High prevalence of somatic symptoms and depression in women with disabling chronic headache

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Abstract—*Objective:* To better define, in women with headache, the relationship of depression and somatic symptoms to headache, characterized by diagnoses, frequency, and disability. *Methods:* At six headache specialty clinics, women with headache were classified using ICHD-II criteria, and frequency was recorded. A questionnaire addressing demographics, age at onset of headache, headache-related disability, somatic symptom, and depression severity was completed. Logistic regression was performed to measure the associations of headache frequency and headache-related disability with somatic symptom and depression severity. *Results:* A total of 1,032 women with headache completed the survey, 593 with episodic (96% with migraine) and 439 with chronic headache (87% with migraine). Low education and household income was more common in chronic headache sufferers and in persons with severe headache disability. Somatic symptom prevalence and severity was greater in persons with chronic headache and with severe headache-related disability. Significant correlation was observed between PHQ-9 and PHQ-15 scores ($r = 0.62$). Chronic headache, severe disability, and high somatic symptom severity were associated with major depressive disorder (OR = 25.1, 95% CI: 10.9 to 57.9), and this relationship was stronger in the subgroup with a diagnosis of migraine (OR = 31.8, 95% CI: 12.9 to 78.5). *Conclusions:* High somatic symptom severity is prevalent in women with chronic and severely disabling headaches. Synergistic relationship to major depression exists for high somatic symptom severity, chronic headache, and disabling headache, suggesting a psychobiological underpinning of these associations.

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The nature of the relationship of depression and headache has been of great interest, given the high prevalence[1,2] and expense[3] of both conditions, and the increased frequency in which they co-occur.[4,5] Painful symptoms may provoke[6] or be a manifestation of major depression,[7] and depression may heighten pain perception.[8] Findings of a bidirectional influence between migraine and major depression suggest a common neurobiology.[5] Regardless of the mechanism of migraine-depression relationship, psychiatric disease complicates headache management and portends a poorer prognosis for headache treatment.[9,10]

Somatic symptoms in headache patients are less well studied than psychological symptoms. Persons with somatic symptoms account for a sizable portion of patients presenting to primary care[11] and subspecialty practices.[12] In some cases somatic symptoms are due to underlying medical conditions, although the pathophysiology of many of these syndromatic disorders remains ill-defined. Although controversial,[13,14] idiopathic somatic symptoms have also been recognized as a possible manifestation of psychiatric disease, termed somatoform disorder.[15] A recent study in a referral headache population reported somatic symptoms to be significantly more common in patients with chronic (as compared to episodic) headache, and in those with associated depression.[16] Limitations of this study include small sample size, lack of use of standardized criteria to make psychiatric diagnoses, and absence of data on income and education, established confounding variables.[17]

The primary purpose of our study is to better define, within a population of women seeking treatment in headache subspecialty clinics, the relationship of headache, characterized by type, frequency, and disability, to current depression and somatic symptoms.

Methods. *Patient selection.* The recruiting phase of this cross sectional survey of headache clinic patients took place between June 2003 and December 2004 in six outpatient headache centers. A pilot study from the research consortium of the American Headache Society Women's Issue's Section on depression, somatic symptoms, and domestic violence in headache, this study's sam-

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pling frame was restricted to women. The reason was that women comprise about 85% of the clinics' population, and the literature suggests that women are much more frequently victims of domestic violence. Participants were examined by a headache specialist, who during the encounter determined the patient's eligibility for the study and invited them to participate. Participation in the study was offered to consecutive women using the following inclusion criteria: women with primary headache disorder as defined by the International Classification of Headache Disorders (ICHD)-II[18] criteria, 18 years and older, willingness to complete a self-administered electronic questionnaire on a Personal Digital Assistant (PDA), e.g., the Palm handheld device. Exclusion criteria included the following: not physically well enough to complete an electronic questionnaire on a PDA, not literate in English. Patients were provided with an IRB approved information sheet that described the purpose of the study, voluntary nature of the study, study aims, methods, and population, and were given opportunity to ask questions. After consenting to participate in the study, the physician entered the primary headache diagnosis, based on the ICHD-II criteria, and the average monthly headache frequency over the prior 3 months, <15 days, or ≥15 days. Per the instruction of the ICHD-II manual we had physicians diagnose antecedent migraine type in addition to other primary headache types. Given that the criteria for chronic migraine were under debate at the time of this study, we recorded the number of days of headache rather than use a complications of migraine diagnosis. The physician or the study personnel provided the subjects with verbal instructions and a brief demonstration to complete the remainder of the survey. A written instruction sheet was also provided to the subjects.

