Overlap between Headache, Depression, and Anxiety in General Neurological Clinics: A Cross-sectional Study

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Abstract

Background: Many studies have reported that depression and anxiety have bidirectional relationship with headache. However, few researches investigated the roles of depression or anxiety in patients with headache. We surveyed the prevalence of depression and anxiety as a complication or cause of headache among outpatients with a chief complaint of headache at neurology clinics in general hospitals. Additional risk factors for depression and anxiety were also analyzed.

Methods: A cross-sectional study was conducted at 11 general neurological clinics. All consecutive patients with a chief complaint of headache were enrolled. Diagnoses of depression and anxiety were made using the Chinese version of the Mini International Neuropsychiatric Interview, and those for headache were made according to the International Classification of Headache Disorders, 2nd Edition. The headache impact test and an 11-point verbal rating scale were applied to assess headache severity and intensity. Logistic regression was used to analyze risk factors of patients with headache for depression or anxiety.

Results: A total of 749 outpatients with headache were included. Among them, 148 (19.7%) were diagnosed with depression and 103 (13.7%) with anxiety. Further analysis showed that 114 (15.2%) patients complaining headache due to somatic symptoms of psychiatric disorders and 82 (10.9%) had a depression or anxiety comorbidity with headache. Most patients with depression or anxiety manifested mild to moderate headaches. Poor sleep and severe headache-related disabilities were predictors for either depression or anxiety.

Conclusion: Clinicians must identify the etiology of headache and recognize the effects of depression or anxiety on headache to develop specific treatments.

Key words: Anxiety; Cause; Complication; Depression; Headache

INTRODUCTION

Headache, depression, and anxiety are highly prevalent in neurological practice. The bidirectional influences and strong interactions between headache and depression and anxiety have been well-documented, but mainly in migraine and tension-type headache studies. Comorbidity of depression or anxiety may cause stronger intensity,[1] longer duration,[2] and more recurrent increased risk of headache.[3] In contrast, more frequent migraines could directly lead to the presence of a depressive or anxiety disorder,[4] which is associated with more severe depression and anxiety.[5] Shared biological pathways and norepinephrine and serotonin neurotransmitters provide one possible explanation for the co-occurrence and associations between pain and depressive and anxiety disorders.[6]

A causal link has been increasingly recognized for the interaction between diseases causing headache and

psychiatric disorders, which is supported by clinical evidence that headache complaints account for 68% of patients with first-episode depression in a general hospital psychiatric unit.[7] Moreover, many psychiatric patients report only headache during a psychiatric disturbance. The International Classification of Headache Disorders, 2nd Edition (ICHD-II), published in 2004, confirmed this headache pattern as a new diagnostic secondary headache category called "headache

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attributed to a psychiatric disorder",[8] which improves clinician awareness for depression and anxiety in clinical practice and optimizes headache management based on etiology.

Several studies have reported a higher frequency of depressive or anxious disorders in subjects with the headache complaints. Marlow et al.[9] reported that nearly one-third of patients who present to primary care offices with a complaint of headache have moderate depression, 25.4% of patients with headache visiting a primary care setting fulfilled the diagnostic criteria for a major depressive episode.[10] Nimnuan et al.[11] found that the prevalence rates of depression and anxiety are 29.2% and 9.7%, respectively, in patients with headache in a tertiary care facility. A population-based study in Brazil reported that 23.8% of cases with any type of headache could be attributed to nervousness, tension, or psychiatric illness.[12] However, no specific number of patients with depression or anxiety, or percentages of patients with comorbidity of headache and a depressive or anxiety disorder were reported. Up to now, little is known regarding the clinical distribution of depression or anxiety as comorbidities or possible causes of headache among outpatients, particularly in neurological clinics.

The purpose of our study was to assess the separate prevalence rates of depression or anxiety as a complication or cause of headache in outpatients with a chief complaint of headache in neurological clinics throughout Chinese general hospitals. In addition, possible predictors for depression and anxiety were investigated. Our results will help physicians increase the identification of headache etiologies in patients with headache complaints and improve treatments for headache-related diseases.

