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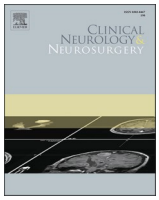
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Other primary headache disorders: Data from the HEAD-MENA-A study in Africa, Asia, and the Middle East

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ABSTRACT

Objective: Other primary headache disorders (OPHD) are under-investigated compared to frequent primary headache types like migraine, tension-type headache, and trigeminal autonomic cephalalgias. Knowledge of the distribution and characteristics of OPHD subtypes is crucial for their recognition. We aimed to determine the prevalence at the hospital and headache clinics and clinical characteristics of OPHDs in patients from 13 countries.

Methods: We analyzed a large dataset from the cross-sectional study Head-MENA-A (Middle East, North Africa, Asia). Consecutive patients over 10 years of age presenting with headaches were included from outpatient, inpatient, and emergency settings. A structured questionnaire addressing demographics, headache characteristics, accompanying symptoms, and triggers was administered. Headache subtypes were diagnosed according to the ICHD-3 criteria.

Results: Among patients complaining of headaches (n = 3722), 106 (2.9%) were diagnosed with OPHD. Fifty-two patients (1.4% of all headache patients) had only OPHD, while 54 (1.5%) had both OPHD and a co-existing primary headache (mostly migraine). All OPHDs were more common in females. The most frequent subtypes were new daily persistent headache and primary stabbing headache (0.2% each among all admitted patients). Photophobia and phonophobia were the most frequent accompanying symptoms, while physical activity (28.8%), stress (15.4%), and the Valsalva maneuver (15.4%) were the most common triggering factors. The majority of triggering factors were more pronounced in patients with both migraine and OPHD.

Conclusions: Other primary headaches are rare and heterogeneous. Their high co-existence with migraine suggests shared predisposing factors, hinting at a "headache continuum" concept for primary headaches.

Abbreviations: F: M, Female: Male; ICHD, International Classification of Headache Disorders; NDPH, New Daily Persistent Headache; NRS, Numeric rating scale; OPHD, Other Primary Headache Disorders; PSH, Primary Stabbing Headache; TACs, Trigeminal Autonomic Cephalalgias; TTH, Tension-Type Headache.

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1. Introduction

Primary headache is an umbrella term currently used to define headache disorders without a clear- cut etiology or secondary cause [1]. A detailed history and careful neurological examination are very important in making a correct diagnosis. Neuroimaging, laboratory studies, and neuro-ophthalmological examination can be essential to exclude secondary causes [2]. In the current International Classification of Headache Disorders 3rd edition (ICHD-3), primary headaches are classified into four categories: 1. Migraine, 2. Tension-type headache (TTH), 3. Trigeminal autonomic cephalalgias (TACs), and 4. Other primary headache disorders (OPHDs) [3]. The last category comprises clinically heterogeneous, diverse and intriguing headache disorders that are relatively rare, compared to the first three major categories, which creates a significant challenge for general physicians [2]. The prevalence of OPHDs among the headache sufferers is estimated around 2.5–2.8% globally; however due to the lack of large-scale studies from various geographic regions, available data on these entities mostly rely on case reports or small cohorts derived from tertiary headache centers [4]. Despite being rare, the majority of these headaches might also present as a clinical phenotype of an underlying secondary etiology; therefore, careful exclusion of a symptomatic origin should be made to conclude a definite diagnosis of a primary headache [5]. In order to identify and distinguish different subtypes of OPHDs in everyday clinical practice, it is crucial to have adequate knowledge about the prevalence and distribution of these headaches among patients seeking medical assistance in emergency and neurology clinics worldwide [6].

We hypothesized that OPHDs may exhibit similar prevalence rates in the MENA-A regions. In addition, we explored the potential for OPHDs to overlap with migraine and also to share triggers with migraine, thus suggesting a “headache continuum”. This study aimed to determine the prevalence of OPHDs at the hospital and headache clinics and the clinical characteristics of OPHDs, diagnosed by headache experts according to the ICHD-3 criteria, to guide the clinicians in charge of these patients [6].

2. Methods

These data are extracted from a comprehensive dataset obtained from a multinational, multicenter, cross-sectional study called Head-MENA-A (Middle East, North Africa, Asia), conducted between April and May 2022 [6]. This analysis represents a secondary, pre-planned analysis of previously collected and published data, focusing specifically on rare primary headache types referred to as "other primary headache types” [6]. The study involved the collaboration of 69 researchers from 13 countries, including African countries (Ivory Coast, Chad, Senegal, Sudan, Ethiopia, and Morocco), Middle Eastern countries (Egypt and Iran), and Asian countries (Tatarstan, Turkish Republic of Northern Cyprus, Azerbaijan, Mongolia, and Türkiye). The study encompassed all consecutive patients aged 10 years and older who sought medical attention primarily due to headache-related issues. Notably, our patient cohort did not feature individuals with OPHDs aged below 18 or above 70 years. This is because no OPHD cases outside these age ranges sought medical assistance for headache within the study duration at the participating centers. It is imperative to highlight that, there were no additional exclusion criteria, except for patients who did not initially report headaches upon admission or declined to participate in the study. The headache type (primary or secondary), other comorbidities, specific treatment for headaches were not exclusion criteria among the main group.

