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High prevalence of comorbidity of migraine in outpatients with panic disorder and effectiveness of psychopharmacotherapy for both disorders: A retrospective open label study

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ABSTRACT

We investigated the comorbidity rate of migraine in outpatients with panic disorder, and the efficacy of pharmacotherapy for both disorders. Fifty-four patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for panic disorder were recruited in the study. Forty-three patients were female, and their age ranged from 20 to 71 (38.8 ± 11.2; mean ± S.D.) years. Forty-one patients had agoraphobia. In these patients, we diagnosed migraine and other types of headache, using the International Classification of Headache Disorders, Second Edition (ICHD-II). Forty-three (79.6%) patients were diagnosed as having some type of headache; 33 (61.1%) migraine, 32 tension-type headache, and one cluster headache. In patients with migraine, treatment for panic disorder also improved their migraine in 19 (57.6%) patients. The mean onset age of panic disorder in patients with migraine was statistically significantly younger than that in non-migraine patients. The Clinical Global Impression Improvement (CGI-I) score of panic disorder was statistically significantly correlated with the CGI-I score of migraine. A high comorbidity rate (61.1%) of migraine was observed in outpatients with panic disorder, and our result suggests that treatment with antidepressants for panic disorder may also be effective for prophylaxis of migraine.

1. Introduction

A strong association between migraine and mental disorders has been reported in several epidemiological and clinical studies. According to these studies (Breslau and Davis, 1992, 1993; Stewart et al., 1992, 1994; Breslau et al., 2001, 2003; Mattsson and Ekselius, 2002; Kececi et al., 2003; Torelli and D'Amico, 2004; Hung et al., 2005; McIntyre et al., 2006; Beghi et al., 2007; Tietjen et al., 2007; Jette et al., 2008; Kalaydjian and Merikangas, 2008), patients with migraine also have a high frequency of mood and anxiety disorders including major depression and panic disorder. Although a high comorbidity rate of panic attacks or panic disorder has been widely reported in patients with migraine (Breslau and Davis, 1992; Stewart et al., 1992, 1994; Breslau et al., 2001; Mattsson and Ekselius, 2002; Jette et al., 2008; Kalaydjian and Merikangas, 2008), few reports (Zaubler and Katon, 1996; Marazziti et al., 1999) have investigated the prevalence of comorbidity of migraine in patients with panic disorder.

We hypothesized that patients with panic disorder were likely to have a high prevalence of comorbidity of migraine, and pharmacotherapy for panic disorder improved not only the symptoms of panic disorder but also those of migraine.

Currently, the International Classification of Headache Disorders, Second Edition (ICHD-II) (Headache Classification Subcommittee of the International Headache Society, 2004) established in 2004 is used to diagnose headache including migraine, and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) is used to diagnose mental disorders including panic disorder. However, no report has used both criteria simultaneously to diagnose migraine and panic disorder.

Regarding pharmacotherapy, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), which are prescribed to treat panic disorder, have also been used for the prophylaxis of migraine (Gomersall and Stuart, 1973; Couch et al., 1976; Couch and Hassanein, 1979; Mathew, 1981; Ziegler et al., 1987; Bank, 1994; D'Amato et al., 1999; Silberstein, 2000; Tomkins et al., 2001). However, there is no report on the effectiveness of these compounds for comorbid panic disorder and migraine.

Therefore, in this preliminary study, we investigated the prevalence of migraine and other types of headache that fulfilled the criteria

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of ICHD-II in patients diagnosed with panic disorder based on the criteria of DSM-IV-TR, retrospectively using face-to-face structured and semi-structured interview techniques, and how the pharmacotherapy for panic disorder affected migraine.

2. Methods

Fifty-four outpatients diagnosed with panic disorder with or without agoraphobia according to the criteria of DSM-IV-TR (American Psychiatric Association, 2000), who attended the Department of Psychiatry, Tokyo Women's Medical University Medical Center East, Shizuoka Municipal Shimizu Hospital or Hadano Kosei Hospital, between April 16 and June 15, 2006, were recruited in this study. We fully explained the study design and aims, and obtained written informed consent to participate in the study from each patient. This study was approved by the ethical committee of Tokyo Women's Medical University.

