UNIVERSITY OF CINCINNATI

Date: 10-Aug-2010

I, Elise Bendik, hereby submit this original work as part of the requirements for the degree of:

Master of Science

in Genetic Counseling

It is entitled:

Joint Hypermobility Syndrome: A Common Clinical Disorder Associated with Migraine Headache in Women

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Joint Hypermobility Syndrome: A Common Clinical Disorder Associated with Migraine Headache in Women

A thesis submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Master of Science In the Department of Pediatrics of the College of Medicine

August 2010

by

Elise Bendik

M.S. University of Illinois, 2007
B.S. University of Tennessee, 2005

Committee Chair: Brad T. Tinkle, M.D., Ph.D.
Abstract

The objectives of our study were to determine if the prevalence, frequency and disability of migraine headache differ between female patients with Joint Hypermobility Syndrome (JHS) and a control population. Twenty-eight patients with JHS and 232 patient controls participated in the case-cohort study. All participants reporting a history of headache within the last year underwent a structured verbal headache diagnostic interview to ascertain the clinical characteristics of each headache type and a headache diagnosis was assigned according to strict criteria of the International Classification of Headache Disorders-II-2004 (ICHD-2). Our study indicates that the prevalence of migraine headache approaches 75% in female patients with JHS and the adjusted odds ratio was 3.19 [95% Confidence Interval (CI) = 1.25, 8.15] for the prevalence of migraine headache in females with JHS as compared to the control group. Our study suggests that migraine headache is another symptom of JHS.
Acknowledgements

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List of Abbreviations

1. Joint Hypermobility Syndrome (JHS)
2. Hypermobility type Ehlers-Danlos syndrome (hEDS)
3. Ehlers-Danlos Syndrome (EDS)
4. International Classification of Headache Disorders-II-2004 (ICHD-2)
5. Migraine Disability Assessment (MIDAS)
6. Neck Disability Index (NDI)
7. Patient Health Questionnaire 9 (PHQ-9)
8. Temporomandibular disorder (TMD)
9. Generalized Anxiety Disorder-7 (GAD-7)
10. Rate Ratio (RR)
11. Odds Ratio (OR)
12. Confidence Interval (CI)
13. Standard deviation (S.D.)
14. Postural orthostatic tachycardia syndrome (POTS)
15. Mitral valve prolapse (MVP)
16. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
**Instructions**

Joint hypermobility syndrome (JHS) is an inherited connective tissue disorder which is defined by the presence joint hypermobility and musculoskeletal symptoms in the absence of systemic rheumatologic disease [1-2]. JHS occurs in up to 10%-15% of the general population, often demonstrating 85-90% female predominance [3-6]. An underlying disorder of collagen contributes to the systemic manifestations of JHS, which can occur at any age and are often progressive [7]. Common musculoskeletal symptoms include joint pain, myalgia, joint instability and dislocations, and non-articular limb pain [8]. It is becoming increasingly recognized that JHS also involves other body systems outside of the musculoskeletal realm that likely share a common pathophysiology due to defects in the collagen network [9]. Some of these conditions found to be associated with JHS include orthostatic intolerance/postural orthostatic tachycardia syndrome (POTS), irritable bowel syndrome, fibromyalgia, anxiety/panic disorders, and depression [4, 9-11].

JHS is largely caused by an undetermined genetic abnormality likely having multiple genetic etiologies and is inherited in an autosomal dominant fashion as a sex-influenced trait [8]. Joint hypermobility is assessed clinically using the Beighton scoring system which is a simple and quick in-office administered test (Figure 1). The diagnosis of JHS incorporates the Beighton score and is determined using the Brighton criteria which is based on clinical evaluation and history (Table 1). The phenotype of JHS is suggested to represent a clinical continuum with the hypermobility type of the Ehlers-Danlos syndrome (hEDS) because of their indistinguishable clinical features [12]. hEDS is the most common form of the Ehlers-Danlos syndromes (EDS), which have an overall prevalence of at least 1 in 5,000 [13]. The current clinical criteria established to diagnose
and distinguish JHS and hEDS are non-specific and not mutually exclusive [12]. Thus, the terms JHS and hEDS are often used interchangeably.