Patient admissions were conducted over five consecutive weeks on specific days that were determined by using "Research Randomizer Program" to ensure randomization. Each participating center started their five consecutive weeks of patient enrollment after they have obtained their own participation approval. Since each center obtained their approvals at different time points, the study could be finalized at eight weeks. The patients were recruited from various settings, including patients admitted and treated in outpatient clinics and neurology services (81.0%), in private hospital clinics (10.0%), and referred to emergency/other inpatient services (9.0%). Out of a total of 13,794 consecutive general neurology admissions for all kinds of neurological complaints, 4144 patients (30.04%) had a primary admission cause of headache. A total of 422 patients (377 from Türkiye, 2 from the Middle East, 5 from Asia, and 38 from Africa) declined to participate in the study and were subsequently excluded. The final analysis included 3722 consecutive patients with headache complaints (27.0%) as the main group.

The enrolled patients were assessed using a structured, standardized questionnaire administered by experienced headache experts, who also apply all necessary diagnostic examinations. The questionnaire collected demographics, headache characteristics, accompanying symptoms, triggering factors, and other relevant data related to the headache profile (See Supplementary File 1, for the study questionnaire). Primary headache disorder was diagnosed based on history, physical examination and neuro-imaging by a neurologist, as the gold standard. There were 70 headache experts assigning the diagnoses, also randomized based on the day, as were the participants. The headache experts classified the headache subtypes based on the diagnostic criteria outlined in the ICHD-3.[3] Headaches were categorized in line with the four main headings of ICHD-3 as; primary headaches (Part I), secondary headaches (Part II), neuropathies & facial pains (Part III), and appendix (Part IV). Other details of the original study are published elsewhere [6, 7].

In the current study, we focused on the prevalence and clinical characteristics of rare primary headaches labelled as “other primary headaches (code 1.4)” in ICHD-3 criteria [3]. We have categorized these rare headaches in line with ICHD-3 as 1. Headaches associated with physical exertion [(code 4.1) primary cough headache, (code 4.2) primary exercise headache, (code 4.3) primary headache associated with sexual activity, (code 4.4) primary thunderclap headache]; 2. Headaches attributed to direct physical stimuli [(code 4.5) cold-stimulus headache, (code 4.6) external-pressure headache]; 3. Epicranial headaches [(code 4.7) primary stabbing headache (PSH), (code 4.8) nummular headache]; 4. Other miscellaneous primary headache disorders [(code 4.9) hypnic headache and (code 10.0) new daily persistent headache (NDPH)].

Ethics committee approval was obtained by the main study investigator (HG) from SBU Van Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2022/05–01, Date: March 02, 2022). Each participating center obtained their participation approvals from their individual centers as stated above, after providing this main approval. All participation approvals were delivered online and submitted to the central ethics committee. Each researcher obtained signed informed consent forms from all participants.

2.1. Statistical analysis

No statistical power calculation was conducted prior to the study. The sample size was based on the available data. Statistical analysis was performed using IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Descriptive statistics were used to describe study population’s characteristics. Continuous variables were expressed as mean ± standard deviation (SD), median and minimum-maximum and categorical variables were expressed as frequency and percentage values. The Shapiro–Wilk normality test was used to test the normality of the distribution of continuous data. Variables with normal distribution were evaluated with parametric tests, whereas non-parametric tests were used for variables without a normal distribution. Independent Sample t-test and Mann Whitney U test were performed for comparing two independent groups. Pearson chi-square test was used to compare categorical variables and frequencies of occurrence, the significance level was accepted as $p < 0.05$ and, p values

were two-tailed. The extensive testing across multiple groups might increase chance findings and inflated error rates therefore post-hoc Bonferroni corrections were applied to address multiple comparisons. Bonferroni-corrected p-value (0.05/3; $p < 0.017$) was considered significant for primary headache subgroup comparisons for triggers. While our analysis aimed for depth in exploring subgroup relationships, interpreting these findings requires caution, balancing hypothesis generation with statistical control in the absence of a predefined plan." 95% confidence intervals were calculated for prevalences. No imputation methods were used for missing data.

3. Results

Of the main group with a primary complaint of headache at the referral (n = 3722), 106 (2.9%; 95% CI [0.02, 0.03]), were diagnosed with OPHD by the neurologists/headache specialists. The comparative ratios of OPHD diagnoses among total patients with headache symptom are visualized for each participating region in Fig. 1. The distribution of these 106 patients with OPHDs among the participating regions were as follows: Türkiye (n = 86, 81.1%), Middle East (n = 7, 6.6%), Asia (n = 7, 6.6%), and Africa (n = 5, 5.7%) (See Supplementary file 2 for the distribution of OPHDs within regions and Supplementary file 3 for the comparisons of OPHD subtypes between these regions).

*Confidence interval (CI) values for given prevalence: Africa: 95% CI [1%− 5%], Asia: 95% CI [3%− 10%], the Middle East: 95% CI [1%− 6%], Türkiye: 95% CI [2%− 3%].

Among all patients with OPHDs, 52 (1.4% of all patients admitted with headache) had an OPHD diagnosis only, while 54 (1.5% of all patients with headache) had both an OPHD diagnosis and an accompanying primary headache disorder. OPHDs were found to coexist with migraine (36.8%, n = 39/106), pure TTH (15.1%, n = 16/106), and TACs (1.9%, n = 2) in individual patients, indicating the co-existence of multiple primary headache types. In three patients, both migraine and TTH diagnoses were observed in addition to OPHDs. Table 1 demonstrates the distribution of OPHD subtypes among all patients with headaches and other primary headache types.