In these patients, we asked about the presence and history of headache including migraine (ICHD-II code 1), tension-type headache (TTH) (ICHD-II code 2), cluster headache (ICHD-II code 3), and other types of headache, according to the criteria of ICHD-II (Headache Classification Subcommittee of the International Headache Society, 2004), using face-to-face structured and semi-structured interview techniques. Diagnosis of panic disorder and headache was conducted independently by three psychiatrists each with at least 5 years' clinical experience. One of the three psychiatrists was a Headache Specialist accredited by the Japanese Headache Society. The other psychiatrists had been trained to diagnose headache by a specialist.

From these data, we investigated the prevalence of the comorbidity of migraine in patients with panic disorder with or without agoraphobia, the correlation between the severity of migraine and that of panic disorder, and the effectiveness of psychopharmacotherapy including antidepressants and benzodiazepines for panic disorder and migraine, using the Clinical Global Impression Severity (CGI-S) score (Guy, 1976) and the Clinical Global Impression Improvement (CGI-I) score (Guy, 1976).

Data analysis was carried out using SPSS (12.0J for Windows Japan, Tokyo, 2003). A P value less than 0.05 was considered statistically significant. All values were presented as mean ± standard deviation (S.D.). Chi-squared test or Fisher's exact test was used to compare the baseline characteristics including sex, CGI-S score of panic disorder before treatment, CGI-I score of panic disorder after pharmacotherapy, the presence of comorbid agoraphobia, the presence of comorbid mental disorder, and the presence of personality disorder in the migraine (M-group) and nonmigraine patients (C-group). Unpaired t-test was used to compare other characteristics of patients including age, onset age of panic disorder, and duration of treatment for panic disorder. The correlation between the CGI-I score of migraine and the CGI-I score of panic disorder was determined by Spearman's correlation coefficient by rank.

3. Results

The baseline characteristics of the patients with panic disorder are shown in Table 1. Forty-three (79.6%) patients were female and 11 were male, and their age ranged from 20 to 71 (38.8 ± 11.2; mean ± S.D.) years. The age at onset of panic disorder ranged from 15 to 62 (33.3 ± 11.6) years, and 41 (75.9%) patients had agoraphobia. Thirteen patients had other comorbid mental disorders; eight had major depressive disorder, two had dysthymic disorder, two had social phobia, and one had a specific phobia. Two patients were also diagnosed with borderline personality disorder. For panic disorder, SSRIs were prescribed as the main medication in 31 patients, TCAs in 13 patients, benzodiazepines in seven patients, and other medication (milnacipran, sulpiride, or olanzapine) in three patients. Seven patients were treated with only SSRIs and one was treated with only TCAs. Other patients were prescribed benzodiazepines for anxiety and/or panic attacks. Four patients were treated with SSRI and TCA. Valproic acid was prescribed for one patient; her CGI-S score was 1 (very much improved) for panic disorder and 5 (no change) for migraine. No patient used any other prophylactic agents for migraine, such as topiramate or gabapentin. Treatment for panic disorder was selected for each patient at the independent discretion of the attending psychiatrist and was not affected by the presence or absence of migraine. Subjects were treated for 3 months to 18 years (3.81 ± 3.45 years).

The CGI-S score of panic disorder before treatment was as follows: four patients were mildly ill, 16 were moderately ill, 27 were markedly ill, and seven were severely ill. The CGI-S score of agoraphobia before treatment was as follows: three were mildly ill, 16 were moderately ill, 19 were markedly ill, two were severely ill, and one was extremely ill. The CGI-I score of panic disorder after treatment was as follows: 28 were very much improved, 22 were much improved, three were moderately improved, and one was minimally improved. The CGI-I score of agoraphobia after treatment was as follows: 16 were very much improved, 12 were much improved, 11 were moderately improved, and two were minimally improved.

Table 1
Baseline characteristics of 54 outpatients with panic disorder.