METHODS

Participants and study design
This study is a part of the China prevalence of depression and anxiety in general neurology clinics study. All subjects were recruited consecutively on two randomly selected work days during a single week at the general neurological clinics of 11 tertiary hospitals across four different economic districts in China from September 10, 2012 to October 11, 2012. Inclusion criteria were as follows: patients with a chief complaint of headache, ≥18 years of age, completion of the self-rated Hospital Anxiety and Depression Scale (HADS), and no tumor, infection, or acute cerebrovascular disease on brain computed tomography or magnetic resonance imaging scans. Exclusion criteria were as follows: patients with problems of consciousness, cognition, vision, language, hearing, or understanding, or unable to complete the questionnaire survey or scale evaluation, or disagreed to participate in the study, had a history of substance abuse and withdrawal, intoxication, medication abuse, trauma, cranial pain, or epilepsy possibly associated with headache. This study protocol was reviewed and approved by the Institutional Review Board of Xuanwu Hospital. Written informed consent was obtained from each subject, either directly or from their guardian, prior to data collection.

Data quality was assured by providing 1 week of training to data collectors and supervisors. Demographic characteristics, clinical information, and psychiatric status were collected using a brief structured questionnaire and assessed by four neurologists in face-to-face interviews. Subjects with a chief complaint of headache were screened with the HADS, but only patients with an HADS score ≥8 were examined further for a depressive or anxiety disorder according to the Mini International Neuropsychiatric Interview (MINI) by a neurology specialist with psychiatric training experience. The diagnosis of headache and headache subtypes was confirmed by a headache specialist at each study center according to the ICHD-II. Patients diagnosed with headache due to pure depression or anxiety had a major depressive disorder or an anxiety disorder fulfilling the MINI criteria; headache, no typical characteristics are known that occurred exclusively during a major depressive or anxiety episode; and headache not attributed to another cause. Patients diagnosed with comorbid headache and depression or anxiety (comorbid depression or anxiety) fit the primary headache and depression or anxiety criteria. Only subjects diagnosed with a major depressive disorder (major depressive episode or dysthymia) or an anxiety disorder (phobia, panic disorder or general anxiety disorder) were used to calculate the prevalence rates of depression and anxiety. The effects of depression or anxiety on headache were furtherly analyzed according to the diagnosis in clinician's prescriptions among patients with depression or anxiety diagnosed by the MINI.

Measures
The ICHD-II was used to classify and diagnose headaches.[8] Headache pain intensity was assessed using an 11-point verbal rating scale (VRS), with 0 indicating "no headache" and 10 indicating "headache as severe as I can imagine",[13] 1–3 was "mild", 4–6 was "moderate", and 7–10 was "severe". Headache-related disability was assessed by the short-form headache impact test (HIT-6).[14] A total HIT-6 score ≤49 was interpreted as "no impact", 50–55 as "mild", 56–59 as "moderate", and >60 as "severe".[15]

Depression or anxiety was screened by the HADS, which incorporates seven questions on anxiety and seven questions on depression.[16] Depression and anxiety were diagnosed according to MINI Chinese version 5.0.0.[17] The assessment was conducted based on the patient's psychiatric state during the past 12 months.

Statistical analysis
All data were analyzed using SAS 9.2 statistical software (SAS Institute, Cary, NC, USA). Descriptive statistics are presented for the participant's demographic and clinical characteristics. Results are presented as the mean ± standard deviation (SD) or percentages, where appropriate. A $P < 0.05$ was considered statistically significant. Stepwise liner logistic regression was used to analyze risk factors of depression or anxiety in patients with

headache. The dependent variable was presence or absence of depression or anxiety. The 11 independent variables were age, gender, education level (elementary school or less, middle school, high school, or college or more), marital status (single, married, divorced, or widowed), headache frequency during the past 6 months (at least 1–2 times, once/day, once/week, once/month, or continuous), presymptoms (yes/no), precipitating factors (yes/no), headache duration (<30 min, 30–59 min, 1–12 h, 13–24 h, 25–72 h, or >72 h), headache intensity (mild, moderate, or severe), headache-related disability (no, mild, moderate, or severe), and poor sleep complaint (yes/no). Odds ratio (OR) estimates and 95% confidence intervals are presented from the logistic regression analysis.

