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Comorbidities in cluster headache and migraine

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Abstract

The aim of this study was to investigate the most frequent comorbid diseases occurring in patients with cluster headache (CH) and, for comparison, in migraine patients.

Over a period of eight years 130 patients with CH and 982 patients with migraine were diagnosed according to ICHD-II criteria. In all patients the presence and type of different diseases were assessed from medical records and coded by the ICD, X revision. Odds ratios (OR) with corresponding 95% confidence intervals (95%CI) were calculated by logistic regression analyses.

Comorbid disorders were present in 56.9% patients with CH and in 56.7% migraine patients. Chronic sinusitis (p = 0.001), malignancy (p = 0.012), diabetes mellitus (p = 0.021), glaucoma (p = 0.038), as well as another primary headache disorders were more frequently present in patients with cluster headache (p = 0.001), than in migraine patients. In the multivariate analysis, chronic sinusitis (OR = 7.6, p = 0.001) and diabetes mellitus (OR = 4.2, p = 0.035), adjusted by gender, age and duration of headache, are more frequently associated with CH than with migraine.

Comorbid disorders in CH patients were frequent and similar to those noticed in migraine patients, except chronic sinusitis and diabetes mellitus.

Key words: Cluster headache; migraine; comorbidity; case-control study; chronic sinusitis; diabetes mellitus.

Introduction

Comorbidity, the term originally coined by Feinstein (1), is the presence of two or more disorders, the association of which is more likely than by chance (2). Migraine is a primary headache disorder, well defined by criteria of International Headache Classification (IHCD-II) and includes episodic and chronic form of disorder, the latter with or without medication overuse (3). Conditions that occur in migraineurs with a higher prevalence than expected include stroke, epilepsy, mitral valve prolapse, Raynaud's syndrome and certain psychiatric disorders, which include depression, mania, anxiety and panic (4). Co-occurring and comorbid disease and the presence of nonheadache symptoms present both therapeutic opportunities and limitations.

The trigeminal autonomic cephalalgias are a group of primary headache syndromes; all marked by unilateral headache and associated with ipsilateral autonomic features. Cluster headache (CH) is the most common of these headache subtypes, whereas paroxysmal hemicrania and SUNCT are rarer. The medical history of the patients with CH is frequently marked by increased gastric ulcer risk, increased gastric acid secretion, head trauma, smoking and alcohol overuse. While comorbid disorders are well studied in patients with migraine, the presence of other diseases in patients with CH has never been systematically investigated.

The aim of this study was to investigate the most frequent diseases occurring in patients with cluster headache (CH) and to compare them to those occurring in migraine patients.

Methods and subjects

Over a period of eight years, from the beginning of 2000 till the end of 2007, 130 patients with CH and 982 patients with migraine were diagnosed and treated in the Headache Centre of the Institute of Neurology Clinical Center of Serbia. According to ICHD-II criteria (3), and the revision of these criteria for chronic migraine and medication overuse (5), the diagnosis of CH, episodic migraine, chronic migraine with or without medication overuse were established. The patients with secondary headache

disorders listed from 5 to 12 in ICHD-II classification, the patients with tension-type headache, as well as the patients with incomplete medical records were excluded from this study.

Demographic features, gender, actual age and duration of the headache disorder were recorded in all patients.

Also, in all patients the presence and type of different diseases, besides the primary headache disorders, were assessed from medical records. Only disorders that were diagnosed according to the International Classification of Diseases (ICD), X revision were included in the analysis. The following diseases, according to the groups of ICD, were recorded and notified by ICD code:

- Malignant neoplasm of the colon (C18), breast (C50), corpus uteri (C54), thyroid gland (C73) and parathyroid glands (C75.0);
- Benign neoplasm of the meninges (D32), pituitary adenomas (D35.2);
- Iron deficiency anaemia (D50);
- Haemorrhagic disorder due to circulating anticoagulants (antiphospholipid antibody syndrome) (D68.3);
- Sarcoidosis (D86);
- Hypothyroidism (E03), hyperthyroidism (E05), diabetes mellitus (E11), premature menopause (E28.3) and polycystic ovary syndrome (E28.2);
- Depression (F32) and anxiety disorders (F41);
- Essential tremor (G25.0), multiple sclerosis (G35), epilepsy (G40), transient global amnesia (G45.4), hydrocephalus (G91) and arachnoid cyst (G93.0);
- Cataracts (H25), degeneration of macula (H35.3) and glaucoma (H40);
- Mitral stenosis (I05.0), hypertension (I10), ischaemic heart diseases (I20, I21), mitral (valve) prolapse (I34.1), cardiac arrhythmias (I47-49), cerebral infarction (I63), Raynaud's syndrome (I73.0) and patent foramen ovale (Q21.1);
- Vasomotor and allergic rhinitis (J30), chronic sinusitis (J32) and asthma (J45);
- Gastric and duodenal ulcers (K25, K26) and irritable bowel syndrome (K58);
- Psoriasis (L40);
- Rheumatoid arthritis (M05), systemic lupus erythematosus (M32), Sjogren's syndrome (M35.0) and cervical spondylosis (M47.8);
- Chronic renal failure (N18) and calculus of kidney and ureter (N20);
- Vertigo (R42);
- Intracranial injury (S06).

We used descriptive statistics and χ^2 tests for comparisons of categorical variables. Odds ratios (OR) with corresponding 95% confidence intervals (95%CI) were calculated by univariate and multivariate logistic regression analyses. The criterion for variables inclusion in multivariate model was statistical significance at the level of $p < 0.05$, obtained by univariate analysis.

Results

The group of CH patients consisted of 130 patients. The group of migraine patients included 647 (65.9%) patients with episodic migraine, 114 (11.6%) patients with chronic migraine without medication overuse and 220 (22.4%) patients with chronic migraine and medication overuse.

There were 47 (36.1%) female patients in CH group and 832 (84.7%) female patients in migraine group (OR = 0.1, 95% CI 0.07-0.2, p = 0.001). CH patients were older (mean 32.8 ± 13.5 years) than migraine patients (mean 21.6 ± 10.1 years) at the beginning of the headache disorder (OR = 0.9, 95% CI 0.9-1.0, p = 0.001). Duration of primary headache disorder was shorter (OR = 1.1, 95% CI 1.1-1.2, p = 0.001) in CH patients (mean 7.3 ± 7.5 years) than in migraine patients (17.2 ± 11.9 years).

There were 74 (56.9%) patients in CH group and 557 (56.7%) patients in migraine group with at least one comorbid disorder. This difference was not significant (p = 0.965).

The majority of patients in each group had only one comorbid disorder, 50 (38.5%) in CH group and 400 (40.7%) in migraine group. There were 15 (11.5%) patients in CH group and 125 (12.7%) patients in migraine group with two comorbid disorders; 9 (6.9%) patients in CH group and 31 (3.2%) patients in migraine group had three comorbid disorders; 1 (0.8%) patient in CH group and 3 (0.3%) had four comorbid disorders; and 1 (0.8%) patient in CH group had five comorbid disorders. These differences were statistically significant (p = 0.022).

In the group of CH patients the most frequent comorbidities are listed in Table 1.

Cerebral infarctions (I63), glaucoma (H40), cataracts (H25), and intracranial injury (S06) were present in 3 (2.3%) of CH patients. Ischaemic heart diseases (I20, I21), hypothyreosis (E05), cardiac arrhythmias (I47-49), and immunologically mediated disorders (M32 and M35.0) were present in 2 (1.5%) of the patients in this group. Essential tremor (G25.0), multiple sclerosis (G35), iron deficiency anaemia (D50), psoriasis (L40), and transitory global amnesia (G45.4) were present in 1 (0.8%) patient with CH.

In the CH group of patients with malignant tumors, there were two patients with breast cancer,

Table 1

The most frequent comorbidities in CH group

Comorbid disorder	N (%) of patients
Chronic sinusitis (J32)	31 (23.8)
Hypertension (I10)	17 (13.1)
Gastric and duodenal ulcers (K25, K26)	12 (9.2)
Cervical spondylosis (M47.8)	10 (7.7)
Depression (F32) and anxiety disorders (F41)	6 (4.6)
Diabetes mellitus (E11)	5 (3.8)
Malignant tumors (C50, C54, C75.0)	4 (3.1)

Table 2

The most frequent comorbidities in migraine group

Comorbid disorder	N (%) of patients
Hypertension (I10)	146 (14.9%)
Gastric and duodenal ulcers (K25, K26)	122 (12.4%)
Cervical spondylosis (M47.8)	61 (6.2%)
Depression (F32) and anxiety disorders (F41)	50 (5.1%)
Epilepsy (G40)	43 (4.4%)
Immunologically mediated disorders (D68.3, D86, J30, M05, M32, M35.0)	38 (3.9%)
Chronic sinusitis (J32)	35 (3.6%)
Iron deficiency anaemia (D50)	31 (3.2%)
Intracranial injury (S06)	30 (3.1%)
Cerebral infarctions (I63)	23 (2.3%)

one patient with endometrial cancer and one with malignant tumor of parathyroid gland.

