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Headaches add to the burden of epilepsy

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Abstract The objective was to investigate and classify headaches in 109 consecutive adult patients with epilepsy. A semi-structured interview was performed in those who confirmed such symptoms (65%). Interictal headaches were present in 52%; 20% had interictal migraine. Postictal headache was reported in 44%. Migraine characteristics were present in 42% of these, and most of them (74%) also suffered from interictal migraine. Six percent had preictal headache. In partial epilepsy, there was an association between headache lateralisation and interictal EEG abnormalities (p=0.02). We conclude that headache, including migraine, is very common in patients with epilepsy. Unilateral headache may represent a lateralising sign in focal epilepsy. Seizures often trigger postictal headaches with migraine features, which often are associated with interictal migraine. Migrainous headaches sometimes proceed into epileptic seizures. The comorbidity of migraine and epilepsy should receive ample clinical attention, as it may influence antiepileptic drug choice, and the headache may need specific treatment.

Keywords Interictal headache • Postictal headache • Preictal headache • Epilepsy • Migraine • Antiepileptic drugs

Introduction

Headache is one of the comorbidities that may add to the burden of epilepsy. The association between headaches and seizure disorders has long been debated and is still poorly understood. Headache may be temporally linked to seizures in different ways. It may occur prior to a seizure (preictal headache), during a seizure (ictal headache), after a seizure (postictal headache) or be unrelated to seizures (interictal headache). Preictal headaches have been reported in 4–15% of patients with epilepsy; ictal headaches are rare, whereas postictal and interictal headaches are common with a frequency of 35%–51% and 31%–64%, respectively [1–12].

The association between epilepsy and migraine is particularly interesting, as both conditions occur in attacks and sometimes may mimic each other. In the last two decades, this link has been extended to treatment, as several antiepileptic drugs also have demonstrated a prophylactic effect against migraine [13], possibly by inhibiting cortical spreading depression [14]. Genetic factors are also strongly implicated in both disorders, and some rare migraine and

epilepsy forms have been shown to coexist in families and may be due to the same mutation [15]. All forms of epilepsy-related headache may have migraine features. Many authors have tried to explore this association, but with rather diverse findings. The prevalence of migraine in individuals with epilepsy varies from 2% to 24% [4, 6, 7, 11, 12, 16–20]. This large variation is probably due to differences in classifications of both disorders, as well as in the selection of patient populations and diagnostic instruments. Comparisons with an appropriate control group have been included only in a few studies [11, 18].

The purpose of this study was to investigate the characteristics and prevalence of headaches in patients with epilepsy based on the International Classification of Headache Disorders, 2nd edition (ICHD-II) [21]. We also wanted to compare our findings with those of a population-based epidemiological study of headache in the same geographical area, the head-HUNT study [22].

Methods

Consecutive adult patients with active epilepsy, referred to the outpatient clinic of the Neurological department at Trondheim University Hospital, were recruited to a research project to investigate the effect of a structured nurse-led intervention programme [23]. At inclusion all patients had had a definite diagnosis of epilepsy for more than one year and at least one seizure during the previous year. Patients with learning disability were excluded. At the closing interview after two years, 109 patients, 65 women and 44 men, mean age 42 (range 20–71) years, completed a questionnaire regarding headache. Consent to be contacted later was given by 102 of them. In those who confirmed headaches, a standardised semi-structured telephone interview was performed, with questions about timing of headache in relation to seizures, in addition to frequency, duration, intensity, localisation, associated features and treatment of the headaches.

The epilepsy was classified according to the criteria of The International League Against Epilepsy (ILAE) [24]. The headaches were classified according to the ICHD-II [21] based on the interview, as either migraine (including probable migraine, migraine without aura, migraine with aura and chronic migraine), tension-type headache (including probable, infrequent episodic, frequent episodic and chronic tension-type headache), combined headache (migraine and tension-type headache) and other headache (other types of headache or unclassified headache).

The headaches were further categorised as preictal, ictal, postictal or interictal. Preictal headache was defined as headache starting not more than 24 h prior to the seizure and lasting until the onset of a seizure. Ictal headache was defined as headache occurring during a simple partial epileptic seizure, and postictal headache as a headache starting within three hours after a seizure and ceasing within 72 h after the attack [21]. Interictal headache was defined as headache starting not earlier than three hours after a seizure, or headache never proceeding directly into an epileptic fit.