The prevalence of OPHDs among all admitted patients with and without headache was 0.8%, 95% CI [0.6%−0.9%], and the most frequent subtypes were NDPH and PSH (0.2% among all patients, each). The ratios of these subtypes among all patients with a diagnosis of OPHD were as follows; NDPH (n = 26, 24.5% of all OPHDs) and PSH (n = 25, 23.6% of all OPHDs) respectively.

The mean age of the patients diagnosed with OPHDs was 40.1 ± 13.6 years, and the female/male ratio was 80/26 (75.5/24.5%) showing a female predominance (Table 2). The age distribution patterns of participants with OPHDs were as follows; 5 patients (4.7%) between 18- 20 years, 23 (21.7%) between 21–30 years, 35 (33.0%) between 31–40 years, 15 (14.2%) between 41–50 years, 21 (19.8%) between 51–60 years, and 7 (6.6%) patients were between 61–70 years of age.

The age distributions of two most common OPHD subtypes (NDPH and PSH) and remaining patients with OPDH were shown in Fig. 2.

There were no patients diagnosed with OPHD, under 18 years and above 70 years of age. The age distribution of PSH ranged from 18 to 60 years, while NDPH had an age distribution of 20 to 70 years. There were no statistically significant differences when the age distributions of these two groups were compared to the other remaining OPHDs group (Mann Whitney u test: p = 0.350) (Fig. 2).

All OPHD subtypes were more frequent in females (up to 3–4 times in cough, cold stimulus and PSH) showing a female predominance in all OPHDs. No significant difference was found between patients with only OPHD diagnosis and patients with OPHDs and an accompanying primary headache disorder in terms of gender (p * =0.788, Pearson chi-square test) or headache severity (Numeric rating scale (NRS) scores: 7.1 + 1.8 vs 7.0 ± 1.7; p = 0.793) respectively (Table 2).

Each patient was also questioned and evaluated in terms of accompanying symptoms of headache. Photophobia (52.8%) and phonophobia (51.9%) were the most common accompanying symptoms for all patients with OPHDs. When patients with only OPHD diagnosis and patients with OPHD and an accompanying primary headache disorder were compared in terms of nausea/vomiting, photophobia, phonophobia and cranial autonomic symptoms, no statistical difference was found (p * =0.692, p * =0.177, p * =0.994 and p * =0.801 respectively) (* Pearson chi-square test) (Table 3).

When all patients with OPHDs were questioned for the triggers of headache attacks, physical activity (28.8%), stress (15.4%), and Valsalva effect (15.4%) were the most commonly cited triggering factors. In patients with OPHD and coexisting migraine, stress (59.0%), physical activity (51.3%), and sleep deprivation (43.6%) were cited as the most common triggering factors. Bright light was found to be a more prominent triggering factor in patients with migraine only and those with both migraine and OPHDs, but not in patients with OPHDs alone. (Table 4).

The distributions of location and lateralization of headaches reported in patients with OPHDs are demonstrated in Fig. 3. The majority of the headache attacks were located in the temporal area (37.9%) followed by frontal and occipital areas (35.9% for each). In terms of lateralization, bilateral (38.7%) and unilateral (35.8%) headache attack rates were

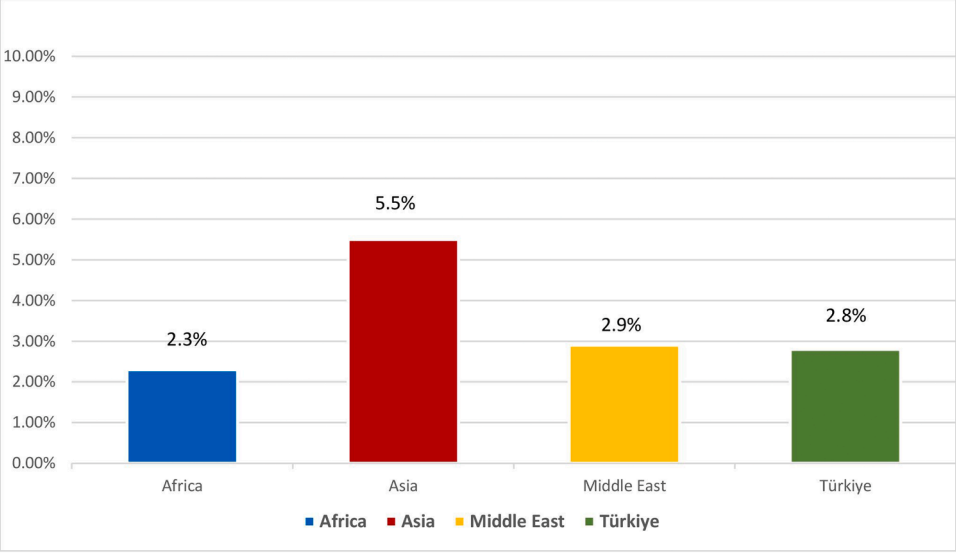


Fig. 1. Prevalence of other primary headache disorders at the hospital and headache clinics within the investigated regions* .

Table 1
Distribution of other primary headache disorders among all patients with headaches and other primary headache types.