Measures. In keeping with recent recommendation for research in headache and psychiatric comorbidity,[19] we used ICHD-II diagnostic headache criteria and reliable, validated questionnaires with clinically relevant cut-off scores to classify headache-related disability (Headache Impact Test [HIT-6]),[20] depression (Patient Health Questionnaire [PHQ]-9),[21] and somatic symptoms severity (PHQ-15).[22]

HIT-6. The HIT-6, a six-item scale, which correlates well with headache severity,[23] has been determined to be reliable and valid in evaluating the impact of headache on health-related quality of life in patients seeking primary and headache subspecialty care.[24] HIT-6 produces a score ranging from 36 to 78. Severity of impact was graded as little or no impact for score ≤49, some impact for 50 to 55, substantial impact for 56to 59, and very severe impact for a score ≥60.

PHQ-9. The PHQ-9 is a self-reported diagnostic and severity measure for current (in the prior 2 weeks) depression using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It has been demonstrated to have superior validity criterion for the diagnosis of major depressive disorder compared to two other established depression screening questionnaires,[25] and it can detect changes over time,[26] and detect subthreshold depression.[27] The five levels of depression severity based on the PHQ-9 scores were minimal for scores 0 to 4, mild for scores 5 to 9, moderate for scores 10 to 14, moderately severe for scores 15 to 19, and severe for scores 20 and above. A study has shown that PHQ-9 scores of ≥15 are associated with 68% sensitivity and 95% specificity in diagnosing major depressive disorder using DSM-IV criteria.[21] PHQ-9 scores between 10 and 14 were associated with other depressive disorder and scores ≤10 represented no depressive disorder. Other depressive disorder is defined as a depressive disorder whose criteria encompass fewer symptoms than are required for any specific DSM-IV diagnoses.[21]

PHQ-15. The PHQ-15 is a self-administered validated questionnaire that measures somatic symptom type and severity over the prior 4 weeks. Each of 15 symptoms were graded by the patient as not bothered at all (scored as 0), bothered a little (scored as 1), or bothered a lot (scored as 2). The PHQ-15 is scored, with the total allowing ranking of somatic symptoms severity as minimal for 0 to 4, low for 5 to 9, medium for 10 to 14, and high for 15 to 30. Both the PHQ-9 and the PHQ-15 are derived from the self-administered Patient Health Questionnaire of the PRIME-MD (Pfizer Inc., New York, NY) used for making criteria-based diagnoses of mental disorders.[28]

Data collection. The electronic questionnaire was designed with Pendragon Forms 3.2 computer software (Pendragon Software Corporation, Libertyville, IL) and addressed the following topics: age, race, household income, highest educational level attained, total number of people in the household, age at onset of headaches, impact of headaches on daily life, and severity of depression and somatic symptoms. There were no personal health identifiers in the questionnaire. The questions were formatted as forced-response items (each item requires a response in order to proceed to the next item) to minimize data entry errors and eliminate missing items. For questions on race, education, and income, an option of "I choose not to answer" was provided for individuals who wanted to withhold this information. The average time taken for completion of the survey was 15 minutes. The physician or the study personnel entered a security code to indicate completion of the survey and for secure data transmission. Data were uploaded to secure central database by synchronizing the PDAs with an Internet-enabled computer using Pendragon SyncServer computer software (Pendragon Software Corporation). The database was maintained with technical support at the University of Toledo Health Science Campus, the primary site for the study. A total of 1,032 surveys were collected from all six centers, which recruited during periods ranging from 6 weeks to 9 months. Names of the individual centers and number of surveys contributed from each are as follows: University of Toledo, OH (189 surveys), Nashville Neuroscience Group, TN (424 surveys), University of Cincinnati, OH (92 surveys), University of Utah Medical Center, Salt Lake City (222 surveys), University of Iowa Hospitals, Iowa City (63 surveys), and Swedish Medical Center, Seattle, WA (42 surveys). Information on race was not available in 2 surveys, on education in 8 surveys, and on household income in 79 surveys as patients selected the "I choose not to answer" option for these survey items. Information on the primary headache diagnosis was missing in 8 surveys.