The patients were asked to grade the usual headache intensity as mild (maintaining normal activities without problems), moderate (maintaining normal activities with difficulty), severe (must give up normal activities and lie down) or extremely severe (impossible to stay still).

The age- and gender-related prevalences of headache were compared to a population-based epidemiological study from the same geographical area, using the same screening question: Have you suffered from headache during the past 12 months? [22].

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 14.0. Chi-square test and independent groups *t*-test were used for comparison of categorical and continuous variables. $p < 0.05$ was considered significant.

Informed consent was given by all patients. The study was recommended by the Regional Committee for Medical Research and approved by the Norwegian Data Inspectorate.

Results

Prevalence of epilepsy-related headaches

Of the 109 patients, 71 (65%) reported headaches. Except for a lower mean age in those with headaches (p=0.026), there were no significant differences regarding sex, age at onset of seizures or type of epileptic syndrome between patients with and without headaches (Table 1).

Consent to further interviews was given by 67 patients with headache (43 women and 24 men, mean age 40, range 20–66 years). Among the headache patients, the intensity of the pain was described as mild by 25 (37%), moderate by 19 (28%) and severe by 22 (33%). None graded their headache as extremely severe. (One patient was not able to describe the intensity.) Ten subjects (15%) had been absent from their job or school or had experienced a considerable dysfunction in daily life, solely because of the headache during the last three months. There was a tendency to a higher frequency of seizures in patients with headaches (*p*=0.074) (Table 1), and this difference was significant in those with moderate or severe headaches (n=41) compared to those with mild or no headaches (n=63) (p=0.002).

By using the same screening instrument, the previously published head-HUNT study found a headache prevalence of 47% in women and 29% in men [22], compared to 69% (*p*<0.001) and 59% (*p*<0.001) in the present study.

Interictal headache was reported by 57 (52%), 48 had postictal headache (44%), seven had preictal headache (6%), but none reported ictal headache. Clinical characteristics of the headaches are given in Table 2.

Interictal headache

Among the 57 patients with this type of headache, the pain was mild in 20 (35%), moderate in 16 (28%) and severe in 20 (35%). In 15 patients (26%) the headaches occurred less frequently than once a month. Twenty-seven (47%) had headache 1–4 days per month and nine (16%) 5–14 days per month. Five patients (9%) had headache more than 14 days per month. One did not know, and one refused the diagnostic interview. Table 3 compares the occurrence of interictal headaches among our patients with the head-HUNT study [22]. There were significantly more headaches in males with epilepsy. Migrainous headaches (including probable migraine) was present in 41% of patients with interictal headaches, 36% had tension-type headache, 9% had combined headache and 14% had other headache types (Table

Table 1 Characteristics of patients with and without headaches

	No headache (N=38)	Headache (N=71)	p
Sex			0.3
Female (%)	20 (53)	45 (63)	0.3
Mean age (years)	46±15	40±13	0.03
Epileptic syndrome			0.9
Partial epilepsy (%)	28 (74)	50 (70)	
Generalised epilepsy (%)	9 (24)	19 (27)	
Unclassified epilepsy (%)	1 (3)	2 (3)	
Mean age at epilepsy onset (years)	19±14 years	15±11 years	0.2
Mean number of antiepileptic drugs	1.6±0.6	1.9±0.6	0.07
Seizure frequency			0.07
No seizures last year (%)	10 (26)	19 (27)	
>One seizure/year, <one seizure/month (%)	17 (45)	19 (27)	
>One seizure/month, <one seizure/week (%)	3 (8)	19 (27)	
>One seizure/week (%)	6 (16)	13 (18)	
Missing information (%)	2 (5)	1 (1)	