	All patients (n = 13794)	Patients with headache (n = 3722)	Patients with migraine (n = 2121)[¥]	Patients with TTH (n = 1199)	Patients with TACs (n = 129)
All OPHDs	106 (0.80%) 95% CI [0.6–0.9%]	106 (2.80%) 95% CI [2%–3%]	39 (1.90%) * ** * 95% CI [1%–3%]	16 (1.30%) 95% CI [0.8–2%]	2 (1.60%) 95% CI [0.4–5%]
Headaches associated with physical exertion					
4.1 Cough headache	2 (0.03%)	4 (0.10%)	2 (0.10%)	1 (0.10%)	0 (0.00%)
4.2 Exercise headache	15 (0.10%)	15 (0.40%)*	7 (0.30%)	4 (0.30%)	0 (0.00%)
4.3 Headache associated with sexual activity	9 (0.06%)	9 (0.20%) * *	1 (0.04%)	1 (0.10%)	0 (0.00%)
4.4 Thunderclap headache	3 (0.02%)	3 (0.10%)	0 (0.00%)	1 (0.10%)	0 (0.00%)
Headaches attributed to direct physical stimuli					
4.5 Cold-stimulus headache	8 (0.06%)	8 (0.20%)	4 (0.20%)	5 (0.40%)	0 (0.00%)
4.6 External-pressure headache	2 (0.01%)	2 (0.10%)	2 (0.10%)	0 (0.00%)	0 (0.00%)
Epicranial headaches					
4.7 Primary stabbing headache	25 (0.20%)	25 (0.70%)	8 (0.40%)	2 (0.20%)	2 (1.60%)
4.8 Nummular headache	11 (0.08%)	11 (0.30%)	3 (0.10%)	1 (0.10%)	0 (0.00%)
Other miscellaneous primary headache disorders					
4.9 Hypnic headache	9 (0.06%)	9 (0.20%) * **	5 (0.20%)	2 (0.20%)	0 (0.00%)
4.10 New daily persistent headache	26 (0.20%)	26 (0.70%)	9 (0.40%)	3 (0.30%)	0 (0.00%)

Abbreviations: n, number; TACs, trigeminal autonomic cephalalgias; OPHD, other primary headache disorder; TTH, Tension type headache
*In three patients: both primary exercise headache and new daily persistent headache coexist * * In one: both primary exercise headache and headache associated with sexual activity, ***In two: both primary exercise headache and hypnic headache, * ** * In three: both migraine and tension type headache, [¥]: Forty-two patients have missing data

Table 2
The gender distributions and the mean visual analog scale scores of the patients with other primary headache disorders.

	F: M (n)	VAS (mean ±SD)	Median (min-max)
All patients with an OPHD diagnosis (n = 106)	80:26	7.2 ± 1.5 (3-10)	
4.1 Cough headache (n = 4)	4:0	5.8± 2.1	6 (3-8)
4.2 Exercise headache (n = 15)	9:6	6.6 ± 1.2	6 (5-9)
4.3 Headache associated with sexual activity (n = 9)	7:2	7.2± 1.9	7(5-10)
4.4 Thunderclap headache (n = 3)	3:0	7.0 ± 2	7 (5-9)
4.5 Cold-stimulus headache (n = 8)	6:2	7.5± 2	8 (5-10)
4.6 External-pressure headache (n = 2)	2:0	8.0± 1.4	8 (7-9)
4.7 Stabbing headache (n = 25)	19:6	7.6± 1.3	8 (5-10)
4.8 Nummular headache (n = 11)	8:3	6.6 ± 1.4	7 (4-8)
4.9 Hypnic headache (n = 9)	6:3	6.8± 1.3	7 (3-9)
4.10 New daily persistent headache (n = 26)	19:7	7.1± 1.8 (5-1	7 (5-10)
Patients with only OPHD diagnosis (n = 52)	40:12	7.1± 1.8 (5-10)	7 (5-10)
Patients with OPHD and an accompanying primary headache disorder (n = 54)	40: 14	7.0 ± 1.7 (3-10)	7 (3-10)

Abbreviations: F, female; M, male; max, maximum; min, minimum; n, number; NRS, numeric rating scale; OPHD, other primary headache disorders; SD, standard deviation.

very similar within OPHDs.

The comparison of headache locations in patients with OPHDs and an accompanying primary headache disorder revealed no statistically significant difference for both OPHDs+ migraine and OPHDs +TTH groups, in terms of strictly unilateral or strictly bilateral locations (p = 0.501). Similarly, the headache locations of bilateral dominant on one side or unilateral switching sides were statistically similar between patients with OPHDs+ migraine or OPHDs +TTH (p = 0.768).

4. Discussion

In this large-sized multinational study conducted in outpatient clinics, and hospital settings, it was found that OPHDs constituted 2.9% of all patients seeking medical assistance for headache complaints and 0.8% of all patients referred to neurologists. These findings highlight the significance of OPHDs as a relatively rare but important subset of primary headache disorders in these regions. The underlying pathophysiology of OPHDs, although still unclarified, is possibly the outcome of a complex interplay between environmental factors such as viruses, diet, weather changes, lifestyle choices, occupational exposures, neuroinflammation, central sensitization and possibly unknown genetic factors. To the best of our knowledge, this is the first multi-national study evaluating the prevalence of OPHDs (at the hospital and headache clinics) by headache experts/ experienced neurologists, in a large group of patients from several different geographic regions. There was a marked female predominance in all subtypes of OPHDs (75.5% vs 24.5%), similar to migraine but contrary to cluster headaches, and the most commonly diagnosed subtypes were NDPH and PSH (24.5% and 23.6%, respectively). Photophobia and phonophobia were reported as the most frequent accompanying symptoms, and physical activity (28.8%), stress (15.4%), and Valsalva effect (15.4%) were the most common triggering factors for headache attacks in patients with OPHDs. Regarding attack triggers, patients diagnosed with both migraine and OPHD exhibited a higher prevalence of various triggering factors, including bright light in this comorbid group.