Statistical analysis. Analysis of categorical data was done using χ^2 or Fisher exact test and evidence of trends in binomial proportions was examined using Cochran-Armitage test statistic. For data with deviation from normality and for analysis of the HIT-6, PHQ-15, and PHQ-9 scores, nonparametric tests including Spearman rho correlation test to examine the relation between the scores were utilized. Multivariate logistic regression analysis adjusting for significant confounders was performed to measure the association of depression and somatic symptom severity with headache frequency and headache-related disability. OR and 95% CI were used to measure the strength of the associations between dependent and predictor variables. Significance of the ORs was examined using Wald's χ^2 statistic and Hosmer and Lemeshow test was used to assess the fit of the regression models.[29] The multicenter sampling frame of this study was taken into account in the analysis by including the centers as a categorical covariate in the estimations procedures. All statistical hypotheses were tested at 0.05 level of significance, and the analysis was performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Results. A total of 1,032 women, aged 18 years and older (mean = 42 years, SD = 11.2), from six different headache clinics, completed the survey. Approximately 10% of those asked did not participate, usually because of acute headache or lack of time following the visit. Very few persons (<1%) who started the survey did not complete it. Every survey was included in the analysis as there were no missing data in patient responses due to the forced-response design of the PDA program. Participants from one of the centers (University of Toledo Health Science Campus) were relatively younger (mean = 38 years, SD = 11), but all the other demographic information was similar across the centers. Migraine was diagnosed in over 90% of the participants. A quarter of the migraineurs also had a second headache diagnosis, usually tension-type headache (table 1).

There were 593 women with episodic headache (<15 headaches per month) and 439 had chronic headache (≥15 headaches per month). The chronic headache sufferers were significantly younger, although the onset of headache was earlier in life in women with episodic headache. Women with chronic headache reported less formal educa-

Table 1 *Study population characteristics (n = 1,032)*

	Headache frequency*		Headache-related disability†	
	Chronic	Episodic	Very severe	Less severe
No. (% of total)	439 (43)	593 (57)	742 (72)	290 (28)
Age, y	40.2 ± 11.4‡	42.9 ± 11.0	40.6 ± 11.2‡	45.2 ± 11.1
Age at headache onset, y	22.2 ± 12.1	21.8 ± 12.0	21.0 ± 11.7§	24.0 ± 12.7
Migraine alone	251 (57.8)	440 (74.6)	488 (66.4)	203 (70.2)
Migraine and medication overuse	20 (4.6)	8 (1)	25 (3.4)	3 (1.0)
Migraine and tension-type	63 (14.5)	52 (8.8)	90 (12.2)	25 (8.6)
Migraine and other headache¶	49 (11.2)	66 (11.1)	78 (10.6)	37 (12.8)
Tension-type alone	30 (6.9)	13 (2.2)	30 (4.1)	13 (4.5)
Other headache alone	21 (4.8)	11 (1.8)	24 (3.2)	8 (2.8)
Race				
White	392 (89.3)	546 (92.1)	669 (90.4)	269 (92.8)
African American	20 (4.6)	23 (3.3)	37 (5)	6 (2)
Hispanic	4 (1.0)	8 (1.3)	6 (1)	6 (2)
Asian	3 (<1)	3 (<1)	4 (0.5)	2 (0.7)
Other	18 (4.1)	13 (2.2)	24 (3.2)	7 (2.4)
Education‖				
Not a high school graduate	15 (3.5)	15 (2.5)	24 (3.3)	6 (2)
High school graduate	154 (35.7)	146 (24.7)	232 (31.5)	68 (23.6)
Undergraduate	79 (18.3)	97 (16.4)	127 (17.3)	49 (17)
College graduate	131 (30.3)	194 (32.8)	230 (31.3)	95 (33)
Postgraduate	53 (12.3)	140 (23.7)	123 (16.7)	70 (24.3)
Household income**				
<$20,000	70 (17.3)	42 (7.7)	91 (13.3)	21 (7.7)
$20,000 to $50,000	136 (33.7)	157 (28.6)	228 (33.4)	65 (24)
$50,000 to $100,000	139 (34.4)	228 (41.5)	258 (37.8)	109 (40.2)
>$100,000	59 (14.6)	122 (22.2)	105 (15.4)	76 (28)

Values are n (%) or mean ± SD. Values may not add to the total due to missing or unavailable information (see Methods).