Table 2 Clinical characteristics of epilepsy-related headaches

Headache	Preictal (n=7)		Postictal (n=48)		Interictal (n=57)	
	n	%	n	%	n	%
Intensity						
Mild	0	0	12	25	20	35
Moderate	3	43	14	29	16	28
Severe	4	57	18	38	20	35
No information	0	0	4	8	1	2
Accompanying symptoms						
Nausea	4	57	17	35	16	28
Vomiting	1	14	5	10	3	5
Photophobia	4	57	25	52	36	63
Phonophobia	4	57	24	50	30	53
Aggravation by moderate physical activity	2	29	8	17	12	21
Quality						
Pulsating	3	43	9	19	11	19
Pressing/tightening	2	29	26	54	33	58
Alternating pressing and pulsating	0	0	5	10	8	14
Other	1	14	4	8	3	5
Uncertain	1	14	1	2	1	2
Fulfilling migraine criteria of ICHD-II	4	57	20	42	28	49
Mean duration of headache (h)	17±26		20±31		24±37	

Table 3 Prevalence of interictal headache in patients with epilepsy compared to population-based findings [22]

	Patients with epilepsy		Population-based		p	
	Females	Males	Females	Males	Females	Males
20–49 years	28 (62%)	16 (50%)	8647 (57%)	4477 (36%)	0.447	0.092
>50 years	10 (50%)	3 (25%)	4304 (35%)	2410 (22%)	0.150	0.777
Total	38 (58%)	19 (43%)	12964 (47%)	6892 (29%)	0.060	0.040

Table 4 Types of interictal headache

Type of headache	n	%
Migraine without aura	17	30
Chronic migraine	1	2
Probable migraine without aura	5	9
Infrequent episodic tension-type headache	9	16
Frequent episodic tension-type headache	7	12
Chronic tension-type headache	1	2
Probable infrequent episodic tension-type headache	3	5
Combined headache	5	9
Probable medication-overuse headache	1	2
Headache attributed to rhinosinusitis	2	4
Unclassified headache	5	9
Interview refused	1	2

4). Only two of the 28 patients with probable migraine, migraine or combined headache had a previously established diagnosis of migraine. Excluding the patients with probable migraine, the interictal migraine prevalence in our study was 20%. There was a female predominance among these patients (77%), but it was not significant (*p*=0.103).

Postictal headache

Of the 48 patients in this group, the headache was graded as mild in 12 (25%), moderate in 14 (29%) and severe in 18 (38%). Three patients with postictal headache were not interviewed, and one was not able to describe the intensity of the headache. Headaches with migraine features were present in 42%, 38% had tension-type headache and 20% had unclassifiable headache.

Thirty-four of the 109 patients suffered from both post- and interictal headache (71% of the patients with postictal headache and 60% of the patients with interictal headache). Accordingly, we found a significant association between postictal and interictal headache (*p*=0.001). Fourteen of 19 patients (74%) experiencing postictal headaches with migraine characteristics also suffered from interictal migraine. In the 17 patients with postictal tension type headache, nine (53%) suffered from interictal tension-type headache.

Preictal headache

Seven patients had headaches that evolved into seizures, and in four of these the headaches were categorised as migraine. These four patients also suffered from interictal migraine. In the three others, the headache started within 30 min prior to the seizure, in one also with migraine qualities (but the duration was too short to be classified as migraine). The intensity of preictal headache was moderate in three and severe in the other four.

Type of epilepsy

In the 78 patients with partial epilepsy, 50 (64%) had headache. Nineteen (68%) of the 28 patients with generalised epilepsy had headache (*p*=0.9). There was no difference in the intensity of the headache between patients with partial vs. generalised epilepsy (*p*=0.8). All generalised epilepsies in this study were idiopathic. In the 78 patients with partial epilepsy, the epilepsy was cryptogenic in 46 and symptomatic in 32. In those with cryptogenic epilepsy, 31 (67%) had headache; in those with symptomatic epilepsy, 19 (59%) had headache (*p*=0.5).

Lateralisation

Mainly unilateral headaches were present in 28 of 50 patients with partial epilepsy (56%), but in only three of 19 with generalised epilepsy (16%) (*p*=0.005).

In 25 of those with partial epilepsy, the pain was predominantly confined to one particular side. In 15 of these (60%) it was ipsilateral to the interictal EEG abnormalities and in seven (28%) it was contralateral (*p*=0.020). Two patients had bilateral EEG abnormalities, and one patient had normal EEGs.

In the seven patients with preictal headache, four had

headache predominantly confined to one side. In two it was ipsilateral to the EEG abnormalities, and in one it was contralateral. One patient had bilateral EEG abnormalities.