4.1. Prevalence, gender, and age distribution of other primary headache disorders

Other primary headache disorders are relatively rare and heterogeneous, which makes it difficult to conduct large-scaled, population-based research in order to outline the clinical characteristics of these headaches [8]. Most of the data are derived from national or single-center studies designed for specific subtypes of OPHDs or from case series [9–13]. In the RegistRare Network study conducted in Italy, the overall prevalence of rare headaches, including those described in Chapters 3 and 4 of the ICHD-3 criteria, was reported as 4.1%. Among these rare headaches, cluster headaches, probable TACs, PSH (0.25%), and NDPH (0.22%) accounted for the majority (86.0%) [9]. In a single-center study from a tertiary neurology clinic in China, 10,135 patients were evaluated and, 12.9% (n = 1327) presented with headache as their primary complaint. Isolated PSH was reported in only 18 patients (1.5%), with a higher prevalence observed among females (61.11%) [10]. Similarly, in a Spanish study involving 725 patients, PSH was found to have a prevalence of 5% [14]. In another multi-center study from Korea, 265 out of 1627 patients (16.3%) had OPHD diagnosis, and the prevalence of PSH was reported as 11.0%. NDPH was reported as the second-most frequent OPHD with a prevalence of 1.6% in the same study [15]. We believe that this wide range of prevalence rates between different clinical studies is possibly related to different

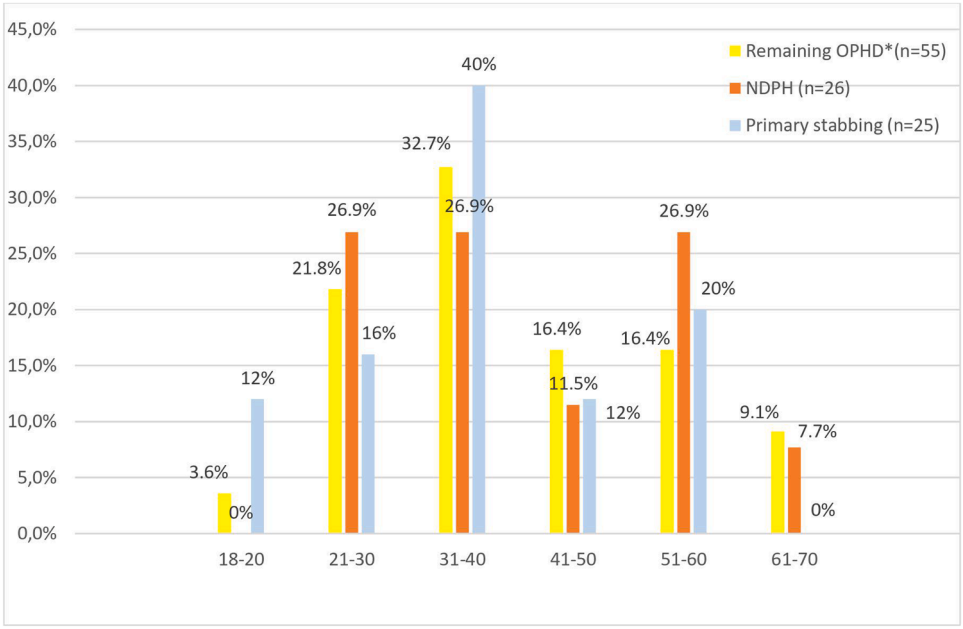


Fig. 2. Age distributions of patients with new daily persistent headache, primary stabbing **Abbreviations:** NDPH, new daily persistent headache; OPHD, other primary headache disorder.

case definitions, under-diagnosis of OPHDs in everyday practice, or due to referral or reporting bias [13].

In line with previous studies, our findings also demonstrate that the most prevalent subtypes of OPHDs were NDPH and PSH, with a higher prevalence among females compared to males [11–13,16]. This observation is consistent with the sex predominance seen in certain rare primary headache disorders, while others do not show such a disparity. It is important to differentiate between sex and gender when considering the possible causes. Sex refers to the biological and physiological characteristics, while gender encompasses the social and cultural roles and expectations associated with being male or female. In the context of rare primary headache disorders, the sex predominance among females appears to be related to biological differences rather than societal gender constructs, although societal factors may play a role. Fluctuations in estrogen levels during the menstrual cycle, as well as hormonal changes during pregnancy and menopause, have been implicated in various headache disorders, including rare primary headache disorders, potentially contributing to the higher prevalence among females [17]. However, sociocultural influences and healthcare-seeking behavior also need to be considered. Upbringing, socialization, and cultural expectations can shape the reporting and perception of pain. Societal norms that discourage males from expressing pain or seeking medical help for headaches may lead to an underestimation of the prevalence of OPHDs among males. Moreover, gender differences in healthcare-seeking behavior can influence the observed sex predominance, as females tend to be more proactive in seeking medical attention and reporting their symptoms, potentially leading to higher diagnosis rates compared to males [17,18]. Overall, the observed sex predominance among females in OPHD is likely influenced by a combination of biological, hormonal, sociocultural, and healthcare-seeking factors. Further research is needed to better understand the underlying mechanisms and to ensure equitable diagnosis and management for all individuals affected by these disorders.