Results

Participant characteristics

A total of 749 participants with headache complaint were analyzed. Subjects included 64% females, and the mean age was 48.9 ± 15.6 years (age range, 18–88 years). Table 1 describes the demographic features, headache characteristics, and other clinical information. Most patients (57.5%) had no or mild headache-related disability. Moderate headache intensity was the most common (43.4%). Few patients had a history of psychiatric disorder (13.6%) or took psychotropic medication (9.6%) in the past years. Approximately, 40% of patients complained of poor sleep.

In this study, approximately 5% of subjects did not participate due to acute headache, lack of time, disability that was too severe to complete the questionnaire, or refused to sign informed consent. Only one participant returned incomplete data, which was considered missing data.

Prevalence rates of depression and anxiety in patients with headache complaint

Table 2 shows the prevalence rates of depression and anxiety in all participates with headache complaints, as well as the distribution of depression and anxiety as a cause of headache or other comorbidity. Among all patients with complaint of headache, the prevalence rates of depression and anxiety were 19.7% and 13.7%, respectively. According to the clinician's diagnoses, 15.2% of patients had headache due to somatic symptoms of depression or anxiety (cause of headache) and 10.9% of patients attributed their primary headache as a comorbidity of depression or anxiety (headache comorbidity). In addition, 39.5% of patients with depression and 28.1% of patients with anxiety developed headache due to somatic symptoms of depression or anxiety. Approximately, 38% and 34% of patients with depression or anxiety considered their depression or anxiety as comorbid with primary headache. Mild to moderate headache intensity was reported among patients with headache complaint (mean VRS, 5.2 ± 2.2) caused by depression or anxiety (mean VRS, 4.7 ± 2.1), which was lower than that in cases of depression or anxiety overlapping with a primary headache attack (mean VRS, 5.7 ± 2.0).

Table 1: Demographic and clinical characteristics of study population

Variables	Results
Age (years)	48.9 ± 15.6
Female	480 (64.0)
Marital status	
Single	627 (86.0)
Married	68 (9.3)
Divorced or widowed	34 (4.7)
Education	
Elemental school or less	205 (29.2)
Middle school	196 (28.0)
High school	140 (20.0)
College or more	160 (22.8)
Headache intensity	
Mild	189 (26.0)
Moderate	316 (43.4)
Severe	223 (30.6)
Headache-related disability	
No	279 (37.2)
Mild	152 (20.3)
Moderate	97 (12.9)
Severe	196 (26.1)
Psychiatric disorder history	102 (13.6)
Psychiatric medicine history	72 (9.6)
Poor sleep complaints	298 (39.7)

The data are shown as mean ± SD, or n (%). SD: Standard deviation.

Table 2: Prevalence of depression or anxiety as different actions in patients with complaints of headache

Variables	n*	Headache intensity	DEP	ANX
Headache complaints	749 (100.0)	5.2 ± 2.19	148 (19.7)	103 (13.7)
Cause of headache	114 (15.2)	4.7 ± 2.13	45 (39.5)	32 (28.1)
Comorbidity of headache	82 (10.9)	5.7 ± 1.98	31 (37.8)	28 (34.1)

The data are shown as mean ± SD, or n (%). *n is the denominator for calculating percentage in depression or anxiety. Cause of headache refers to headache due to somatic symptoms of depression or anxiety. Comorbidity of headache refers to be headache due to the overlap of depression or anxiety with attacking primary headache. DEP: Depression; ANX: Anxiety.

Risk factors for predicting depression or anxiety in patients with a chief complaint of headache

Table 3 summarizes the descriptive statistics of four possible risk factors that may contribute to depression in patients with headache complaint: marital status, presymptoms, headache-related disability, and poor sleep. Single patients and those with headache presymptoms and poor sleep had an increased risk for depression compared to those without. Severe headache-related disability was predictive of depression and increased the risk of depression 5.5-fold.