Analgesic drugs

Only three patients (4%) treated their headaches with medication prescribed by a doctor. Two of them suffered from severe headaches, and in one the intensity was moderate. One had tried a triptan, but reported no effect. The majority of patients used over-the-counter analgesics, and the effect was generally good or quite good (in 89% of 44 patients with interictal headache, in 90% of 28 patients with postictal headache and in three of four with preictal headache). Of those with mild headaches, 68% had good or quite good effect. The percentage was also 68% among those with moderate headaches, whereas it was 63% among those with severe headache.

Antiepileptic drugs

Patients with headaches tended to use a higher number of antiepileptic drugs (1.9) than those without headaches (1.6) (p=0.072) (Table 1). The drug load was not markedly higher in those with moderate or severe pain than in those with mild or no pain (p=0.082). Table 5 shows the distribution of antiepileptic drugs used in these patients. The percentage of patients using at least one antiepileptic drug with a demonstrated prophylactic effect against migraine (valproate, topiramate, gabapentin) was similar in those with migraine (43%) and in those without or with any other type of headache (42%). In the patients without headache, 39% used valproate, topiramate or gabapentin.

Discussion

A surprisingly large proportion of patients with epilepsy in our study (65%) reported headaches, and in one third of them the intensity was reported as severe. In a large population-based study from the same area, using the same screening question, 38% reported headaches [22]. However, the mean age was somewhat lower in our study (42 years) and the percentage of females somewhat higher (60%), compared to the population-based study (49 years and 54%). In the population-based study, the prevalence of headaches was fairly constant through the ages 20–49 in both women and men. Accordingly, we divided our patients into two groups, younger or older than 50 years, and compared our findings to that study, thus trying to control for age and gender (Table 3). We could not control for socio-economic status, which is known to influence headache

prevalence, but this may be low in subjects with epilepsy as part of the consequences of having seizures. Our findings suggest that headaches are considerably more common in people with epilepsy compared to the average population. In addition, due to the antimigrainous effect of some of the antiepileptic drugs, it may be that the true prevalence of headache in this group was underestimated. On the other hand, this effect may have been offset by the fact that some patients may have developed headache as a side effect to some of these drugs. The fact that migraine is most common in young to middle-aged adults may explain that patients with headaches in the present study had a lower mean age compared to those without. A clearly higher prevalence of headaches in subjects with epilepsy has also been found for children (46% compared to 3% in the control group) [11]. Nevertheless, one study found that headaches generally did not occur more often in individuals with epilepsy [9].

Unilateral headaches occurred more frequently in patients with partial epilepsy than in those with generalised epilepsy in this study, 56% vs. 16% (p=0.005). There was a tendency to a higher frequency of seizures in patients with headaches. In the study of Yankovsky et al. [12], which only included patients with intractable epilepsy referred for epilepsy surgery, the prevalence of headaches was also high (59%), but nevertheless lower. One study demonstrated a negative effect of comorbid migraine on the prognosis of epilepsy [25].

Interictal migraine (probable migraine excluded) occurred in 20% of our patients, in contrast to a migraine prevalence of 12% in the general population [22]. However, the identification of migraine was based on somewhat different methods in the two studies. Although the questions were similar, a semi-structured telephone interview was applied in our study, whereas in the population-based study a questionnaire was filled in by the patients themselves and returned from home.

Table 5 Headaches in relation to antiepileptic drugs (used by 5 or more patients)

Type of drug	No headache %	Headache %	Interictal migraine %
Carbamazepine (n=13)	62	38	23
Gabapentin (n=8)	38	63	50
Levetiracetam (n=49)	33	67	29
Lamotrigine (n=53)	34	66	25
Oxcarbazepine (n=9)	33	67	33
Pregabalin (n=7)	14	86	43
Topiramate (n=11)	18	82	36
Valproate (n=26)	38	62	15
Zonisamide (n=5)	0	100	40

n, number of patients

Hence, the results cannot be directly compared. Surprisingly, one study found that only two of 100 consecutive patients with epilepsy suffered from migraine, and both had classic migraine. The remaining interictal headaches (29 patients) were unclassifiable [12]. Notwithstanding, in our study, 22 patients with interictal headache fulfilled the ICHD-II migraine criteria.