Although age at diagnosis is widely distributed across various clinical studies, the mean age of the two most common OPHDs were similar to the age distribution of all patients with OPHDs in our patients [14,19,20]. We noted that age distribution of PSH was more restricted between 10–60 years of age, since there were no patients diagnosed over 60 years of age.

4.2. Accompanying symptoms and triggers of other primary headache disorders

Most of the common accompanying factors and triggers of headache attacks observed in common primary headaches were also valid for OPHDs. Strikingly, patients diagnosed with both OPHDs and migraine reported a significant increase in headache trigger rates compared to patients with isolated OPHDs. Bright light, for example, came to the forefront as a significant trigger in patients with OPHD and migraine (23.1%) when compared to the patients with only OPHD (0%) that suggests “light” as a more specific headache trigger for patients with migraine [21–23].

Photophobia was the most frequent accompanying symptom in our patients with OPHDs (52.8%), closely followed by phonophobia (51.9%), which is quite similar to migraine patients. Recent studies disclosed that photophobia was the most bothersome symptom in migraine patients in the United States [24]. In a recent study from Taiwan, phonophobia (280/1188, 23.6%) was also strikingly high as an accompanying symptom [25]. Most of the relevant studies focusing on the mechanisms of photosensitivity and phonophobia investigated patients with migraine, hence further studies are needed for OPHDs to further investigate the higher rates of photo/phonophobia in these headaches [26]. Only a few studies exist that specifically focus on these characteristics of PSHs as a common OPHD. A Chinese study demonstrated that 27.8% had accompanying symptoms with photo/ phonophobia as the most common complaint [10]. Another study from Türkiye reported potential triggers for PSH, particularly in the patients with co-morbid migraine, as head motion, rapid alterations in posture, physical exertion, and light, similar to our results [27].

As major triggers of headache attacks; physical activity (28.8%), stress (15.4%), and Valsalva effect (15.4%) came to the forefront in our patients with OPHDs. On the other hand, in patients with both OPHD and migraine, stress (59%) became the most frequent trigger followed by physical activity (51.3%) and sleep deprivation (43.6%), respectively.

Stress is a common provoking factor all across the world, free of countries and races, in almost all types of primary headaches [28]. Especially in patients with migraine, there is an increased sensitivity and vulnerability, and stress is one of these most common triggers that may

Table 3
Accompanying symptoms of headache in patients with other primary headache disorders.

	Nausea/ vomiting	Photophobia	Phonophobia	Cranial autonomic symptoms
Patients with an OPHD diagnosis (n = 106)	51 (48.10%)	56 (52.8%)	55 (51.9%)	11 (10.4%)
4.1 Cough headache (n = 4)	3 (75.00%)	3 (75.0%)	3 (75.0%)	1 (25.0%)
4.2 Exercise headache (n = 15)	4 (26.70%)	7 (46.7%)	6 (40.0%)	0 (0.0%)
4.3 Headache associated with sexual activity (n = 9)	3 (33.30%)	1 (11.1%)	2 (22.2%)	0 (0.0%)
4.4 Thunderclap headache (n = 3)	0 (0.00%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4.5 Cold-stimulus headache (n = 8)	5 (62.50%)	4 (50.0%)	4 (50.0%)	3 (37.5%)
4.6 External-pressure headache (n = 2)	1 (50.00%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4.7 Stabbing headache (n = 25)	17 (68.00%)	19 (76.0%)	21 (84.0%)	4 (16.0%)
4.8 Nummular headache (n = 11)	4 (36.40%)	5 (45.5%)	4 (36.4%)	1 (9.1%)
4.9 Hypnic headache (n = 9)	3 (33.30%)	4 (44.4%)	4 (44.4%)	1 (11.1%)
4.10 New daily persistent headache (n = 26)	14 (53.8%)	15 (57.7%)	13 (50.0%)	1 (3.8%)
*Patients with only OPHD diagnosis (n = 52)	24 (46.20%)	24 (46.20%)	27 (51.90%)	5 (9.60%)
*Patients with OPHD and an accompanying primary headache disorder (n = 54)	27 (50.00%)	32 (59.30%)	28 (51.90%)	6 (11.10%)

Abbreviations: n, number; OPHD, other primary headache disorder.
*Patients with only OPHD diagnosis and patients with OPHD and an accompanying primary headache disorder were compared in terms of nausea/vomiting, photophobia, phonophobia and cranial autonomic symptoms respectively. (p * =0.692, p = 0.177, p = 0.994 and p = 0.801 respectively) (* Pearson chi-square test was applied for all)

precipitate headache over a central mechanism through direct activation of the ascending reticular pathway [29,30]. In addition, acute stress might affect the biological modulatory pathways leading to hypersensitivity of the cortex in these patients [31]. Stress, particularly in patients with comorbid migraine, is reported to be a frequent trigger in NDPH and affects up to 26.0% of the patients [32]. Other headache triggers such as physical activity and sleep deprivation are also quite common triggers in both NDPH and patients with migraine [30,33].

4.3. Other characteristics of other primary headache disorders

In terms of headache severity, the mean NRSs of patients with only an OPHD diagnosis was similar to patients with OPHD and co-existing primary headache. Lower NRS scores were observed in patients with cough headache, nummular headache and exercise headaches in our group. Due to the rarity of many OPHDs, i.e., external pressure headaches, the severity cannot be concluded reliably. There are only a handful of studies with heterogeneous reports regarding the headache severity [1,34–36]. In the relevant studies, pain of external-pressure headache is described as “moderate”, although prolonged external

Table 4
Triggering factors of headache attacks in patients with other primary headache disorders and migraine.