Sex (female/male)	43/11
Age (years) [range]	38.8 ± 11.2 [20–71]
Onset age of panic disorder (years) [range]	33.3 ± 11.6 [15–62]
Duration of treatment for panic disorder (years) [range]	3.81 ± 3.45 [0.25–18]
Severity of panic disorder before treatment (3/4/5/6 in CGI-S)[a]	4/16/27/7
CGI-I score of panic disorder after treatment (1/2/3/4)[b]	28/22/3/1
Comorbid agoraphobia	41 (75.9%)
Severity of agoraphobia before treatment (3/4/5/6/7 in CGI-S)[a]	3/16/19/2/1
CGI-I score of agoraphobia after treatment (1/2/3/4)[b]	16/12/11/2
Comorbid mental disorders[c]	13 (24.1%)
Comorbid personality disorder	2 (3.7%)
Use of selective serotonin reuptake inhibitors (SSRI)[d]	33 (61.1%)
SSRIs were prescribed as the main medication	31 (57.4%)
Use of tricyclic antidepressants (TCA)[d]	15 (27.8%)
TCAs were prescribed as the main medication	13 (24.1%)
Use of benzodiazepines	33 (61.1%)
Benzodiazepines were prescribed as the main medication	7 (13.0%)
CGI-I score of migraine after treatment (1/2/3/4/5)[b]	8/7/4/1/13
CGI-I score of TTH after treatment (1/2/3/4/5)[b,e]	1/3/4/2/12

[a] CGI-S, Clinical Global Impression Severity score; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, extremely ill.
[b] CGI-I, Clinical Global Impression Improvement score; 1, very much improved; 2, much improved; 3, moderately improved; 4, minimally improved; 5, no change.
[c] Major depressive disorder, dysthymic disorder, social phobia and specific phobia.
[d] Use of these medications at entry into study.
[e] 10 patients do not apply.

Of 54 patients with panic disorder, 43 (79.6%) had the presence and/or history of some type of headache. Thirty-three (61.1%) patients were diagnosed with migraine; 15 migraine without aura (ICHD-II code 1.1), eight typical aura with migraine headache (1.2.1), one typical aura with nonmigraine headache (1.2.2), one typical aura without headache (1.2.3), three chronic migraine (1.5.1), and five probable migraine without aura (1.6.1). Thirty-two (59.3%) patients were diagnosed with TTH; 12 infrequent episodic TTH (2.1), 11 frequent episodic TTH (2.2), three chronic TTH (2.3), one probable infrequent episodic TTH (2.4.1), three probable frequent episodic TTH (2.4.2), and two probable chronic TTH (2.4.3). One (1.9%) patient was diagnosed with cluster headache (3.1). Three patients were diagnosed with other types of headache. Twenty-four patients had complicated migraine and TTH, including one patient with migraine without aura, probable chronic TTH and cluster headache.

Regarding the 33 patients with migraine (M-group), 26 (78.8%) were female and seven were male, and 24 (72.7%) had agoraphobia. In 26 (78.8%) patients, the onset of migraine preceded that of panic disorder. SSRIs were prescribed mainly in 18 patients, TCAs in 10 patients, benzodiazepines in three patients, and other medications in two patients.

No statistically significant correlation was found in the severity of panic disorder, the outcome of panic disorder with pharmacotherapy or the presence of agoraphobia, between M-group and nonmigraine patients (C-group) (Table 2). The mean onset age of panic disorder in M-group (30.4 ± 9.5 years) was statistically significantly younger than that in C-group (37.4 ± 13.4 years) ($t = 2.26$, $df = 52$, $P = 0.03$). Although only two patients (9.5%) in C-group had major depressive disorder as a comorbid mental disorder, 11 patients (33.3%) in M-group had other comorbid mental disorders; six had major depressive disorder, two had dysthymic disorder, two had social phobia, and one had a specific phobia (Fisher's exact test = 0.04).

The CGI-I score of migraine after treatment for panic disorder was as follows: eight were very much improved, seven were much improved, four were moderately improved, one was minimally improved, and 13