Several studies suggest that migraine headaches are more common in patients with JHS. Hakim and colleagues [9] found that the prevalence of migraine headache was 40% in patients with JHS and 20% in a control population. Similarly, Kanjwal and colleagues [11] conducted a study in a clinic for autonomic disorders and demonstrated that migraine occurred in 73% of patients with both JHS and POTS in comparison to 23% of those with POTS but without JHS (p=0.001). Jacome and colleagues [14] reported that 11 out of 18 patients with diagnosis of EDS referred to a subspecialty neurology clinic experienced migraine headaches. These studies however represent very preliminary data as the first two studies did not use criteria from the International Classification of Headache Disorders (ICHD) for their diagnoses of migraine headache and the third was a case series and thus lacked a control group for comparison.

The purpose of this study was to characterize the relationship between primary headache disorders and JHS using validated diagnostic tools in a case cohort design. The primary objective of this study was to determine if JHS was associated with an increased prevalence, frequency, and disability of migraine headache. A secondary objective was to determine if the prevalence, frequency, and disability of tension-type headache differed between these two populations.
Methods

Subjects

Consecutive patients meeting diagnostic criteria for JHS/hEDS recruited from two separate practice sites of the Connective Tissue Clinic at Cincinnati Children’s Hospital Medical Center between the dates of January 1, 2010 to July 1, 2010 were screened for admission into the study as cases. The clinical diagnoses of JHS/hEDS were established by a board-certified clinical geneticist (BTT) based on the established clinical criteria (Table 1). Control patients were selected from two primary care internal medicine practices in the greater Cincinnati area from June 1, 2009, to April 30, 2010. Consecutive cases and controls that met the inclusion and exclusion criteria listed below were asked to participate in this study.

Participants aged 18 to 65 years old who were English speaking and able to provide written informed consent were eligible to participate in the study. Subjects were excluded if they had any of the following conditions: 1) past history of secondary headache disorder due to a brain aneurysm or brain tumor, 2) specific chronic illnesses such as malignancy, chronic renal failure, tuberculosis, lupus, rheumatoid arthritis, sarcoidosis, hypereosinophilic syndrome, Wegner’s granulomatosis, Churg-Strauss vasculitis, or polyarteritis, and 3) currently pregnant. These conditions were excluded because these disorders and/or their treatments could potentially modulate the prevalence, frequency, and disability of headache disorders.
Headache diagnosis

All participants who reported experiencing a headache in the previous year unrelated to respiratory infection, head trauma, or hangover underwent a structured verbal headache diagnostic interview. The structured interview was designed to capture the clinical characteristics of each headache type and was previously validated to diagnose migraine, tension-type, and other primary headache disorders [15]. Interviews were performed by a trained research coordinator at the time of an office visit to the practice or by telephone at a later date. If more than one headache type was reported then only the two headaches with the greatest pain intensity were recorded by the interviewer. The interviewer was aware of the respective clinic setting from which the participant was derived.

After reviewing information gathered during the structured interview, a board certified headache specialist (VTM) assigned headache diagnoses according to the strict criteria of the International Classification of Headache Disorders-II-2004 (ICHD-2). Migraine headache was defined as ICHD-2 diagnoses 1.1-1.5 and tension type headache as 2.1-2.3. To define the frequencies of migraine and tension-type headaches, participants were queried on the number of days per month that they experienced a given headache type. Only headaches meeting diagnostic criteria for either migraine or tension-type headache were assigned a frequency. If a participant experienced two headaches of the same type (e.g. either both migraine or both tension-type), then the headache with the highest reported frequency was used as the headache frequency for that patient. The headache specialist was also aware of the respective clinic setting from which the participant was derived.
Characterization of Cases

All cases underwent additional clinical characterization which was not replicated in the control population. A neurological examination was performed to screen for the presence of secondary headache disorders and a musculoskeletal examination was performed to confirm the diagnosis of JHS.