Triggering factors	Migraine only (n = 1818)	OPHD only (n = 52)	Both OPHD & migraine (n = 39)	P[a]
Hunger	841 (46.3%)$_a$	3 (5.8%)$_b$	14 (35.9%)$_a$	**<0.001**
Menstruation	546 (30.0%)	1 (1.9%)	11 (28.2%)	**NA**
Dehydration	404 (22.2%)$_a$	2 (3.8%)$_b$	3 (7.7%)$_{a,b}$	**0.001**
Bright light	481 (26.5%)	0 (0.0%)	9 (23.1%)	**NA**
Weather changes	459 (25.2%)$_a$	2 (2.8%)$_b$	5 (12.8%)$_{a,b}$	**<0.001**
Tiredness	775 (42.6%)$_a$	7 (13.5%)$_b$	16 (41.0%)$_a$	**<0.001**
Watching TV	254 (14.0%)	2 (3.8%)	4 (10.3%)	0.091
Playing games	185 (10.2%)	1 (1.9%)	1 (2.6%)	**NA**
Smells	405 (22.3%)$_a$	1 (1.9%)$_b$	5 (12.8%)$_{a,b}$	**NA**
Sleep deprivation/ oversleeping	995 (52.5%)$_a$	5 (9.6%)	17 (43.6%)$_a$	**<0.001**
Stress	1131 (62.2%)$_a$	8 (15.4%)$_b$	23 (59%) $_a$	**<0.001**
Physical activity	1095 (60.2%)$_a$	15 (28.8%)$_b$	20 (51.3%)$_{a,b}$	**<0.001**
Valsalva effect	294 (16.2%)	8 (15.4%)	6 (15.4%)	0.980
Fever	32 (1.8%)	3 (5.8%)	0 (0.0%)	0.113

Abbreviations: n, number; NA, not applicable, OPHDs, other primary headache disorders; &, and pa: Pearson chi-square test
P values obtained from the Chi-Square testing between three groups. Indices (a, b, a,b) were added into table, in order to specify the statistically significiant differences obtained from Bonferroni corrected pairwise comparisons (0.05/3; p < 0.017)

pressure might cause a more severe headache with migrainous features [34,37,38]. Cough headache is another occasional headache, and pain is usually reported on a spectrum from mild to severe [1,35,36]. The rare occurrence and episodic nature of these headaches in the lives of affected individuals hinder the organization of homogeneous and detailed studies at a single center.

Regarding the localization of headache attacks in OPHDs, temporal area followed by frontal and occipital areas were the most frequent localizations in our series. In terms of lateralization, bilateral and bilateral one-side dominant (49.1%) were slightly more common than unilateral and unilateral switching sides (48.1%). However, in Takase et al.’s study, 26 patients out of 30 patients with NDPH had bilateral headache [39,40]. Another study focusing on clinical patterns of PSH reported a unilateral and localized pain with migrating feature [41]. The pain is usually located at the trigeminal area, but extra-trigeminal locations might also be involved [19,41]. Our results demonstrate that, due to the heterogeneity of the subgroups of OPHDs, the lateralization and location of headache attacks might show intense variability.

4.4. Primary headache disorders as a “continuum”

The concept of a dynamic headache continuum suggests that genetic factors, along with environmental and individual influences, interact to alter the nociceptive system and contribute to the development of headaches. Specific genetic variants have been associated with increased susceptibility to migraine, providing insights into underlying mechanisms and potential targeted therapies in the future [42–44]. Genetic factors, along with environmental triggers and individual factors, can modify the nociceptive system, resulting in variations in headache presentation and the potential transformation from one headache type to another. This dynamic interplay highlights the complex nature of headaches and underscores the importance of considering multiple factors in understanding and managing different headache types [45]. A remarkable manifestation of this concept is between

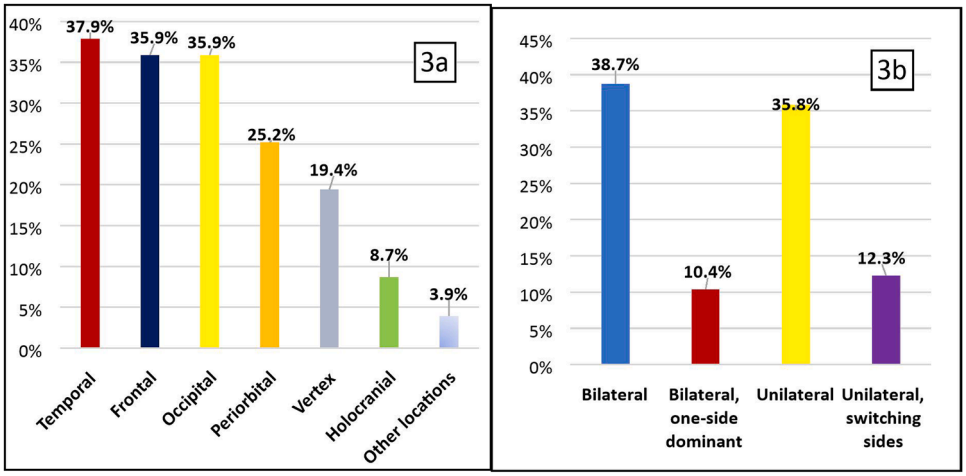


Fig. 3. Headache locations and lateralization in patients with other primary headache disorders (OPHD). a) The distribution of headache locations in patients with OPHDs. b) The distribution of headache lateralization in patients with OPHDs.

