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Primary headache and epilepsy: A multicenter cross-sectional study

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ABSTRACT

The prevalence and characteristics of interictal headache, epilepsy and headache/epilepsy comorbidity were assessed in 858 women and 309 men aged 18–81 years from headache and epilepsy centers in Italy. The research hypothesis was that comorbidity among patients with either disorder would be expected to be higher than in the general population.

Interictal headache was diagnosed in 675 cases (migraine 482; tension-type headache 168; other types 25), epilepsy in 336 (partial 171; generalized 165) and comorbidity in 156 (1.6% from headache centers; 30.0% from epilepsy centers). Patients with epilepsy, headache and comorbidity differed in a number of demographic and clinical aspects. However, for both headache and epilepsy, a family history of the same clinical condition was equally prevalent in patients with and without comorbidity. These findings do not support the purported association between headache and epilepsy.

1. Introduction

The comorbidity of headache and epilepsy is still poorly understood. The correlation has been the focus of most investigations [1,2], and comorbidity with other primary headaches is virtually unknown. Several epidemiological studies indicate that migraine and epilepsy may be strongly associated: the prevalence of migraine in patients with epilepsy ranged from 14 to 24%, and the prevalence of epilepsy in migraine subjects ranged from 1.1 to 17% [3–5]. An association with migraine has been reported in specific epileptic syndromes, including benign occipital epilepsy of childhood and benign rolandic epilepsy [6,7]. Comorbidity of epilepsy included migraine in a national survey done in Canada [4,8]. In addition, a population-based case–control study in Iceland showed a higher risk of unprovoked seizures among children with migraine with aura [9]. However, other studies have found no correlation between migraine and epilepsy, with conflicting results and questioning the existence of a definite comorbidity [10–13]. Except for a prospective study of patients seen in an outpatient clinic (which showed that seizure control over time was different in patients with epilepsy with and without migraine) [14], there is no unequivocal evidence of phenotypic differences between patients with headache *and* epilepsy and those with headache *or* epilepsy.

These contrasting results may be explained by differences in the target populations, diagnostic criteria, study design and methods. Many of these studies have been limited to referral epilepsy patients, had no appropriate control groups, and/or used ill-defined diagnostic criteria [3,4,14–18]. There is no conclusive evidence to date of a real causal relationship between the two disorders [1,2,19].

The aim of this study was, therefore, to assess the prevalence and clinical characteristics of epilepsy/headache comorbidity (and

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its major diagnostic subgroups) among patients from headache and epilepsy centers. The research hypothesis was that, if there is an association between epilepsy and headache, the prevalence of comorbidity among patients with either disorder would be expected to be higher than in the general population.

2. Materials and methods

This was a multicenter, cross-sectional study carried out between September 2005 and June 2007 in nine headache and eleven epilepsy centers of Northern and Central Italy.

2.1. Case definition

The study population comprised consecutive outpatients aged 18 years or older referred to the participating centers for diagnosis and/or care. Patients seen for a first medical consultation and patients attending a follow-up visit were included. Subjects with secondary headache (including ictal or postictal headache) and/or symptomatic epilepsy were excluded, based on history, clinical assessment, and brain CT/MRI, where clinically indicated. Written informed consent was obtained from each participant. Since at the time of the study Italian law did not require ethical approval of an observational study, we did not seek ethics committee approval.

Primary headache was diagnosed as a lifetime history of migraine with or without aura and tension-type headache according to the revised criteria for headache classification of the International Headache Society [20]. Epilepsy was defined as a lifetime history of two or more unprovoked seizures [21]. Epilepsies were coded with reference to the 1989 ILAE classification of the epilepsy syndromes [22]. To verify the correctness of the diagnosis of epilepsy and headache and classify all cases in diagnostic subgroups, details on seizure types and headache symptoms were selectively collected during the interview (see below) using ad-hoc checklists. Eligible subjects were divided into three diagnostic subgroups: headache (migraine or tension-type headache alone), epilepsy (idiopathic or cryptogenic epilepsy alone) and comorbidity (headache and epilepsy combined).