To screen for the presence of a temporomandibular disorder (TMD), cases were asked the following questions: 1) Do you have pain on chewing or upon widely opening the jaw?; 2) Has your jaw ever locked?; and 3) Do you hear noises on opening of the jaw? The presence of possible TMJ disorder was defined as a response of “yes” to 2 of the 3 diagnostic questions [16].

When available, reports from echocardiograms, cervical spine imaging, and brain MRIs from cases were obtained by chart review to determine the presence of valvular disease, cervical disc disease, or intracranial lesions, respectively. Valvular disease was defined as mild or greater mitral, aortic, or triscupid regurgitation or stenosis, or mild or greater mitral valve prolapse. Disc disease was defined as current or past impingement of the nerve or narrowing of the foramen noted on MRI scan.

Cases completed written questionnaires and reported the presence or absence of the following physician-diagnosed comorbid disorders: fibromyalgia, depression, sleep apnea, POTS, arthritis, periodic limb movement, and restless leg syndrome.
Written Questionnaires

All participants were asked to complete the following validated, self-administered questionnaires: 1) the Patient Health Questionnaire-9 (PHQ-9), 2) the Generalized Anxiety Disorder-7 (GAD-7), and 3) the Migraine Disability Assessment (MIDAS) (if headaches were reported). The PHQ-9 and GAD-7 identify probable cases of depression and generalized anxiety, respectively, and rate the severity [17-18]. The MIDAS questionnaire assesses the number of days per three months with headache-related disability [19]. In participants with a diagnosis of migraine or tension-type headache, the MIDAS score defined their degree of disability due to headache. Cases were additionally asked to complete the Neck Disability Index (NDI), which is a clinically-validated tool to rate disability due to neck pain based upon reported difficulty in performing activities of daily living [20].

Medications

Current medication use was either reported directly from the patient or extracted from the medical chart. Migraine abortives were defined as triptans, ergots, butalbital-containing medications, narcotics, non-steroidal anti-inflammatories, and isomeptane/acetaminophen compounds, and migraine preventatives as beta blockers, calcium channel blockers, antidepressants, anticonvulsants, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers.
Statistical analysis

Analyses were performed to study the associations between types of headache (migraine, tension-type) and JHS in 260 females between the ages of 18 and 65. Males were under-represented in the JHS study sample (n=3), and were not included in the analyses due to small numbers and possible gender differences with respect to associations between JHS and study outcomes. Prior to the analyses, descriptive statistics of outcomes and independent variables were calculated. Differences between JHS groups were tested with respect to the prevalence of migraine and migraine subtypes, tension-type headaches, and frequencies of each type of headache. Three headache outcomes were analyzed. Logistic regressions were performed to analyze migraine and tension-type headaches (presence/absence). Poisson regressions were analyzed to study migraine and tension-type headache frequencies (number of days per month) and migraine disabilities (number of days per three months). For each analysis the independent variables were JHS (presence/absence), and binary age (<45, ≥45). Age was included since age had been shown to be associated with the prevalence of migraine [21] and JHS [22] in previous studies. The binary categorization of age in this study resulted from visual assessment of smooth plots of migraine and tension probabilities versus continuous age. Age slopes changed at approximately age 45 years for both types of headache, although distributions of probabilities were different for migraine and tension-type headaches (Figures 2 and 3). Analyses and graphs were performed using SAS Version 9.3, (SAS Institute, Cary, NC) and R, Version 2.6.2. A p-value < 0.05 determined statistical significance, unless stated otherwise.
Results

Demographics

Twenty-eight cases and 232 controls were enrolled in the study. Mean age was significantly different between cases and controls (35.6 vs. 46.8 years of age; p-value < 0.01). Both mean GAD-7 and PHQ-9 scores measuring generalized anxiety and depression, respectively, were greater in those with JHS as compared to controls (p values < 0.01); generalized anxiety and depression were rated to be moderate in individuals with JHS compared to mild in the control patients. The demographics of the study population are summarized in Table 2.