In the group of migraine patients the most frequent comorbidities are listed in Table 2.

Mitral (valve) prolapse (I34.1) and patent foramen ovale (Q21.1) were present in 18 (1.8%) of migraine patients, calculus of the kidney and ureter (N20) in 12 (1.2%), diabetes mellitus (E11) in 11 (1.1%), syndrome of polycystic ovaries (E28.2) in 10 (1.0%), vertigo (R42) in 10 (1.0%) of these patients. Glaucoma (H40), essential tremor (G25.0), malignancies (C18, C50, C54, C73), ischaemic heart diseases (I20, I21), psoriasis (L40), pituitary adenomas (D35.2), hypothyreosis (E03), hyperthyreosis (E05), multiple sclerosis (G35), hydrocephalus (G91) and arachnoid cyst (G93.0) in less than 1% of migraine patients.

In the migraine group of patients with malignant tumors, there were three patients with thyroid gland cancer, one with breast cancer, one with endometrial cancer and one with cancer of the colon.

The comorbidities that were significantly different in CH and migraine group are listed in Table 3. All comorbidities listed in Table 3 were more frequently present in CH patients than in migraine.

In the multivariate analysis, chronic sinusitis (OR = 7.6, 95% CI 3.7-15.7, p = 0.001) and diabetes mellitus (OR = 4.2, 95% CI 1.1-15.9, p = 0.035), adjusted by gender, age and duration of headache as potential confounding factors, are more frequently associated with CH group than with migraine group.

Discussion

Our study comprises several important findings. First, it shows that in CH comorbid disorders are present in more than half of the patients, and equally prevalent as in migraine patients. Migraine has been noted to be comorbid with a variety of illnesses (4). Some of the migraine comorbidities are well defined medical disorders, such as stroke, hypertension, hypothyroidism, asthma, allergy and endometriosis (6-11). Some syndromes with unknown etiology are associated with migraine, like irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome (12-14). Psychiatric disorders, particularly depression and anxiety, have been associated with migraine (15). Bidirectional relationships between migraine and some of these disorders pointed to the neurobiological link (15) and aggregation within families, has implicated genetic ties, like in FHM type II for migraine and epilepsy (16). The same variety of pathophysiological relationships as in migraine might be relevant for CH.

The second important finding is that comorbid disorders in CH patients were similar to those found in migraine patients. It has been hypothesized that all primary headaches are manifestations of the same fundamental migraine pathophysiological process with clinical features that vary in pain intensity, inverse frequency and duration and presence of trigeminal autonomic symptoms (17). Six patients with CH had migraine and one patient with migraine had CH, i.e. less than 1% of all patients. There are several methods to examine whether two disorders are different diseases or two different clinical presentations of the same disorder. Besides the genetic, biochemical and neuroimaging studies, comorbid disorders could, possibly, provide some information about the link between primary headache disorders. Based on our results, chronic sinusitis, malignancies, diabetes mellitus and glaucoma were more frequent in patients with CH. Anemia, essential tremor, depression and anxiety were expected to be more

Table 3

Results of the univariate analysis

Comorbid disease	CH (N of patients)	Migraine (N of patients)	OR (95% CI)*	p-value
Chronic sinusitis	31/130	35/982	8.5 (5.0-14.3)	0.001
Malignant tumors	4/130	6/982	5.2 (1.4-18.5)	0.012
Diabetes mellitus	5/130	11/982	3.5 (1.2-10.3)	0.021
Glaucoma	3/130	1/982	4.6 (1.1-19.5)	0.038
Another primary headache disorders**	6/130	1/982	47.5 (5.7-397.5)	0.001

* OR – odds ratio, 95% CI – confidence interval

** In CH group 4/6 patients had episodic migraine and 2/6 patients had chronic migraine with medication overuse. In migraine group 1/982 patient had cluster headache. Patients with two types of primary headache disorders were put in CH or migraine group according to type of headache that was the reason for the treatment in our Headache Center.

prevalent in migraine. Contrary to this expectation,, these disorders had an almost equal prevalence in CH and migraine. The prevalence of disorders more frequently found in CH according to the univariate analysis, was corrected by gender, age and illness duration in the multivariate analysis. As a result, only chronic sinusitis and diabetes mellitus remained in the multivariate model more prevalent in CH than in migraine.