2.2. Data collection

Data were collected by direct interview using an ad hoc questionnaire focusing on selected demographic and clinical features. Demographic data included age, sex, education, occupation, and marital status. History of headache and/or epilepsy in first-degree relatives was also collected. Features of headache included age at onset and clinical aspects of attacks. The characteristics of headache attacks were reported separately for migraine and tension-type headache and assessed for frequency, duration, location, quality and intensity of pain, worsening with physical activity, and associated autonomic symptoms. Features of epilepsy included age at onset, seizure pattern, circadian rhythm, and provoking factors.

The prevalence of comorbidity was defined as the ratios of the number of cases with epilepsy and headache combined to the total number of headache and, separately, of epilepsy patients. Within each diagnostic subgroup, comparisons were made with reference to demographic and clinical features.

2.3. Statistical analysis

Data were summarized for categorical variables as frequencies and proportions, comparing groups with the chi square test or Fisher's exact test, as appropriate. Medians (with range) were used to summarize continuous variables, and groups were compared using the Mann–Whitney test. A p value of 0.05 was considered the limit of statistical significance. All the data were entered into an electronic database, and calculations were done using the SPSS software for Windows, 13.0 release (SPSS Inc, Chicago, IL, USA).

3. Results

All 1167 subjects contacted agreed to participate. The sample comprised 858 women (73.5%) and 309 men (26.5%), with a median age of 39 years (range 18–81). A diagnosis of interictal headache was reported in 675 cases (57.8%), and 336 (28.8%) had a diagnosis of epilepsy; 156 (13.4%) had comorbidity (Table 1).

More than half the patients (685, 58.7%) were recruited in headache centers and 482 (41.3%) in epilepsy centers. There were 145 patients with comorbidity (30.0%) from epilepsy centers and 11 (1.6%) from headache centers. The median percentage of subjects with headache identified in epilepsy centers was 38.5% (range 15.6–58.5), and the median with epilepsy identified in headache centers was 0% (range 0–12.9).

Migraine (with or without aura) was the commonest headache type (572, 68.8% of all headache cases) followed by tension-type headache (232, 27.9%); 82 (17.0%) patients with migraine/epilepsy comorbidity came from epilepsy centers, and 63 with tension-type/epilepsy comorbidity (13.0%) came from epilepsy centers. Migraine without aura was observed in 477 subjects (57.4%) and with aura in 95 (11.4%). Other headache types were present in 25 (comorbidity 2) patients who were excluded from further analyses on headache type.

Several demographic characteristics differed in the three diagnostic groups (Table 1). Compared to headache and comorbidity, a higher proportion of men and individuals aged 55 years or older had epilepsy. Patients with epilepsy (with or without comorbidity) were less educated and employed than patients with headache. Patients with epilepsy were more frequently single than the other two diagnostic groups.

Table 1
Demographic characteristics of patients with headache, epilepsy and comorbidity.

Variable	Headache (675)	Epilepsy (336)	Comorbidity (156)
	No. (%)	No. (%)	No. (%)
Sex**			
Women	520 (77.0)	226 (67.3)	112 (71.8)
Men	155 (23.0)	110 (32.7)	44 (28.2)
Age*** (years)			
<35	261 (39.4)	138 (41.7)	59 (38.1)
35–54	299 (45.2)	100 (30.2)	71 (45.8)
55+	102 (15.4)	93 (28.1)	25 (16.1)
NS	13	5	1
Education****			
No/basic	229 (34.1)	184 (55.3)	79 (50.9)
High school	343 (51.1)	129 (38.7)	66 (42.6)
University	99 (14.8)	20 (6.0)	10 (6.5)
NS	4	3	1
Marital status*			
Single	214 (32.8)	124 (37.2)	51 (32.7)
Married	391 (60.0)	184 (55.3)	91 (58.3)
Widowed	13 (2.0)	18 (5.4)	7 (4.5)
Divorced	34 (5.2)	7 (2.1)	7 (4.5)
NS	23	3	–
Occupation***			
Blue/white collar	432 (64.7)	170 (50.7)	93 (60.4)
Pensioner	51 (7.6)	66 (19.7)	21 (13.6)
Housewife	116 (17.4)	52 (15.5)	19 (12.3)
Student	50 (7.5)	27 (8.1)	7 (4.5)
Unemployed	19 (2.8)	20 (6.0)	14 (9.1)
NS	7	1	2

NS = not specified.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.
**** $p<0.0001$.