Comorbid medical disorders were commonly encountered within the JHS patients. Those most frequently encountered included arthritis in 53.6% (15/28), fibromyalgia in 39.3% (11/28) and POTS in 17.9% (5/28), followed by restless leg syndrome (17.9%, 5/28), sleep apnea (14.3%, 4/28), and periodic limb movement (9.1%, 3/28). A large percentage of cases displayed symptoms of temporomandibular dysfunction (74.1%, 20/27). Echocardiogram reports from 18 cases showed 3 cases with trivial to mild tricuspid regurgitation without other valvular diseases. Cervical disc disease was present in 3 cases based upon available MRI and/or CT reports, but neck pain was very common as demonstrated by results of the NDI questionnaire. The mean NDI score in the JHS population was 20.1 ± 7.2 S.D. out of 50, which indicated that their functional disability due to neck pain was moderately severe. Additionally, all neurological exams were normal in the JHS group.
**Migraine headache**

The overall prevalence of migraine was 75% in the JHS group and 43.3% in the control group (Tables 3 and 4). Migraine without aura and typical aura with migraine were diagnosed in 67.9% and 32.1% of patients in the JHS group and in 39.4% and 10.4% of those in the control group. Use of migraine abortives was almost identical between the two groups, while cases were significantly more likely to use migraine preventatives (p<0.01). The adjusted odds ratio was 3.19 [95% Confidence Interval (CI) = 1.25, 8.15] for the prevalence of migraine headache in the JHS group as compared to the control group after adjusting for the effects of age modeled as a binary variable (< 45 and ≥ 45 years of age).

The overall frequency of migraine was 10.5 days per month in the JHS group and 5.6 days per month in the control group. Migraines were found to be significantly more frequent in cases both when controlling for the influence of age and preventative medication use. The adjusted rate ratio for migraine frequency was 1.67 (95% CI = 1.01-2.76) in the JHS cases as compared to the controls. Headache-related disability, as measured by the MIDAS questionnaire, was greater in migraineurs with JHS than in control migraineurs. The rate ratio was 2.99 (95% CI = 1.66-5.38) for the frequency and cases compared with controls after controlling for age and medication use (Table 5).

**Tension-type headache**

The overall prevalence of tension-type headache was 42.9% in cases and 47.6% in controls. The adjusted risk ratio for the prevalence of tension-type headache was 0.75 (95% CI = 0.33-1.77) in the cases compared with controls. Infrequent episodic and
frequent episodic tension-type headache occurred in 3.6% and 32.1% of cases and 25.1% and 23.4% of controls. Infrequent episodic tension-type headache was significantly more common in the control population (p=0.01) (Tables 3 and 4).

In contrast, the overall frequency and headache-related disability associated with tension-type headache was significantly greater for JHS patients. Additionally, the adjusted risk ratio when correcting for age and medication use was 2.66 (95% CI = 1.40-5.05) for migraine frequency and 6.32 (95% CI=2.89-17.44) for headache-related disability in patients with tension-type headache (Tables 3 and 4).
Discussion

The main finding of our study was that the prevalence of migraine headache in female subjects with JHS was over three times greater than that observed in a control patient population. Tension-type headache, on the contrary, showed no increased prevalence in cases compared to controls. Such a strong association between JHS and migraine headache suggests that JHS may represent a phenotypic marker for the presence of migraine headache in women.