migraine and TTH. Migraine attacks can frequently present with TTH-like symptoms such as muscle tension and neck pain, whereas TTH attacks can be accompanied with typical migraine-like symptoms [44]. In a population-based, 5-year follow-up study that examined persistence and changes of headache diagnoses, it was found that only 42.9% of individuals with a definite migraine diagnosis maintained the same diagnosis after 5 years. Among the remaining people with migraine, 23.3% received a new diagnosis of definite TTH, 11.6% evolved into probable TTH, 6.4% transitioned to probable migraine, and 15.8% became headache-free. Similar changes were also observed in individuals with TTH, indicating that the transitions between migraine and TTH were unpredictable and complex. These findings suggest the presence of unknown modifiers and modulators influencing the diagnostic changes of headaches over time [45]. Headache continuum concept has further been supported by family and twin studies [46]. In a genome-wide association study (GWAS), UK Biobank data (n = 223, 773) was analyzed, and 28 genomic loci were identified for a broadly defined headache phenotype, where half of these loci were novel associations related to migraine, but the other half were not related to any specific type of headache [46]. The concept of a headache continuum has also been suggested for the spectrum of TACs in several studies [47]. The question of whether these disorders should be considered as part of a headache spectrum or separate primary headache diagnoses is still a subject of debate. Further research and investigations are needed to gain a deeper understanding of the relationship between TACs and their classification within the headache continuum, similar to OPHDs [47]. The fact that this study is a clinical study, prevents us from drawing certain conclusions about a possible underlying genetic predisposition for OPHDs. We believe that unknown genetic and environmental factors might play a role in the development of OPHDs but, this is an issue that needs to be illuminated with solid evidence in future studies. Further research is needed to unravel the complex interactions between these factors and their impact on OPHD pathogenesis [48].

Central sensitization (CS) might also play a role in the development of OPHDs. It refers to the hyperexcitability of the central nervous system above the thalamic level, leading to increased pain sensitivity. Investigating a presumptive role of CS in OPHDs can provide valuable insights for pain management and improve our understanding of these headache disorders [49]. Similar to migraine, CS might have a role in the development of OPHDs by modulating pain perception and transforming pain. Recent studies suggested that the hyperexcitability of free nerve endings and dysfunction of nociceptive Schwann cells might lead to the transient dysfunction of pain gating mechanisms as a result of various factors such as aging, mechanical stimuli, inflammation and CS in PSH, which is one the most frequent OPHDs in our study [41]. Other than PSH, a stabbing headache can also develop as a rare manifestation of secondary etiologies such as vasculitis, brain neoplasms, encephalitis, thalamic hemorrhage, autoimmune disorders, multiple sclerosis, ischemic stroke, and intracranial hypertension that should be taken into consideration when managing these patients [50].

A few previous studies have also reported that the coexistence of PSH with other primary headaches, especially migraine, is not uncommon, with rates reaching up to 40.0% [10,14,51]. Furthermore, in patients with NDPH, two separate phenotypes were identified recently, as migrainous or TTH-like [16]. We observed that OPHDs remarkably coexisted with migraine and other primary headaches in line with these studies. These data suggested that distinct primary headache types might be the pieces of a primary headache spectrum, which is a complex puzzle to be solved by further genetic and clinical studies.

4.5. *Strengths and limitations*

Our study has many strengths. First of all, it is the largest study evaluating headache patients from various regions of the world, including 13 different countries. All consecutive patients with a headache complaint were evaluated in different geographic localizations, synchronously by neurologists with expertise in headache diagnosis, with a standardized protocol. Thus, the underdiagnosis problem is kept at the minimum level, and all headache diagnoses were compatible with ICHD-3 diagnostic criteria. In addition, all patients were investigated in terms of an underlying secondary cause by a preliminary workup, including neuroimaging. On the other hand, as in all multicenter studies, our study has some limitations. First, this study is performed in outpatient clinics, and hospital settings, which prevents the generalization of our results to the general population therefore the prevalence rates of OPHDs reflects the prevalence rates in hospital and headache clinic settings. In addition, Türkiye was reflected in a great percentage, which may create a bias in terms of patient admission characteristics. Another limitation is that we examined patients between the ages of 10 and 70. Consequently, we may have missed some patients with specific OPHDs, such as hypnic headache with onset in the elderly or those with pediatric presentations. The rate of pediatric patients (0.5%) in the overall study group was very low, which could have had an influence on our results. Moreover, due to the cross-sectional design, treatment results and follow-up data were unavailable in our study.

5. Conclusion

Other primary headache disorders are rare and present with marked heterogeneity. Among OPHDs, PSH and NDPH are the most common

subtypes. The remarkable co-existence of OPHDs with more prevalent primary headaches, particularly migraine, suggests the existence of a complex interplay between unknown pathophysiological mechanisms along with environmental factors and, sensitization phenomena. Additionally, the presence of comorbid migraine increases an individual's susceptibility to various headache triggers. Recognizing OPHDs during routine visits is crucial for planning effective treatment strategies, especially in patients with comorbid primary headaches.

Ethics declarations

Ethics approval and consent to participate

Ethics committee approval was obtained by the study coordinator (HG) from University of Health Sciences, Van Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2022/05–01, Date: March 02, 2022). Researchers obtained online informed consent forms from all volunteered patients.

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Declaration of Competing Interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Consent for publication

Not applicable.

Availability of data and material

All data and materials generated in this study are available upon request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2023.108112.

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