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The main clinical features of migraine (with and without aura) and tension-type headache in patients with headache and comorbidity are summarized in Table 2. Migraine without aura was more severe in all aspects in patients with headache than in those with comorbidity. This was not the case for patients with migraine with aura, except for the duration of headache attacks, which lasted more than 24 h in a higher proportion of individuals with the disease alone than in those with comorbidity. Tension-type headache lay midway between, with duration of attacks, aggravation by physical activity, median number of attacks per month and headache days higher in patients with the disease alone than in those with comorbidity. A family history of headache was commoner in patients with migraine than in patients with comorbidity, and the prevalence was similar in patients with comorbidity and those with headache alone. In contrast, a family history of epilepsy predominated in patients with comorbidity across all headache subgroups.

Partial epilepsy was diagnosed in 265 cases (53.9% of patients with epilepsy) and generalized epilepsy in 227 (46.1%). A family history of headache, but not epilepsy, predominated among patients with comorbidity when compared to patients with epilepsy alone (Table 3). In both groups (partial and generalized epilepsy), the disease characteristics were not significantly different in subjects with epilepsy and those with comorbidity.

Patients with comorbidity in headache centers differed from those in epilepsy centers in a number of headache aspects, namely intensity, localization, duration, and quality of pain (Table 4). In the former group, symptoms were generally more severe and disturbing than in the latter group. Epilepsy features were similar in the two groups (Table 4).

4. Discussion

4.1. Observed and expected prevalence of headache, epilepsy and comorbidity

In the present study, the prevalence of headache/epilepsy comorbidity was 30.0% in patients from epilepsy centers and 1.6% in those from headache centers. These rates are surprisingly similar to those

Table 2
Clinical features of patients with headache and comorbidity by headache type.

Variable	Migraine without aura	Migraine without aura (comorbidity)	Migraine with aura	Migraine with aura (comorbidity)	Tension-type headache	Tension-type headache (comorbidity)
	(398)	(79)	(84)	(11)	(168)	(64)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Family history of headache						
Yes	268 (67.3)**	41 (51.9)	58 (69.0)	7 (63.6)	94 (56.0)	27 (42.2)
No	130 (32.7)	38 (48.1)	26 (31.0)	4 (36.4)	74 (44.0)	37 (57.8)
Family history of epilepsy						
Yes	26 (6.5)***	15 (19.0)	4 (4.8)**	3 (27.3)	8 (4.8)***	12 (19.0)
No	372 (93.2)	64 (81.0)	80 (95.2)	8 (72.7)	160 (95.2)	51 (81.0)
NS		**				1
Localization						
Unilateral	318 (79.9)****	45 (57.0)	60 (73.2)	6 (60.0)	11 (6.7)	4 (6.8)
Bilateral	67 (16.8)	31 (43.0)	21 (25.6)	4 (40.0)	147 (89.6)	54 (91.5)
Uni-bilateral	13 (3.3)	–	1 (1.2)	–	6 (3.7)	1 (1.7)
NS	–	3	2	1	4	5
Intensity						
Mild	7 (1.8)*	3 (4.0)	2 (2.5)	1 (9.1)	26 (16.6)	14 (23.0)
Moderate	64 (16.1)	20 (26.7)	11 (13.8)	1 (9.1)	99 (63.1)	40 (65.6)
Severe	324 (82.0)	52 (69.3)	67 (83.8)	9 (81.8)	32 (20.4)	7 (11.5)
NS	3	4	4	–	11	3
Duration (hours)						
<4	15 (3.8)****	15 (26.3)	14 (17.7)*	5 (50.0)	29 (18.1)****	28 (47.5)
4–24	215 (54.4)	29 (39.2)	38 (48.1)	4 (40.0)	69 (43.1)	25 (42.4)
>24	165 (41.8)	30 (40.5)	27 (34.2)	1 (10.0)	62 (38.8)	6 (10.2)
NS	3	5	5	1	8	5
Quality of pain						
Throbbing	314 (80.3)	57 (76.0)	56 (68.3)	9 (81.8)	13 (7.9)	9 (14.8)
Oppressive/constrictive	55 (14.1)	15 (20.0)	22 (26.8)	2 (18.2)	146 (88.5)	52 (85.2)
Mixed	22 (5.6)	3 (4.0)	4 (4.9)	–	6 (3.6)	–
NS	7	4	2	–	3	3
Autonomic symptoms						
Yes	390 (98.5)****	66 (89.2)	77 (95.1)	9 (90.0)	42 (32.8)*	17 (28.8)
No	6 (1.5)	8 (10.8)	4 (4.9)	1 (10.0)	86 (67.2)	42 (71.2)
NS	2	5	3	1	40	5
Aggravation by physical activity						
Yes	331 (83.8)*	53 (72.6)	62 (76.5)	8 (72.7)	68 (42.2)*	34 (59.6)
No	64 (16.2)	20 (27.3)	19 (23.5)	3 (27.3)	93 (57.8)	23 (40.4)
NS	3	6	3	–	7	7
Median no. of attacks/month (range)	4 (1–30)**	3 (0–20)	3 (0–25)	2 (1–10)	4 (1–30)**	3 (1–30)
NS	6	4	5	1	11	4
Median no. of headache/day (range)	6 (1–30)***	5 (0–28)	5 (1–25)	3.5 (1–10)	10 (1–90)****	4 (1–30)
NS	29	9	16	1	12	3
Median disease duration, years (range)	18 (0–59)	17 (1–60)	20 (0–82)	26 (0–53)	10 (0–62)	14 (0–75)
NS	31	3	6	1	16	5