* Chronic headache (≥15 headache days/month), episodic (<15 headache days/month).
† Very severe disability defined as a HIT-6 score of 60 or higher.
‡ $p < 0.001$, § $p = 0.006$.
¶ Migraine in addition to post-traumatic or cluster headache.
‖ Associated with headache frequency ($p < 0.001$) and disability ($p = 0.018$).
** Associated with headache frequency ($p < 0.001$) and disability ($p < 0.001$).

tion ($p < 0.001$) and lower household income ($p < 0.001$) compared to those with episodic headaches. Low education and income levels were associated with increased headache frequency and vice versa. These associations remained significant after adjusting for depression (as measured by PHQ-9) and also after adjusting for somatic symptom severity (as measured by PHQ-15).

Seventy-two percent (n = 742) of the women in this study reported having very severe headache impact (HIT-6 score ≥60), with higher proportion in the chronic headache group (88% vs 60%, $p < 0.001$). Women reporting very severe impact were significantly younger at the time of enrollment and also reported onset of headaches at an earlier age. Women with very severe impact reported lower household income and lower education levels. The association of increased impact with low income levels remained significant after adjusting for either depression or somatic symptom severity, whereas this was not true with education.

In separate analyses, women at lower education levels had higher scores on PHQ-9 ($\chi^2 = 32.8$, $df = 4$, $p < 0.001$) and PHQ-15 ($\chi^2 = 29.9$, $df = 4$, $p < 0.001$). Similarly, women at lower income levels revealed high PHQ-9 ($\chi^2 = 57.6$, $df = 3$, $p < 0.001$) and PHQ-15 ($\chi^2 = 35.5$, $df = 3$, $p < 0.001$) scores.

Somatic symptom severity as measured on the PHQ-15 was reported as high in 31%, medium in 39%, low in 27%, and minimal in 4% of the study population. Univariate analysis of each of the 14 non-headache symptoms in the PHQ-15 revealed that 11 items were more commonly endorsed (i.e., "bothered a lot") by women with chronic headache compared to those with episodic headache (figure). Adjusting for age, education, and income in multivariate regression models, eight of these symptoms were signifi-

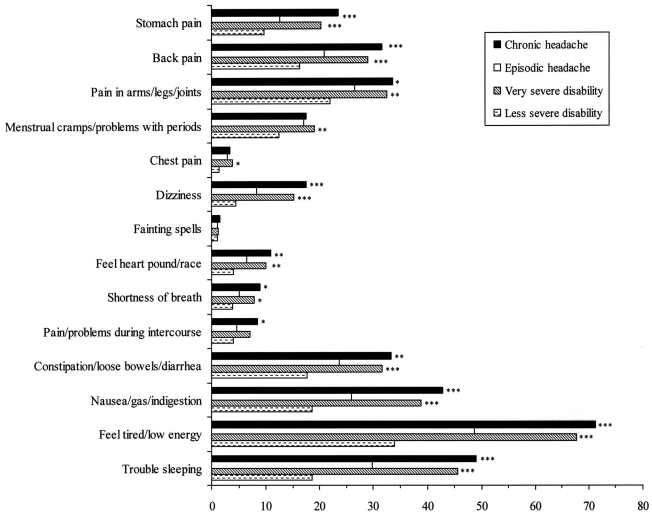

*Figure. Prevalence (in percentage) of somatic symptoms in women by headache frequency and headache-related disability. *p < 0.05; **p < 0.01; ***p < 0.001.*

cantly associated with chronic headache, including stomach pain (OR = 1.8, 95% CI: 1.3 to 2.6); back pain (OR = 1.7, 95% CI: 1.2 to 2.3); dizziness (OR = 2.1, 95% CI: 1.4 to 3.2); pain or problems during intercourse (OR = 1.8, 95% CI: 1.0 to 3.0); constipation, loose bowels, or diarrhea (OR = 1.6, 95% CI: 1.2 to 2.2); nausea, gas, or indigestion (OR = 1.9, 95% CI: 1.4 to 2.5); feeling tired or having low energy (OR = 2.5, 95% CI: 1.9 to 3.4); and trouble sleeping (OR = 2.1, 95% CI: 1.6 to 2.7). Women with chronic headache were three times more likely than those with episodic headache to report a high degree of somatic symptom severity (OR = 3.4, 95% CI: 1.6 to 7.3). The association between chronic headache and high somatic symptom severity remained significant after controlling for depression (OR = 1.7, 95% CI: 1.2 to 2.4).