JHS/hEDS, although a dominant genetic condition, shows remarkable sex-influence. Past studies have demonstrated that 85-90 percent of patients with JHS are women [3, 5]. Of the original 31 patients recruited into our study, 28 (90.3%) were female; therefore, the female predominance noted in this study is similar to population-based studies from the literature. This overrepresentation of females in JHS is thought to be due to hormonal influences on ligamentous laxity [23].

Headache Frequency and Disability

The frequency and disability of migraine and tension-type headaches were also modulated by the presence of JHS. Female migraineurs with JHS experienced 1.7 times more days with migraine and 3 times more days with headache-related disability than the control group. Additionally, the frequency of tension-type headaches was 2.7 times greater in those with JHS than in controls while headache-related disability was 6.3 times greater. These data suggest that the frequency and disability of headache is increased in the JHS group regardless of the headache type.
Theories of Migraine Pathogenesis

Our findings suggest the disorder of collagen likely present in JHS likely results in a mechanism that also modulates migraine prevalence. Although headache pathogenesis in JHS remains uncertain, several mechanisms could explain why migraine headaches are more common in female patients with JHS.

The underlying change in collagen in JHS could lead to abnormal vascular reactivity that could predispose to the development of migraine headache. Yazici and colleagues [24] found aortic stiffness to be lower and aortic distensibility to be higher with Doppler ultrasound in patients with mitral valve prolapse (MVP) and JHS as compared with those with MVP alone. Past studies have also reported that arteriopathies such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as well as carotid artery dissection are associated with attacks of migraine with aura [25-26]. Interestingly, migraine with aura was overrepresented in our patients with JHS as 43% (9/21 patients) of the migraineurs with JHS were diagnosed with typical aura with migraine as opposed to 24% within the control population. Therefore, JHS could represent a type of arteriopathy associated with an increased frequency of attacks of migraine with aura.

JHS could also be associated with a dysautonomia leading to attacks of migraine headache. Autonomic testing has revealed evidence of α- and β-adrenergic hyperactivity in patients with JHS [27]. It has been postulated that distensible vessels may result in increased venous pooling, which then may cause a compensatory hyperadrenergic state [28]. Gazit and colleagues [27] reported that orthostatic hypotension, POTS disorder, and orthostatic intolerance occurred in 78% of patients with JHS as compared with 10% of
controls. In our study, POTS was self-reported by 17.9% of JHS patients, which is likely an underrepresentation of this disorder since autonomic testing was not performed in all patients.

**Comorbid Medical Disorders**

The comorbid medical disorders that are associated with JHS are varied and include TMD, cervical disc disease, fibromyalgia, depression and anxiety. These disorders could produce their own separate headache disorder or modulate headache outcome measures in those with primary headache disorders.

TMD is a common disorder found within patients with JHS. DeCoster and colleagues [29] reported that 71.4% of patients with JHS experienced symptoms of TMD, which is similar to the 74.1% prevalence seen in our study. The presence of TMD could produce head pain referred to the temporal regions of the head. Interestingly, migraine headaches were more likely to be located in the temporal region in JHS patients than controls (85.2% vs. 51.9%; p<0.01). This could suggest that the presence of TMD modulates the location of migraine headache. It is also possible that the presence of TMD could affect the frequency and disability of primary headache disorders.

Neck pain and cervical disc disorders are frequently encountered within JHS patients. Cervical disc disease was noted in 11% of our JHS patient, but neck pain was far more common as evidenced by the fact that 77.8% percent of JHS patients (21/27) experienced moderate or greater disability noted on the Neck Disability Inventory. Neck pain can occur as a result of cervical disc disease, myofascial trigger points, or cervical spine hypermobility. Rozen et al. [30] postulated that cervical hypermobility was a
predisposing factor for the development of new daily persistent headache in patients with JHS. Neck disorders could lead to cervicogenic headaches or exacerbate underlying primary headache disorders. Convergence of cervical nerves with the spinal trigeminal nucleus could provide a theoretical basis for headaches in those with cervical spine disorders.

