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Original Reports

Anxiety and Depression Are Associated With Migraine and Pain in General: An Investigation of the Interrelationships

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Abstract: There is a well-established comorbidity between migraine and anxiety and depression (A/D). Here, we investigate whether this relationship is specific for migraine and A/D or whether other types of pain are also consistently associated with A/D. In addition, we test whether there is a consistent association between migraine and other types of pain when comorbidity with A/D is controlled for. Data on A/D, migraine, and 6 nonheadache pain locations (back, neck, orofacial area, abdomen, joints, and chest) were analyzed in 2,981 participants from the Netherlands Study of Depression and Anxiety (NESDA). It was tested whether the prevalence of pain in each individual location, as well as the total number of pain locations, depended on A/D and migraine status. A/D was consistently associated with pain in all measured locations. Migraine was also associated with pain in all anatomical sites, but these associations weakened substantially after correction for A/D severity, suggesting that a considerable part of the comorbidity of migraine and other types of pain may be explained by A/D. These findings emphasize the importance of accounting for A/D in studies of pain comorbidity. This will contribute to a better understanding of the mechanisms underlying A/D and pain.

***Perspective:** Anxiety and depression are consistently associated with pain, regardless of anatomical site. These disorders may be important factors in the co-occurrence of different pain disorders. Awareness of this comorbidity and a better understanding of the underlying mechanisms may facilitate adequate treatment of both types of conditions.*

***Key words:** Migraine, depression, anxiety, comorbidity, pain.*

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There is a well-established comorbidity between migraine and anxiety and depression (A/D). While both anxiety and depression individually are associated with an increased risk of migraine, the risk of migraine is even higher in patients with comorbid anxiety and depression.[24] A limited number of studies have investigated the order of onset of migraine, anxiety, and depression. One study reported that anxiety tended to precede migraine, whereas depression most commonly followed migraine onset.[24] However, a study that focused on depression only reported a bidirectional association between migraine and depression, with either migraine or depression occurring first, and each disorder predicting the onset of the other.[8] Migraine is probably the best-studied pain disorder in the context of comorbidity with

A/D.[8,22,23,25,38] Other pain disorders have not received the same amount of attention; however, several of them have also been reported to be comorbid with A/D, including back pain, fibromyalgia, and irritable bowel syndrome.[10,12,23,34] Migraine has also been reported to be comorbid with other pain disorders, consistent with the observation that pain disorders in general tend to cluster within patients.[11,35] For instance, studies in adults have reported comorbidity of migraine with musculoskeletal pain,[33] fibromyalgia,[14,17] and neck pain.[9] In children, headaches in general and migraine in particular were found to be comorbid with conditions including recurrent abdominal pain and neck-shoulder pain.[3]

Although the complex pattern of comorbidity between pain disorders and anxiety is well established, many studies still focus on specific disorders and do not take other comorbidities into account. This makes it difficult to integrate these findings into a comprehensive theory explaining the mechanisms underlying these comorbid relationships. The aim of the present paper is to perform a systematic study of these comorbidities, taking migraine (being among the best-studied pain disorders in the context of psychiatric comorbidity) as a starting point. With this study, we intend to answer 2 questions: first, is there a specific relationship between migraine and A/D, or is the comorbidity of A/D and pain disorders independent of anatomical site? And second, is there a consistent association between migraine and other pain disorders after correction for the well-known comorbidity of migraine and A/D?

Methods

Participants

This study was conducted in 2,981 participants from the Netherlands Study of Depression and Anxiety (NESDA). This is a longitudinal cohort study that includes individuals with current (6-month recency) and remitted diagnoses of anxiety and/or depressive disorders, as well as healthy controls. Participants were recruited from a variety of settings: 1,610 entered the study through primary care, 807 were recruited from specialized mental health care, and 564 came from 2 population-based studies on mental health.[26] Of these participants, 1,002 (34%) were male and 1,979 (66%) were female. The participants were aged between 18 and 65, with a mean age of 41.9 ($\pm$13.1) years. All participants underwent a 4-hour baseline assessment at 1 of 7 clinic sites between September 2004 and February 2007. The assessment included an interview on somatic health, functioning and health care use, and the administration of several written questionnaires.[19] Pain assessments and measurements of A/D were repeated in a 2-year follow-up assessment that started in 2006. Migraine was only measured at the first assessment. A detailed description of data collection procedures in the NESDA study can be found elsewhere.[26] The research protocol was approved by the Ethics Committee of participating universities, and all respondents provided written informed consent.

Measures

Anxiety and Depression

During the baseline assessment, current and lifetime diagnoses of anxiety and depressive disorders according to DSM-IV criteria[1] were made in all 2,981 participants, with the Composite International Diagnostic Interview (CIDI), v.2.1.[37] The anxiety diagnoses included social phobia, panic disorder, agoraphobia, and generalized anxiety disorder; depressive disorder diagnoses included major depressive disorder and dysthymia. Based on these diagnoses, patients were classified into 5 categories: 1) no anxiety or depression; 2) remitted anxiety and/or depression; 3) current anxiety only; 4) current depression only; and 5) current anxiety and depression. Individuals were only included in the remitted anxiety and/or depression category if no current diagnoses were present. The current diagnosis categories include both first-onset cases and individuals with a previous history of anxiety and/or depression.

Two additional measures were used to assess the severity of anxiety and depressive symptoms. The severity of anxiety was measured using the 21-item Beck Anxiety Inventory (BAI).[6] On this scale, a score of 0 to 9 is thought to indicate normal anxiety, 10 to 18 indicates mild-moderate anxiety, 19 to 29 indicates moderate-severe anxiety, and 30 to 63 indicates severe anxiety.[7] Depression severity was measured with the self-rated Inventory of Depressive Symptomatology (IDS-SR_{30}),[29,30] which consists of 30 questionnaire items addressing all DSM-IV symptom domains for major depressive disorder, as well as some associated symptoms and melancholic and atypical features. Scores on this scale can vary between 0 and 84. A score of 0 to 13 is defined as no depression, 14 to 25 as mild depression, 26 to 38 as moderate depression, 39 to 48 as severe depression, and 49 to 84 as very severe depression (www.ids-qids.org). Several items in the BAI and IDS are potentially confounded with pain symptomatology: the BAI includes 1 item on numbness/tingling sensations (potentially confounded with migraine aura), and 1 on abdominal pain; the IDS includes 4 items on sleeping problems (which can exacerbate pain symptoms[16]), 1 item on the presence of aches and pains, and 1 item on other bodily symptoms (including chest pain). To test the potential confounding effects of these items, we also calculated scale scores that did not include these items. BAI scores were available for 2,946 participants (99%), and an IDS score was available for 2,942 participants (99%) from the first wave of data collection. Two-year follow-up data were available for 2,596 subjects (87%).[15] Of these participants, 2,503 and 2,504 provided complete BAI and IDS information, respectively.

Migraine

Migraine symptomatology was assessed in the context of the baseline assessment, using a written questionnaire that included items on the following symptoms relevant for an ICHD-II[2] migraine diagnosis: having had at least 5 episodes of migraine, headaches lasting 4 to 72 hours, pulsating quality, moderate/severe pain intensity,