We found that more than 40% of postictal headaches presented with distinct migraine features. Yankovsky et al. found 48% [12]. In a study by Leniger et al., 56% of peri-ictal headache was classified as migraine [16], while Förderreuther et al. reported 34% [7]. These findings are in accordance with our study. Ito et al. found somewhat lower numbers, 29% and 26% [4, 10]. They also found an association between postictal and interictal migraine. However, it has not previously been recognised that as many as 70% of patients with postictal headache with migraine features also suffer from migraine of similar quality interictally. Patients with pronounced postictal headaches should be asked specifically about interictal headaches with migraine characteristics.

Ito and Schachter also found an association between post- and interictal headaches. Of their patients, 80% reported that their postictal headache had similar characteristics to the interictal [3]. These findings support the hypothesis of a common pathophysiology for post- and interictal headache, and also that seizures may serve as one of several triggering factors for headache. It has been demonstrated that migraine-like postictal headaches occur more often with seizure onset in the posterior parts of the brain compared with frontal lobe onset [10].

In the ICHD-II, a migraine-triggered seizure is described as a seizure preceded by a migraine aura. The term migralepsy has been used to denote epileptic seizures occurring between the migrainous aura and the headache phase. In our study, five patients had preictal headaches with migrainous qualities, albeit only four with sufficient duration (>4 h) to be classified as migraine. None experienced migraine auras, in contrast to other studies [19, 20].

We found a significant correlation between lateralisation of headaches and EEG abnormalities in patients with partial epilepsy (p=0.020), but far from absolute. In patients with preictal headache, this was less clear than in the series reported by Yankovsky et al. They found a correspondence in nine of 11 patients (82%) [26], as opposed to two of seven in the present study. However, the number of patients with preictal headache was small in both studies and side of focus was not routinely assessed by seizure recordings in our patients.

Ictal headaches are very rare and were not present among our patients in spite of the fact that "hemicrania epileptica" and "cephalic auras" with sensations in the head, including headache, as sole ictal manifestation, are recognised by the ICDH-II [21] and the International League Against Epilepsy, respectively [27]. Throbbing headaches as part of the manifestations of simple partial seizures were reported in 3 of 109 patients with epilepsy in one study [9]. The symptomatic overlap between migraine and epilepsy should not be forgotten. Migraine auras and simple partial seizures with sensory symptomatology may sometimes represent differential diagnoses [28].

Only 4% of our patients treated headaches according to a medical prescription, despite the high prevalence of severe headache (33%). Similar findings have been reported by others [7, 11, 12]. The common beneficial effect of over-the-counter analgesics may explain why this issue is rarely discussed with a doctor. An excellent response to triptans has been reported in four patients with postictal headache, of whom two were reported to have occipital epilepsy [29, 30]. People with epilepsy should be encouraged to discuss their headaches with their doctor, and doctors should routinely ask patients with epilepsy about headaches.

Headache is a common side effect of many antiepileptic drugs. There was a tendency to an increased drug load, assessed by the number of antiepileptic drugs in patients with headache, and the group with moderate to severe headaches had significantly more seizures. An anti-migraine or a headache-inducing effect of antiepileptic drugs could not be assessed in this study. Gender influences drug selection; particularly, valproate is avoided in fertile women, and many patients who use newer drugs have more severe epilepsy. A potential beneficial effect of the antiepileptic drug on headache may be offset by the headache precipitative properties of the epileptic seizures, as well as the interictal stress of living with two disorders occurring in unpredictable attacks. Less headache in patients treated with carbamazepine (Table 5) may be due to more controlled epilepsy in patients who remained on the traditional first-choice treatment for partial epilepsy.

Conclusions

Patients with epilepsy often suffer from troublesome headaches that may contribute to a reduced quality of life. Postictal and interictal headaches are common, preictal headaches occur in some, whereas ictal headaches are rare. Unilateral headaches may represent a lateralising sign for seizure onset. There is often an association between interictal and postictal headaches. Seizures often trigger headaches with migrainous features, and migraine may sometimes proceed into epileptic seizures.

Migraine is common in patients with epilepsy, particularly in females. This comorbidity is important, as headaches often receive less attention than the more acute and dramatic symptoms of seizures. In epilepsy, questions concerning migraine should be an integral part of the history, as comorbidity may influence the antiepileptic drug choice, and the migraine may need specific treatment.

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