Table 4 shows descriptive statistics of four possible risk factors that may contribute to anxiety in patients with headache complaint: headache duration, precipitating factors, headache-related disability, and poor sleep. Similar to the risk factors for depression, severe headache-related

Table 3: Risk factors for depression in patients with headache complaints analyzed by stepwise liner logistic regression

Variables	P	OR	95% CI
Marital status			
Married		1.000	
Single	0.005	2.760	1.365–5.581
Divorced or widowed	0.364	1.689	0.545–5.236
Presymptom			
No		1.000	
Yes	0.009	2.117	1.206–3.716
Headache-related disability			
No		1.000	
Mild	0.117	1.793	0.864–3.719
Moderate	0.104	2.017	0.865–4.705
Severe	<0.001	5.544	2.971–10.348
Poor sleep complaints			
No		1.000	
Yes	<0.001	2.907	1.760–4.802

OR: Odds ratio; CI: Confidence interval.

Table 4: Risk factors for anxiety in patients with headache complaints analyzed by stepwise liner logistic regression

Variables	P	OR	95% CI
Headache duration			
<30 min		1.000	
30–59 min	0.034	3.049	1.085–8.569
1–12 h	0.192	0.607	0.287–1.285
13–24 h	0.779	0.853	0.282–2.581
25–72 h	0.555	0.676	0.184–2.481
>72 h	0.374	1.701	0.527–5.487
Precipitating factor			
No		1.000	
Yes	0.010	2.224	1.213–4.076
Headache-related disability			
No		1.000	
Mild	0.234	1.684	0.713–3.977
Moderate	0.352	0.551	0.157–1.931
Severe	0.001	3.388	1.600–7.177
Poor sleep complaints			
No		1.000	
Yes	0.001	2.661	1.464–4.839

OR: Odds ratio; CI: Confidence interval.

disability and poor sleep were risk factors for anxiety. About 30–59 min headache duration and precipitating factors were significantly related with an increased risk of anxiety.

DISCUSSION

This cross-sectional study was conducted at 11 general neurology clinics throughout China and reported three important findings. The first was that a symptomatic overlap of headache, depression, or anxiety commonly existed in outpatients with a chief complaint of headache at general neurological clinics, and 15.2% of patients had a depressive or anxiety disorder. The second finding was that the intensity

of mild to moderate headache was most common in patients likely caused by depression or anxiety. Finally, some factors may predict the risk of depression or anxiety in patients with headache complaint.

We found that 19.7% of depression cases and 13.7% of anxiety cases occurred in patients with headache complaints in neurology clinics, which may have been the cause for headache or a headache complication. These rates were lower than those observed in two other clinical studies. Maeno *et al*. reported a prevalence of 25.4% major depressive episodes in primary care patients with a chief complaint of headache.[10] However, other depression subtypes were not assessed. Another case-control study found that 32% of primary care patients with a chief complaint of headache were diagnosed with a major depressive disorder.[9] But depressive disorders were assessed through the self-administered 9-item patient health questionnaire, and no standard diagnostic instruments were used. Various study designs and different instruments used for evaluation may have contributed to the differences in prevalence rates of depression. In addition, sample bias was also a noninvasive factor as subjects in these two studies were collected from primary care centers. Approximately, 17.2% of Polish neurological outpatients suffer from depression[18] consistent with this explanation. No study has reported the prevalence of anxiety in patients with headache complaint, until now. We reported here that 13.7% of patients with a chief complaint of headache had an anxiety disorder.

This study reported the distributions of depression and anxiety in patients complaining of headache according to a clinician's diagnosis. Approximately, 15% of patients suffered headache due to depression or anxiety, and 10.9% had comorbidity of depression or anxiety with a headache attack. Our observations confirmed those of a previous study in which physical pain symptoms correlated significantly with depression and anxiety, which may have been due to a common pathogenesis based on an imbalance in neurotransmitters, such as serotonin, noradrenaline, or dopamine.[6] Some earlier studies described that different headache intensities frequently indicate different causes (e.g., tension-type headache reveals mild to moderate intensity[19] and severe and more pain in migraines).[20] We found that mild to moderate headache occurred in patients with pure depression or anxiety (mean headache intensity score, 4.7), consistent with Vaccarino *et al*.'s finding that somatic symptoms of headache are moderate in patients diagnosed with a major depressive disorder.[21]

Treatment for psychiatric disorder has not traditionally been included in conventional headache management. Our research shows a higher proportion of patients with headache combined with depression or anxiety. We also observed some features of patients with headache that may have been attributed to depression or anxiety as the headache episodes were often longer, from several hours to 1 day, and more significant psychic symptoms occurred (i.e., fatigue, depression, apathy, angry, poor sleep, decreased appetite, and weight loss) than in patients with other headache diseases.