NS = not specified.
25 patients with other headache types (including 2 with comorbidity) were omitted from this table.
* $p<0.05$.
** $p<0.01$.
*** $p<0.005$.
**** $p<0.001$.

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Table 3
Clinical features of patients with epilepsy and comorbidity by epilepsy type.

Variable	Partial epilepsy	Partial epilepsy (comorbidity)	Generalized epilepsy	Generalized epilepsy (comorbidity)
	(171)	(94)	(165)	(62)
	No. (%)	No. (%)	No. (%)	No. (%)
Family history of epilepsy				
Yes	27 (15.8)	14 (15.1)	42 (25.5)	17 (27.4)
No	144 (84.2)	79 (84.9)	123 (74.5)	45 (72.6)
NS	–	1	–	–
Family history of headache				
Yes	24 (14.0)****	47 (50.0)	19 (11.5)****	29 (46.8)
No	147 (96.0)	47 (50.0)	146 (88.5)	33 (53.2)
Seizure pattern				
Single	148 (89.7)	76 (84.4)	145 (90.6)	52 (89.7)
Cluster	16 (9.7)	10 (11.1)	13 (8.1)	6 (10.3)
Mixed	1 (0.6)	4 (4.4)	2 (1.3)	–
NS	6	4	5	4
Circadian rhythm				
Day	108 (70.6)	50 (58.8)	91 (57.2)	38 (65.5)
Night	23 (15.0)	14 (16.5)	41 (25.8)	10 (17.2)
Mixed	22 (14.4)	21 (24.7)	27 (17.0)	10 (17.2)
NS	18	9	6	4
Provoking factors				
Yes	51 (35.4)	32 (40.5)	68 (46.6)	25 (50.0)
No	93 (64.6)	47 (59.5)	78 (53.4)	25 (50.0)
NS	27	15	19	12
Median no. of seizures in previous month (range)	0 (0–150)	1 (0–300)	0 (0–120)	0 (0–80)
NS	6	1	24	1
Median disease duration, years (range)	17 (1–56)**	12 (0–49)	14 (0–62)	15 (0–43)
NS	12	12	5	11

NS = not specified.
** $p<0.01$.
**** $p<0.001$.

Table 4
Clinical features of patients with comorbidity in epilepsy and headache centers.