Widespread chronic pain, inherent to fibromyalgia and often present in JHS, may also contribute to the intensification of headache. Ofluoglu and colleagues [31] reported that 64% of patients with fibromyalgia had joint hypermobility as compared to 22% of a control population. Our cases self-reported a diagnosis of fibromyalgia in 39.1%. Studies have suggested up to 50% of individuals with fibromyalgia have enhanced pain perception [10]. Altered modulation of pain in patients with fibromyalgia may lower the threshold for both migraine and tension-type headaches.

The prevalence of depression and anxiety is increased in patients with JHS. Hakim and colleagues [9] reported that depression and anxiety occurred in 38% and 32% of JHS patients respectively as compared to 8% and 12% within a control population. In our study, the severity of depression and anxiety was greater in the JHS group than the control group as evidenced by their scores on the GAD-7 and PHQ-9 questionnaires. Past studies in migraineurs have confirmed that depression and anxiety disorders are associated with an increased prevalence of migraine headache [32-34]. The presence of depression at baseline was also related to greater amounts of headache-related disability. [34]. Jette and colleagues [35] found individuals with coexistence of migraine and mental health disorders have poorer health outcomes compared to individuals in which only one of the conditions exists. Therefore, the comorbid psychiatric disorders
associated with JHS could increase the likelihood of developing migraine headache and alter its disability.

**Other Headache Disorders**

JHS may predispose to other headache disorders such as Arnold Chiari malformation, intracranial hypotension, and carotid/vertebral dissections. Each of these disorders has been associated with Ehlers-Danlos syndrome and other collagen-related disorders [36-38]. While we did not perform diagnostic testing to exclude these disorders in all of our patients with JHS patients, there were no clinical findings to suspect these disorders.

**Strengths and Limitations**

Our study has some important strengths compared to past studies. First, our cases with JHS/hEDS were well characterized by a geneticist with special expertise in the diagnosis and management of these disorders. Second, this is the first study to confirm an association between JHS and migraine headache adhering to the ICHD-II diagnostic criteria and to compare these patients to a control group within primary care. Third, we used a validated verbal interview that enabled us to accurately collect the characteristics of each headache type. Fourth, this is the only study to determine the frequency and disability of headache disorders as outcome measures.

Interpretation of our results is not without limitations. First, our cases were enrolled from a subspecialty genetics clinic and we cannot exclude the possibility that these patients had a more severe clinical phenotype of JHS than those encountered in the general population. Therefore, our results may not generalize to other patient
populations. Second, we did not exclude patients with JHS from our control population. However, even with this limitation, our conclusions would not be significantly changed as this would have artificially inflated the migraine prevalence in the control group, which would only serve to lessen the association between JHS and migraine headache. Third, the frequency of analgesic use was not ascertained in this study and therefore we cannot exclude the possibility that medication overuse might have contributed to an increased frequency and disability of headaches within JHS patients.

**Conclusions**

Our study indicates that the prevalence of migraine headache approaches 75% in female patients with JHS and is 3X greater in these patients than controls. The prevalence of tension-type headache was not increased compared to controls suggesting that a JHS phenotype is specific to migraine headache. The frequency and disability of migraine headache were also significantly increased in JHS patients. The increased risk of migraine in our JHS population supports the hypothesis of a common pathophysiology in these conditions. These preliminary findings will need to be replicated in population-based studies before firm associations can be established between migraine headache and JHS.
Bibliography


26. Dodick DW. Examining the essence of migraine- Is it the blood vessel or the brain? A debate. Headache 2008;48:663-667