Chronic sinusitis was present in 3.6% of migraine and 23.8% of CH patients. The estimated prevalence of rhinosinusitis in general population is about 16% (18). The role of sinusitis for migraine diagnosis and misdiagnosis was carefully studied in SAMS (19). The majority of the patients with prior diagnosis of sinus headache could be diagnosed, according to ICHD-II criteria (3), as migraine or probable migraine and two patients as TACs. Besides the triggers and localization of the headache pain that could be attributed to sinus disorder, the frequent association of autonomic features was the main reason for misdiagnosis. To our best knowledge, the relationship between sinus headache and CH was not studied yet. We obtained the diagnosis of chronic sinusitis from the medical records of our patients. In majority of these patients the diagnosis was established based upon rhinoscopy, nasal endoscopy, and sinus X-ray examination. However, nasal congestion and/or rhinorrhea are autonomic symptoms classically associated with pain in CH. Thus, mistaking autonomic changes of nasal and sinus mucosae as signs of chronic sinusitis is potentially a major confounding factor in our study. Another explanation is that recurrent mucosal edema and inflammation may lead to peripheral sensitization of trigeminal nerve afferents, and further sensitization of 2nd and 3rd order nociceptors and hence contribute to the occurrence of CH. Finally, it could be that the autonomic manifestations of CH favour the development of chronic sinusitis. Noteworthy, migraine attacks were also shown by endoscopy to be associated with nasal mucosal swelling that resolves after administration of sumatriptan (20). To better define the precise nature of the association between CH and chronic sinusitis prospective studies are necessary.

The higher prevalence of comorbid diabetes mellitus in CH is a novel finding of our study. According to the Serbian Burden of Disease Study, the estimated prevalence of diabetes mellitus type II on 2000 in general population of Serbia was 4.5% in males and 4.8 % in females (21). Diabetes mellitus was frequently present in some migraine patients associated with other vascular risk factors, such as hypertension and hyperlipidemia (14). Diabetes mellitus was present in 3.8% of CH patients, which is a significantly higher prevalence than in migraine patients. Hypertension was present in 13.1% of CH patients, which was similar to migraine patients. Cerebral infarctions were present in 2.3% of CH patients. The life-style habits of CH patients could contribute to the development of diabetes. Alcohol usage is higher in patients with CH than in controls and is statistically significant if one considers heavy drinkers (22). We did not collect data about prior treatments in our patients. Some patients with CH were possibly treated with prednisone that could have triggered diabetes. Besides these causes and consequences, the possibility of a common underlying pathological process cannot be excluded. Hypothalamic activation is noted in CH (23), paroxysmal hemicrania (24) and SUNCT (25). The hypothalamus is involved in hormone synthesis, regulation of the autonomic nervous system, thermoregulation, biological rhythms, emotional behavior, arousal, and cardiovascular control (26). Dysfunctioning orexin systems that play a role in feeding, sleep-wake cycle, neuroendocrine and autonomic functions (27, 28), as well as in the modulation of pain processing (29)

could be a possible link between CH and diabetes mellitus.

We found malignant tumors in 12 patients in our sample. Unexpectedly, among these, there were 3 patients with thyroid cancer.

There are several limitations to our conclusions. As the study was performed in a tertiary referral center, a selection bias is possible, but, as mentioned, we included consecutive clinic patients diagnosed with CH and migraine. The second limitation is that the data of comorbidities were collected retrospectively from medical records, although we included only disorders with a formal diagnosis according to the International Classification of Diseases, X revision. The same approach was used in other studies of comorbidities (10). A third shortcoming is that we were not able to determine the prevalence of the medical disorders identified in headache patients in the general Serbian population due to lack of an established disease registry.

The number of examined patients and the application of ICHD-II criteria for headache diagnosis enables correct estimation of CH comorbidities compared to migraine. Because frequent comorbidities, are noticed in more than half of CH patients, once a diagnosis of CH has been established, clinicians should pay attention to indices of chronic sinusitis, diabetes mellitus, hypertension, gastric ulcer, depression and anxiety, as well as malignancies.

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