Variable	Epilepsy centers	Headache centers
	(145)	(11)
	No. (%)	No. (%)
Family history of epilepsy		
Yes	27 (18.8)	4 (36.4)
No	117 (81.3)	7 (63.6)
NS	1	
Epilepsy type		
Partial	88 (60.7)	6 (54.5)
Generalized	57 (39.3)	5 (45.5)
Seizure pattern		
Single	118 (85.5)	10 (100.0)
Cluster	16 (11.6)	–
Mixed	4 (2.9)	–
NS	7	1
Circadian rhythm		
Day	79 (59.4)	9 (90.0)
Night	23 (17.3)	1 (10.0)
Mixed	31 (23.3)	–
NS	12	1
Provoking factors		
Yes	54 (45.0)	3 (33.3)
No	66 (55.0)	6 (66.7)
NS	25	2
Median no. of seizures in previous month (range)	0 (0–300)	1 (0–8)
Median disease duration (years)	12 (0–49)	23 (15–35)
Headache type*		
Migraine without aura	70 (48.6)	9 (90.0)
Migraine with aura	11 (7.8)	–
Tension-type headache	63 (43.8)	1 (10.0)
Other	1	1
Localization of pain*		
Unilateral	47 (34.8)	8 (80.0)
Bilateral	87 (64.4)	2 (20.0)
Uni-lateral	1 (0.7)	–
NS	10	1
Intensity of pain**		
Mild	17 (12.4)	1 (10.0)
Moderate	61 (44.5)	–
Severe	59 (43.1)	9 (90.0)
NS	8	1
Duration of pain** (hours)		
<4	48 (35.8)	–
4–24	55 (41.0)	3 (33.3)
>24	31 (23.1)	6 (66.7)
NS	11	2
Quality of pain***		
Throbbing	68 (49.6)	7 (70.0)
Oppressive/constrictive	68 (49.6)	1 (10.0)
Mixed	1 (0.7)	2 (20.0)
NS	8	1
Autonomic symptoms		
Yes	83 (62.1)	9 (90.0)
No	50 (37.6)	1 (10.0)
NS	12	1
Aggravation by physical activity		
Yes	87 (65.9)	8 (88.9)
No	45 (34.1)	1 (11.1)
NS	13	2
Median no. of attacks/month (range) in previous year	3 (0–30)	3.5 (0–30)
Median no. of headache days/month	4 (1–30)	6 (0–30)
Median disease duration, years (range)	16 (0–35)	17 (2–51)

NS = not specified.
* $p<0.05$.
** $p<0.01$.
*** $p<0.005$.

expected in the general population, where active epilepsy is seen in 0.5–1% of cases [23,24], lifetime prevalence of epilepsy in 8.2% of cases, and chronic headache accounts for 39–47% of cases [25,26]. Migraine sufferers accounted for 17.0% of cases in epilepsy centers, not far from the 14% lifetime prevalence in the general population [27]. This observation does not support the notion of an association between headache and epilepsy.

Our findings are in line with other reports. In a population-based study from a small Norwegian community, only 1% of cases with active epilepsy had migraine [13]. The prevalence of epilepsy was 1.7% in an unselected cohort of patients with migraine with no evidence of an increased uni- or bidirectional risk [10]. In a retrospective study aiming at identifying distinct constellations of comorbid disorders occurring in migraineurs, epilepsy was never found [12]. Our findings contrast with a recent Canadian study which found that migraine was more common in people with epilepsy and epilepsy was more common among migraineurs than in the general population [8]. However, those findings were based on self-reports and were, thus, subject to response bias and misclassification. As respondents were asked specifically about selected conditions, the prevalence of comorbidity might have been overestimated among patients with migraine and epilepsy simply as a reflection of interview bias. Our data are also at variance with an Icelandic study which found migraine with aura was a risk factor for unprovoked seizures. However, that study was done in patients younger than 16 years, a population different from ours. We cannot, thus, exclude the possibility of comorbidity between headache (migraine) and epilepsy in children and adolescents.

4.2. Demographic and clinical features of headache, epilepsy and comorbidity

Although in our patients with epilepsy and headache the prevalence of comorbidity was close to what was expected, headache types tended to differ in patients with and without comorbidity in

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relation to several demographic and clinical aspects. Compared to headache and comorbidity, a higher proportion of men and elderly individuals had epilepsy. Patients with epilepsy were less educated and employed than patients with headache while patients with epilepsy alone were more frequently single than the other two groups. The different epidemiological characteristics and socio-cultural implications of the two diseases may at least partially explain these findings.

Migraine without aura and, to a lesser extent, tension-type headache tended to be more severe without comorbidity than when associated with epilepsy. Then, patients with comorbidity in headache centers had more severe and disturbing pain than patients in epilepsy centers. Disease severity (leading to medical consultation in a headache center) is one possible explanation for the differences. These findings are at variance with the results of a small clinic-based series from a single hospital comparing patients with epilepsy, migraine and comorbidity seen in a headache and an epilepsy center [5]. That study found migraine with aura and other headache features (severe pain, worsening upon activity, phonophobia and photophobia) were significantly more frequent in patients with comorbidity than in those with headache alone. The differences can perhaps be explained by our larger sample and more heterogeneous population.