Table 1: Joint Hypermobility Syndrome Diagnostic Criteria*

<table>
<thead>
<tr>
<th>Major criteria</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>A Beighton score of 4/9 or greater (either currently or by history)</td>
</tr>
<tr>
<td>2.</td>
<td>Pain for longer than 3 months in 4 or more joints</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>A Beighton score of 1-3/9 if 50 years of age or older</td>
</tr>
<tr>
<td>2.</td>
<td>Pain in 1-3 joints for 3 months (including the back), or spondylosis and/or spondylolisthesis</td>
</tr>
<tr>
<td>3.</td>
<td>Dislocation/subluxation of more than 1 joint or in a single joint on more than one occasion</td>
</tr>
<tr>
<td>4.</td>
<td>Soft tissue rheumatism at 3 sites including epicondylitis, tenosynovitis, and bursitis</td>
</tr>
<tr>
<td>5.</td>
<td>Marfanoid habitus: tall, slim, span:height ratio &gt;1.03, upper:lower segment ratio &lt;0.89 (adult), and arachnodactyly</td>
</tr>
<tr>
<td>6.</td>
<td>Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring</td>
</tr>
<tr>
<td>7.</td>
<td>Eye signs: drooping eyelids or near-sighted or down-slanting eyes</td>
</tr>
<tr>
<td>8.</td>
<td>Varicose veins or hernia or uterine/rectal prolapse</td>
</tr>
</tbody>
</table>

**Excluded in the presence of:**

1. Marfan syndrome
2. Ehlers-Danlos syndrome other than the hypermobility type

The hypermobility syndrome is diagnosed in the presence of two major criteria or one major and two minor or four minor criteria or two minor criteria with an independently diagnosed first-degree relative.

*Adapted from Grahame et al., 2000
### Table 2. Demographics and Clinical Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cases with JHS (n=28)</th>
<th>Controls (n=232)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>35.6</td>
<td>46.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Race n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>26 (92.9%)</td>
<td>200 (88.9%)</td>
<td>0.52$</td>
</tr>
<tr>
<td>African American</td>
<td>1 (3.6%)</td>
<td>21 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (3.6%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Mean generalized anxiety severity score$\sim$ (S.D.)</td>
<td>7.1 (5.1)</td>
<td>4.4 (5.1)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Mean depression severity score$\S$ (S.D.)</td>
<td>9.3 (3.8)</td>
<td>4.9 (5.2)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

* P-value obtained using t-test
$ P$-value corresponding to test the difference in percentage of Caucasian and other races between case and control groups
$\sim$ GAD-7 score: scale of 21, 0-5 mild, 6-10 moderate, 11-15 moderately severe, 16-21 severe generalized anxiety
$ P$-value corresponding to test the difference in percentage of Caucasian and other races between case and control groups
$\S$ PHQ-9 score: scale of 27, 0-5 mild, 6-10 moderate, 11-15 moderately severe, 16-27 severe depression
Table 3. Number (%) of JHS Cases and Control Patients Who Reported Migraine and Tension Headaches

<table>
<thead>
<tr>
<th>Headache Characteristics</th>
<th>Total (Total =260)</th>
<th>JHS Cases (n=28)</th>
<th>Controls (n=232)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine total n (%)</td>
<td>121&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 (75)</td>
<td>100 (43.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>110&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19 (67.8)</td>
<td>91 (39.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Typical aura with migraine</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9 (32.1)</td>
<td>24 (10.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tension total n (%)</td>
<td>122&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12 (42.9)</td>
<td>110 (47.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Frequent episodic tension-type</td>
<td>63&lt;sup&gt;d&lt;/sup&gt;</td>
<td>9 (32.1)</td>
<td>54 (23.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infrequent episodic tension-type</td>
<td>59&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (3.5)</td>
<td>58 (25)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean headache frequency (S.D.) (days/month)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>120</td>
<td>10.5 (9.5)</td>
<td>5.6 (7.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Tension-type</td>
<td>121</td>
<td>10.3 (9.4)</td>
<td>3.0 (4.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean migraine-related disability† (S.D.) (days/3 months)</td>
<td>252</td>
<td>28.7 (29.5)</td>
<td>4.7 (11.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Headache location of migraine« n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>121</td>
<td>17 (63)</td>
<td>155 (73.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>Temporal</td>
<td>121</td>
<td>23 (85.2)</td>
<td>109 (51.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vertex</td>
<td>121</td>
<td>10 (37)</td>
<td>53 (25.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Parietal</td>
<td>121</td>
<td>12 (44.4)</td>
<td>58 (27.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Occipital</td>
<td>121</td>
<td>16 (59.2)</td>
<td>98 (46.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Medication use n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine preventatives</td>
<td>123</td>
<td>20 (71.4)</td>
<td>103 (44.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Migraine abortives</td>
<td>213</td>
<td>23 (82.1)</td>
<td>190 (81.9)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