Univariate analysis of each of the 14 non-headache symptoms in the PHQ-15 revealed that 12 items were more commonly endorsed ("bothered a lot") by women with very severe impact compared to the less impacted group. The pattern of the symptoms frequency stratified by HIT-6 scores (≥60 vs <60) was similar to that stratified by headache frequency (≥15 days/month vs <15 days/month) (figure). Examined in an adjusted multivariate analysis, women with very severe impact were nearly 5 times more likely to have high somatic symptoms severity (OR = 4.6, 95% CI: 3.0 to 6.9). This relationship was maintained after adjusting for coexistent depression, with an adjusted OR of 3.1 (95% CI: 1.9 to 4.9).

Based on the PHQ-9 scores, the prevalence rate of current major depressive disorder for the entire study population was 18%. Seventeen percent reported other depressive disorders. Analysis indicated a strong association between headache frequency and depression after adjustment for age, education, and income. Compared to those with episodic headache, chronic headache sufferers were four times more likely to report symptoms of major depressive disorder (OR = 4.4, 95% CI: 2.9 to 6.5) and about twice as likely to present with symptoms of other depressive disorders (OR = 1.8, 95% CI: 1.3 to 2.7). The prevalence rate of major depressive disorder in patients with chronic headache was 29% (n = 129). Women reporting very severe

Table 2 *Effect of headache frequency and headache-related disability on the risk for high somatic symptom severity*

Headache frequency	Headache-related disability	No. (%)	High somatic symptom severity, OR (95% CI)
–	–	237 (23)	1.00
+	–	53 (5)	3.3 (1.5–7.6)*
–	+	356 (35)	4.7 (2.7–8.0)*
+	+	386 (37)	8.6 (4.9–14.7)*

Headache frequency: chronic headache (+) and episodic headache (−). Headache disability: very severe disability (+) and less severe disability (−).

* $p < 0.01$.

headache impact were six times more likely to endorse symptoms of major depressive disorder (OR = 6.2, 95% CI: 3.3 to 11.4) and about three times more likely to endorse symptoms of other depressive disorder (OR = 2.7, 95% CI: 1.7 to 4.3).

Increase in the PHQ-9 scores was associated with an increase in the PHQ-15 scores (r = 0.62, $p < 0.001$). Stratifying by headache frequency, this association between depression and somatic symptoms remained, and was slightly stronger in chronic headache sufferers (r = 0.63, $p < 0.001$) than those with episodic headache (r = 0.57, $p < 0.001$). The difference in the strength of the relation was also apparent between women with very severe headache impact (r = 0.58, $p < 0.001$) compared to those with less severe headache impact (r = 0.54, $p < 0.001$).

Table 2 shows the relationship of headache frequency and headache impact to high somatic symptom severity in a stratified analysis. Both chronic headache and very severe headache impact were independently associated with high somatic symptom severity, and combined (headache frequency ≥15 days/month and HIT-6 ≥ 60) the OR for high somatic symptom severity was additive (OR = 8.6, 95% CI: 4.9 to 14.7). This relationship remained significant after adjusting for major depression (OR = 5.8, 95% CI: 3.3 to 10.1). Subgroup analysis of migraine patients (n = 949) did not alter the association between these variables.

Table 3 illustrates the relationship of headache frequency, headache impact, and somatic symptom severity in determining the risk for major depressive disorder. None of these variables was independently associated with major depressive disorder, but with two variables in combination, the ORs for a significant association with major depressive disorder ranged from 4 to 10. It can be noted that presence of high somatic symptom severity largely determined the overall strength of association with major depressive disorder, followed by headache frequency and, finally, by headache-related disability (as measured by HIT-6). Women with chronic headache, very severe headache-related disability, and high somatic symptom severity were 25 times more likely to have major depressive disorder compared to those without any of these conditions. Analysis of data restricted to patients with migraine (n = 949) indicated a stronger relationship of headache frequency, disability, and somatic symptom severity with major depressive disorder. The risk of major depressive disorder in persons with frequent, disabling migraines in

Table 3 *Effect of headache frequency, headache-related disability, and somatic symptom severity on the risk for major depressive disorder*