Selection bias might explain the fairly high proportion of cases with migraine (68.8%) and the lower proportion of cases with tension-type headache (27.9%) in our sample compared to the rates documented in the general population (15% vs. 4% vs. 60%) [28]. Another possible explanation is the use of antiepileptic drugs (e.g., valproate, topiramate) which are also effective for preventing migraine [29]. However, as selection bias and treatments may not entirely explain the differing clinical features in patients with and without comorbidity, the question is still open whether or not these clinical conditions (headache with or without epilepsy) have different pathophysiologic mechanisms.

As with disease severity, selection and interview bias may explain the predominance of family history of headache among our patients with migraine and tension-type headache. A family history of headache was more common in patients with comorbidity than in patients with epilepsy regardless of the type. This is inconsistent with the report by Ottman and Lipton [17] but might be simply explained by the presence of headache and its family history. The same applies to family history of epilepsy in patients with comorbidity compared to patients with epilepsy alone. In contrast, for both clinical conditions, the same prevalence of family history in patients with and without comorbidity is worth noting and provides additional evidence against common features in the pathogenic mechanisms.

Except for a family history of headache, there was no correlation between epilepsy and comorbidity as regards a number of epilepsy features. Although the distribution of partial and generalized epilepsies (53.9 vs. 46.1%) was not significantly different from that expected in the general population (60 vs. 40%) [30], the apparent lack of significance might be explained here by the heterogeneity of the syndromes underlying idiopathic/cryptogenic generalized and partial epilepsies.

4.3. Study strengths and limitations

The study has strengths and limitations. The major strength is the enrolment of patients with different primary headaches and the use of concurrent controls (headache epilepsy-comorbidity vs. headache or epilepsy alone). This facilitates comparisons between groups in the same population using the same method. To some extent, controls help in calculating the prevalence of either disease as expected in the general population, under the assumption that there is no association between headache and epilepsy. The fairly large sample and the range of sources also contribute to the robustness of our findings and the general application of the results to the Italian population at large.

A strong limitation of our study is the use of a referral rather than a community-based population. Patients seen in epilepsy and headache centers tend to have more severe varieties of the underlying clinical conditions. This is particularly evident for headache, a symptom that leads a patient to consult a headache center when it interferes with daily living activities and impairs the quality of life [25]. However, comorbidity should have been more frequent than expected among patients with epilepsy and headache recruited in referral centers [31], but our data are in contrast with this: in a population-based sample, comorbidity should have been even less frequent.

Selection bias may also explain the higher-than-expected proportion of females in our epilepsy population. However, as headache is more prevalent in women than in men, the fact that there were more cases with comorbidity might have been a chance finding. Another limitation is the technique used for data collection, which was not standardized or done by blinded interviewers. Interview bias, thus, cannot be excluded, but it is not likely to affect patients with and without comorbidity to different extents.

Another limitation is the possibility that more patients with epilepsy/headache comorbidity might have been identified in this cohort after longer follow-up. In this regard, comorbidity would have been underestimated. Finally, the study patients are a prevalent rather than an incident population. Patients were most likely selected among those with a long disease duration, in need of lengthy care in a tertiary center both for epilepsy and for headache management.

5. Conclusions

The prevalence of comorbidity in patients with epilepsy and in those with headache roughly overlaps that of the general population, suggesting that there is no association between the two conditions. For both, family history was equally prevalent in patients with and without comorbidity. Headache, epilepsy and comorbidity tend to differ as regards certain demographic and clinical characteristics.

Conflict of interest statement

Dr. Tonini declares that there is no conflict of interest.

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Dr. Atzeni declares that there is no conflict of interest.

Dr. Bogliun declares that there is no conflict of interest.

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Dr. Beghi serves as Associate Editor of *Epilepsia* and on the editorial advisory boards of *Amyotrophic Lateral Sclerosis, Clinical Neurology & Neurosurgery*, and *Neuroepidemiology*; on scientific advisory boards for Eisai Inc., GlaxoSmithKline, and Sintofarm; has received funding for travel and speaker honoraria from Sanofi-Aventis; has served as a consultant for Bial; and receives research support from Sigma-Tau Pharmaceuticals, Inc., Kedrion SpA, Janssen, Eisai Inc., and Sanofi-Aventis.

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