 mg/day) of amitriptyline in the prophylaxis of migraines (18); and, our migraine patients also benefited from a low dose of amitriptyline. In a study, conducted by Gomersall et al., 42 % of patients receiving amitriptyline had a benefit from the treatment (19); and, in our study, this rate was 47.6 %.

In one study, it was reported that fluoxetine decreased total pain index in migraines (20); and, our migraines patients benefited from fluoxetine treatment.

In a small placebo-controlled migraines prophylaxis study, conducted by Landy et al, it was reported that sertraline had no effects on the frequency and the severity of headache (21); and in our study, sertraline had moderate effects on migraine headache. Since our study was based on screening files, it is an important detail that the effects of accompanying depression on the treatment could not be assessed.

Tension-type headache (TTHA) is the most frequent of primary-type headache disorders. In the general population, overall prevalence ranges from 30 % to 78 % (4). TTHA rate in our headache outpatient clinic was 26.6 %. This is a high rate, considering the prevalence of tension-type headaches in primary headaches. This may be caused by the fact that our patients were followed up by headache outpatient clinic.

In literature, 86 % of patients with TTHA were reported to be women (22). Our study, the rate of women was 84 %, which was in line with that of the literature. When the characteristics of pain were evaluated, it was reported that in TTHA, 37.1 % were generalized headaches. In our study, we have determined this rate as 41.3 %. Although photophobia is mentioned more frequently with migraines, it has been reported that it could accompany TTHA at a rate of 13 %. In our study, we have detected photophobia in TTHA at a rate of 12.1 %.

Unilateral headache has been determined in 10 % to 20 % of patients with tension-type headache. In our study, unilateral pain in TTHA was 12.3 %. Unilateral pain in episodic TTHA was 18 % (11). In our study, this rate was 21 %.

In a study, conducted by Rasmussen, the prevalence throbbing character in TTHA has been reported to be 14 % (25). We have determined the rate of throbbing pain in TTHA as 19 %. In episodic type TTHA, while throbbing pain was seen at a rate of 20 % elsewhere (11), in our study, this rate was 24 %.

In TTHA the rate of compression pain has been reported as 51.2 % (14). This rate was close to our found rate of 52.6 %. Vomiting accompanies pain in TTHA at a rate of 5 % (11). In our study, the rate of vomiting was 6 %.

In the literature, it is suggested that prophylactic pharmacotherapy of TTHA with tricyclic antidepressants be initiated. Amitriptyline must be initiated at a low dose (10-25 mg/day) and must be titrated considering therapeutic efficacy and side effects (26). In TTHA treatment, tricyclic antidepressants are more effective in headache treatment as compared to SSRIs (27); and, in our patients with TTHA, the ones, using amitriptyline had greater benefits. Lance and Curan, have reported that the use of 10-25 mg/day amitriptyline use decreased headache (28); and, 90 % of our patients with chronic TTHA have benefited from 10-25 mg amitriptyline.

Mana et al., have reported that a fluvoxamine dose of 50-100 mg/day was effective in chronic TTHA (29). Our patients with chronic TTHA have benefited from a 100 mg/day fluvoxamine treatment.

Singh and Misra, have reported that sertraline, a SSRI was not effective in chronic TTHA (30). However, unlike what has been observed in the literature, our patients with chronic TTHA have stated that they benefited from sertraline treatment.

Cluster headaches are the most frequently seen headache among trigemino-autonomic cephalgias. Eighty to 90 % of patients consist of males (31). Unlike what has been reported in the literature, all of our cluster patients were males (100 %). Average age in cluster headache was reported as 38,1 (min.18, max.60) (32). Mean age of our cluster patients was 32,8±7,9 (24-51).

In a study, conducted by Manzoni et al., the prevalence of throbbing pain in cluster headache has been reported as 41.7 % (32). In our patients, throbbing pain in cluster patients was 66.7 %. In the same study, the initial localization of pain was reported as ocular by 40 %. In addition, vomiting accompanied pain at a rate of 40 % (32). In our study, the onset of pain was 44.4 % ocular. Nausea was seen during pain at a rate of 55.6 %.