Headache frequency	Headache-related disability	Somatic symptom severity	No. (%)	PHQ-9*	Risk for major depressive disorder: All headache (n = 1,032), OR (95% CI)	Risk for major depressive disorder: Migraine (n = 949), OR (95% CI)
–	–	–	218 (21)	3	1.00	1.00
+	–	–	40 (4)	3	0.7 (0.1–5.3)	0.8 (0.1–7.2)
–	+	–	253 (25)	5	1.6 (0.6–4.0)	1.8 (0.7–4.9)
–	–	+	19 (2)	9	1.1 (0.1–9.6)	1.1 (0.1–10.2)
+	+	–	206 (20)	7	3.6 (1.5–8.6)†	4.1 (1.6–10.6)‡
–	+	+	103 (10)	10	8.4 (3.4–20.8)‡	10.1 (3.9–26.5)‡
+	–	+	13 (1)	11	10.1 (2.3–44.2)†	18.2 (3.8–86.7)†
+	+	+	180 (17)	15	25.1 (10.9–57.9)‡	31.8 (12.9–78.5)‡

Headache frequency: chronic headache (+) and episodic headache (–). Headache disability: very severe disability (+) and less severe disability (–). Somatic symptom severity: high severity (+) and medium to minimal severity (–).

* Median PHQ-9 score.
† $p < 0.01$, ‡ $p < 0.001$.

PHQ = Patient Health Questionnaire.

addition to severe somatic symptoms increases by 32-fold (table 3).

Discussion. In our study of female headache clinic patients, somatic symptoms and depression were common. One-third of our study population had high somatic symptom severity. Of the six symptoms involving extra-cephalic pain, pain in extremities/joints, back pain, and stomach pain were the most prevalent. Somatic symptoms that overlapped with those on the depression instrument (feeling tired/low energy, and trouble sleeping) were nearly twice as common as the pain symptoms. One fifth of our study population endorsed symptoms on the PHQ-9 suggesting current major depressive disorder, and this is in keeping with other studies of migraine patients.[30] Furthermore, based on the increase in PHQ-9 scores with increasing PHQ-15 scores, our data suggest that an increase in somatic symptom severity is associated with increased depression. There is a growing literature on the overlap of depression and somatic symptoms.[31] In one primary care center study, half the depressed patients reported multiple unexplained somatic symptoms,[32] whereas in another primary care study, 35% of patients with somatization also had major depression.[33] Somatic symptoms may be a manifestation of psychiatric disease, and the question arises as to whether the PHQ9 and PHQ 15 instruments are measuring the same entity, referred to as transdiagnostic confounding effects.[34] Our finding that the association of somatic symptom severity with headache frequency, as well as with headache impact, remained significant after controlling for major depression suggests that somatic symptom severity and major depression are distinct variables. Of note is a recent study in a non-clinical population, which demonstrated that somatic symptoms predict major depression for the following year.[35]

When patients were stratified by headache frequency, chronic headache was associated with higher somatic symptoms severity and greater frequency of major depressive disorder than episodic headache. Other studies have similarly highlighted the increased frequency of somatic complaints,[36,37] particularly painful symptoms,[38-40] in persons with chronic headache. The pattern of individual somatic symptom prevalence stratified by headache frequency was comparable to that found in a recent study.[16] Although somatic symptoms were highly prevalent in our study, the PHQ-15 is not a diagnostic instrument for somatoform disorders,[22] a category within the DSM-IV which is hotly debated because of highly divergent potential influences.[13] Our finding of 29% prevalence of major depression in the cohort with chronic headache is in keeping with the prevalence rates of major depression (23% to 57%) reported with chronic headache in other clinic-based studies.[41,42] There remains some controversy in the literature as to the association of headache frequency with depression, with one recent study demonstrating increasing headache frequency with increasing depression scores,[43] and another study reporting no influence of depression on headache attack frequency.[44] In this headache clinic population, we found income and education to be important covariates. In keeping with other studies, income and education levels diminished with increasing severity of the following: headache frequency,[17,40,45] headache impact, somatic symptoms, and depression.[32,46-48]

A novel finding from our analysis is the utility of this particular headache-related disability measurement (HIT-6) in predicting headache frequency, somatic symptoms severity, and depression. Importantly, persons with frequent headache, severe headache-related disability, and multiple physical symptoms have a very high likelihood of having current major depressive disorder. Analysis suggests a synergistic relationship of these variables. We hypothesize that severe headache, severe somatic symptoms, and major depression may be linked through dysfunction of the serotonergic system and studies are under way to test this theory.