<sup>a</sup> P-values were obtained by Student t-tests for continuous variables and chi-square or Fisher’s Exact tests for categorical variables.

<sup>b</sup> Migraine status was available for 28/28 cases and 231/232 controls.

<sup>c</sup> Migraine subtype was available for 22/28 cases and 137/232 controls. Percents are based on the available data.

<sup>d</sup> Tension status was available for 28/28 cases and 231/232 controls. Tension subtype was available for 15/28 cases and 195/232 controls. Percents are based on available data.

<sup>†</sup> MIDAS score, days per 3 months, 0-5 minimal or infrequent, 6-10 mild or infrequent, 11-20 moderate, 21+ severe disability
Table 4. Odds Ratios (OR) and Rate Ratios (RR) Measuring the Effects of JHS on Migraine and Tension-type Headaches

<table>
<thead>
<tr>
<th>Headache Type</th>
<th>Prevalence a (Total=260)</th>
<th>Headache Outcome</th>
<th>Disability b (Days/3 Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine (n=121)</td>
<td>3.19 (1.25, 8.15)</td>
<td>Frequency (Days/Mo)</td>
<td>Disability (Days/3 Mo)</td>
</tr>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted RR (95 CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.67 (1.01, 2.76)</td>
<td>2.99 (1.66, 5.38)</td>
<td></td>
</tr>
<tr>
<td>Tension (n=122)</td>
<td>0.75 (0.33, 1.77)</td>
<td>2.66 (1.40, 5.05)</td>
<td>6.32 (2.89, 17.44)</td>
</tr>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted RR (95 CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a OR adjusted for age (<45, ≥45 years)
b RR adjusted for age (<45, ≥45 years), and migraine preventative medications (yes, no)
* Age was inversely related to Disability-Migraine [RR=0.47 (0.26, 0.84)], Disability-Tension [RR=0.31 (0.12, 0.81)], Frequency-Tension [RR=0.55 (0.31, 0.98)]
Figure 1. The Beighton scoring system. A quick and easy-to-use scoring system for the presence of generalized joint laxity utilizing a 9-point scale. The examination entails: 1) Passive dorsiflexion of the fifth finger. If the proximal interphalangeal joint can be bent to less than 90° relative to the back of the hand, this is considered positive and a score of ‘1’ is assigned for each side measured. 2) Passive apposition of the thumb to the forearm. If the thumb is able to touch the forearm a score of ‘1’ is also assigned for each side. 3) Elbow hyperextension is measured on each side. A positive score is obtained if the elbow can hyperextend greater than 10°. 4) Knee hyperextension is measured in the same manner as the elbow. 5) Forward flexion of the spine. A positive score is obtained when the patient is able to place the palms flatly on the ground while standing with knees straight. Generalized joint laxity is diagnosed with a score of ≥5 (out of 9). However, overall joint laxity is influenced by gender, age, training, and racial background. *Figure reproduced from “Joint Hypermobility Handbook” with permission from Left Paw Press.*
Figure 2. A Smooth Curve of Probabilities of Migraine Headache versus Age for 259 Patients. Solid line (___) for control Dash line (--) for JHS.
Figure 3. Smooth Curve of Probabilities of Tension Headache versus Age for 259 Patients. Solid line (—) for control Dash line (--) for JHS