Among autonomous findings, accompanying cluster findings, watering of eyes was reported in literature to be 82 %, conjunctival redness to be 58 to 84 %, nasal discharge to be 68 to 76 % (31). In our study, among autonomous findings, watering of eyes was seen at a rate of 88.9 %, conjunctival redness at a rate of 88.9 %, nasal discharge at a rate of 77.8 %. These were similar to the figures in the existing literature.

It is known that alcohol triggered cluster attacks. In one study, it has been reported that alcohol provoked pain at a rate of 31.6 % (32). In our study, alcohol was a provocative factor in 33.3 % of the cases. In acute attack, it has been reported that the inhalation of 7 liters of pure oxygen provided a 90 % decrease in pain within 7-10 minutes (31). In compliance with the literature, inhalation of oxygen in our cluster patients has caused a significant decrease in pain. Verapamil, lithium, methysergide, ergotamine, corticosteroids and valproic acid are recommended in the prophylactic treatment of cluster headache. The first choice is verapamil and 240-360 mg/day is the most common dose. The dose may be titrated considering effects and side effects (33). Benefit has been obtained from 240 mg/day verapamil treatment in our cluster patients.

Among the conditions requiring radiological study in cluster headaches are the advanced age of onset of headache, irregular periodicity of headache, atypical clinical condition (constant headache), progressively worsening headache, headache accompanied by confusion, loss of consciousness or convulsions, and the detection of a significant pathological findings in neurological examination or laboratory tests.

In structural brain lesion diagnosis, computerized tomography (CT) and magnetic resonance imaging (MRI), the imaging procedures are the first choice (33). The cranial CTs of our cluster patients were reported as normal.

In many headache centers, the prevalence of excessive drug use headaches has been reported as 5 to 10 % (34). In our study, this rate was 6.8 %. The 39.5 % of excessively used drugs consisted of non-steroidal antiinflammatory drugs, the 20 % acetylsalicylic acid and the 18.3 % ergotamine compounds (35). The 47.1 % of excessively used drugs by our patients consisted of non-steroidal antiinflammatory drugs, the 26.5 % acetylsalicylic acid and the 17.6 % ergotamine compounds.

It has been reported that 73.3 % of patients with excessive drug use headache were women (35). In our study, the rate of female patients was 88.2 %. The 56.7 % of patients with drug abuse headache were married and the 39 % were single. In our study, the 88.2 % were married, the 11.7 % were single, and the mean age was 34,8±7.8. It has been shown that valproate was effective in the prophylactic treatment of excessive drug use headache (36). Our patients with drug abuse headache, have benefited from valproate treatment.

Trigeminal neuralgia is the most frequently seen neuralgia syndrome in elderly and it is seen more commonly in women as compared to men at a rate of 3:2 (37). In our study, in line with the literature, the rate of women with trigeminal neuralgia to men was determined as 3:2. Trigeminal neuralgia is typically unilateral, yet in 4 % of patients, it may be bilateral. In our study in for 10 % (n:1) of patients, it was bilateral.

In trigeminal neuralgia, the first choice treatment of many physicians is carbamazepine. In more than 80 % of patients, it provides pain relief both in the beginning and in the short term (39-40). Among our patients with trigeminal neuralgia, 85 % were on carbamazepine. The 25 % of patients using carbamazepine stated that they moderately benefited from the treatment, the 75 % said they greatly benefited from treatment; and, the patients who took amitriptyline had moderate benefits. In the oldest classification of IHS, there was no type of headache disorders such as sexual activity headache. Therefore, some type of headache disorders were not seen in these headache patients.

CONCLUSION

Headache is almost a universal human experience. For some, while it is a disturbing symptom, occurring occasionally, for some, it is a restrictive chronic condition or the first symptom of a life-threatening condition. There are very few studies in our country containing demographic information for headaches, which are listed among important public health problems due to a high prevalence. Therefore, in this study, we aimed to break down clinical particulars of the headaches of patients visiting our headache outpatient clinic. Specific headache outpatient clinics may prove beneficial for providing regular information concerning headache and the determination of treatment responses of patients and the variance in responses as well as additional headaches and clinical courses. Since our data in this study, dated prior to 2004, 1988 diagnostic criteria have been used and the non-use of new diagnostic criteria is a deficiency. With new diagnostic criteria, studies conducted on larger patient groups, are required.

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Conflict of Interest

No conflict of interest was declared by the authors.

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