Strengths of this study include the large sample size, geographically distinct locations of the participating clinics, and the methodology we employed. Diagnosis of the headache type and frequency were determined by a headache specialist using the ICHD-II criteria. Evaluation of depression and somatic symptom severity was performed using instruments which, although novel in headache research, have well-documented validity and reliability. The PDA technology, which patients found very easy to use, had the advantage of ensuring that there are no missing data fields. The rapid paperless transfer of data to a central database eliminated errors in data entry.

Weaknesses of this study include the omission of a number of variables that may have positively contributed to the analysis. These include noting the presence of aura, the presence of medication uses and overuse, and the exact frequency of headache. Use of antidepressants, for example, may have modulated (likely minimized) the association of headache and depression found in the study. Since the instruments we used measured only current depression and somatic symptoms severity, our data do not allow us to establish a temporal sequence for onset headache and comorbid conditions. The cross-sectional nature of the study does not allow for speculation on causality. The inclusion of only female patients in this study limits the generalizability of the findings to other populations.

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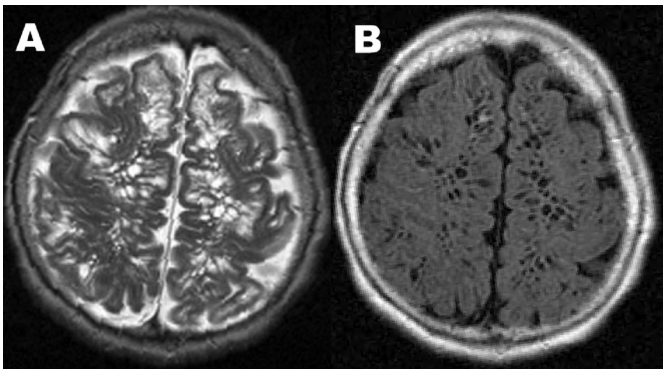

Figure 1. Axial T2 (A) and FLAIR (B) weighted MRI demonstrating dramatically enlarged Virchow Robin spaces.

Swiss cheese brain

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A 66-year-old woman with hypertension and hypercholesterolemia presented with 2 days of cough, low-grade fever, and severe encephalopathy. Nasal influenza A antigen was detected. As her fever resolved, her mental status returned to normal. Brain MRI revealed extensive non-enhancing T2 hyperintensities (figure 1).

This swiss cheese appearance is caused by unusually large Virchow-Robin spaces (VRS), normal perivascular extensions of the subarachnoid space. Large VRS can be a phenomenon of aging or cerebral atrophy, particularly over the hemispheric convexity.[1]

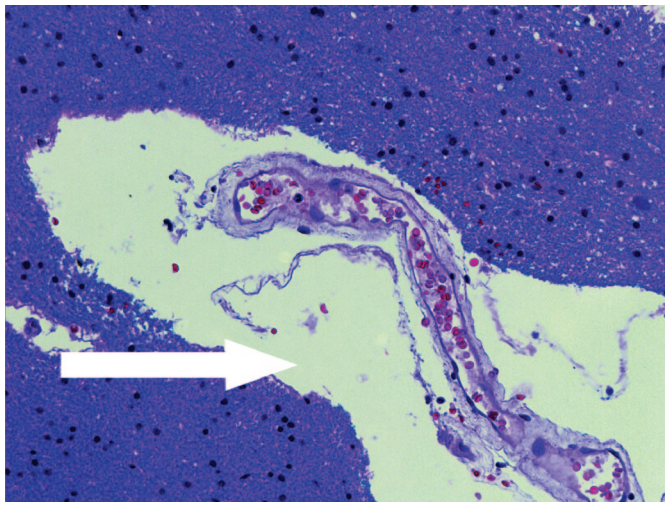

Figure 2. H-E preparation of temporal lobe biopsy, showing enlarged perivascular space (arrow).

VRS 2 cm in diameter have been described in normal patients.[2] VRS are FLAIR and T1 hypointense, and T2 hyperintense.

Left temporal lobe biopsy was performed during unrelated elective aneurysm clipping, to exclude neurodegenerative diseases that might cause ex vacuo enlargement of VRS or cystic conditions—e.g., infectious or post-infarction cysts, cerebral lacunes, ependymal, neuroepithelial, or arachnoid cysts.[2] The biopsy revealed dilated perivascular spaces (figure 2), confirming the diagnosis.

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