These findings indicate that clinicians should properly prescribe antidepressant and antianxiety drugs to relieve headache, particularly when a suspected headache has not responded to various headache medications and psychiatric symptoms are clinically prominent.

Several studies have explored the risk factors of depression or anxiety in patients with headache and some headache subtypes. Mitsikostas and Thomas[22] reported that headache duration and frequency were significantly associated with an increased risk of depression or anxiety. Zwart et al.[23] showed that headache frequency was strongly associated with depression and anxiety. But in our research, headache frequency could not be confirmed as indicator for depression or anxiety. We found that severe headache-related disability and poor sleep were significant predictors for either a depressive or anxiety disorder. Tietjen et al.[24] reported that headache disability was related with depression and anxiety, but the relationship was restricted to obese migraineurs. In addition, we discovered two additional risk factors of depression: marital status (single) and headache presymptoms (i.e., fluctuating mood, dizzy, fatigue, loss of appetite, or disturbed sleep). These results were similar to those of a rural residence survey in India by Sharma and Shah who determined that single subjects or those who lost a spouse were more susceptible to headache or depression.[25] Yong et al.'s study reported that headache presymptoms were a risk factor of depression but only in migraineurs.[26] Interestingly, we found that headache duration and precipitating factors (i.e., spicy food, cold conditions, tired, angry, and limited sleep) were also significantly associated with anxiety. In contrast, Maeno et al.[10] reported that headache duration predicts a higher risk for a major depressive episode. Our study added another perspective regarding the relationship between headache duration and episodes of a psychiatric disorder. No study has reported an association between precipitating factors of headache and depression or anxiety, until now.

Sleep disturbances involve the genesis and perpetuation of pain, anxiety, and depression.[27] Poor sleep quality affects episodic headaches[28] and recurrent headaches[29] can cause anxiety and depression.[30] In this study, we investigated patients with headache complaint to confirm the association between poor sleep and risk of depression or anxiety. We show, for the 1st time, that a comorbidity of poor sleep (i.e., poor sleep quality, early awakening, or dreaminess) increased the risk of depression in patients with a chief complaint of headache (OR, 2.907) than without, as well as an increased risk for an anxiety disorder (OR, 2.661). These results suggest that clinicians should pay close attention to sleep problems and evaluate their patients early for proper treatment.

Several limitations of this study need to be mentioned. First, temporality and causation of anxiety and depression symptoms could not be evaluated due to the cross-sectional design. Second, stress from depression or anxiety was not excluded due to the lack of records and major life event analyses of patients, which may have slightly increased the prevalence rates of depression and anxiety. Third, the prevalence of headache attributed to depression and anxiety was not determined precisely because no follow-up headache results were obtained after pharmacotherapy with antidepressive or antianxiety medications.

Despite these limitations, our study is novel as we systematically investigated the clinical profiles of patients with depression and anxiety with a chief complaint of headache in several Chinese general neurological clinics. Our results will provide a useful reference for further longitudinal studies of headache attributed to a psychiatric disorder or psychiatric comorbidity of headache in clinical populations. Our results will raise the awareness of physicians to identify the pathogenesis of headache overlapping with depression or anxiety and facilitate appropriate treatments or referral for psychological care.

In conclusion, two distinct effects of depression or anxiety on headache, which occurred as a cause for headache or as a complication of headache, were manifested in patients with headache as a chief complaint in several Chinese neurological clinics. Clinicians should identify the pathogenesis of headache and recognize its effects on depression or anxiety to carry out effective treatments and improve headache management.

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Conflicts of interest

There are no conflicts of interest.

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