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Physical Comorbidity of Migraine and Other Headache in United States Adolescents

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Abstract

Background—Evidence regarding associations of headache with other somatic conditions in children has been largely based on clinical samples. The objective of this study was to examine the pattern and extent to which other physical conditions are comorbid with migraine and other headaches among youth in a representative sample of the US population.

Methods—The National Comorbidity Survey-Adolescent Supplement (NCS-A) is a face-to-face survey of adolescents aged 13–18 years in the continental United States. Sufficient information to assess the International Headache Society criteria for Migraine with and without Aura over past 12 months was available in the diagnostic module. A caretaker/parental self-administered report

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Tarannum M Lateef: responsible for design of study analyses, interpretation of data and drafting and revising multiple versions of manuscript.

Lihong Cui: responsible for all analysis and interpretation of data, as well as contributing to manuscript drafting

Karin Nelson: contributions include conceptualization of study, data analysis and manuscript revisions

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Kathleen Merikangas: responsible for data acquisition, design of study, interpretation of data and analysis and contributing to drafts of the manuscript.

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(PSAQ) was used to assess a broad range of other physical conditions. The sample for these analyses included 6843 adolescents with systematic caretaker/parent reports.

Results—Individuals with any headaches reported higher rates of other neurologic conditions such as epilepsy (OR 2.02 [95% CI: 1.04–3.94]), persistent nightmares (OR 2.28 [95% CI: 1.34–3.87]), and motion sickness (OR 1.6 [95% CI: 1.07–2.4]), as well as abdominal complaints (OR 2.36[95%CI: 1.59–3.51]). Adolescents with migraine more often reported asthma (OR 2.22 [95% CI: 1.26–3.92]) or seasonal allergies (OR 1.66 [95%CI: 1.12–2.48]) compared to those with non-specific headache.

Conclusions—Adolescent migraine is associated with inflammatory conditions such as asthma and seasonal allergies, and with epilepsy, persistent nightmares and motion sickness. Findings suggest that comorbid medical conditions should be evaluated comprehensively in determining treatment options in youth with headache. Such comorbidity could also be an important source of clinical and etiologic heterogeneity in migraine.

BACKGROUND

Headache is common in childhood and adolescence. Recent population-based data indicate that more than 1 in 4 older American adolescents suffer from frequent or severe headache, including migraine (1). Recurrent headaches can negatively impact the lives of children and adolescents in several ways and to a degree similar to that in children with other chronic conditions such as arthritis or cancer (2). Despite the impact of headache on pediatric, and in particular adolescent health, only three population-based American studies (3–5), all utilizing mailed questionnaires, have examined the prevalence of migraine and other headache types among youth in the U.S. using criteria from the International Classification of Headache Disorders, second edition [ICHD-II]) (28)

Previous studies reveal that individuals who suffer from migraine or other severe headaches also suffer from a wide range of other medical conditions than those without headaches. Headache-related disability among adults in the US can be largely explained based on the associated physical and mental comorbidity (6). Medical conditions reported with increased frequency among adults and children with migraine or headache include asthma and atopic disorders (7–12), stroke (13) and cardiovascular risk factors (14–17), sleep problems (19), motion sickness (18), epilepsy (32–34), epistaxis (20) and, in women of reproductive age, menorrhagia (21) and pre-eclampsia (22). Most of these studies have been performed in adults and few have been population-based. Identification of mechanisms for comorbidity may provide clues regarding sources of heterogeneity of migraine and other headaches, permit the delineation of more homogenous sub-groups for clinical and genetic studies (23), and aid in clinical management and prevention.

The objective of this study was to examine the association between headaches in general and migraine specifically and a range of other somatic conditions in a nationally representative sample of U.S. adolescents, using ICHD-II criteria.

METHODS

Sample

The NCS-A is a nationally representative face-to-face household survey of the prevalence and correlates of mental disorders among U.S. adolescents aged 13–18 years. It was performed between February 2001 and January 2004 by the Survey Research Center of the Institute for Social Research at the University of Michigan. The sample was based on a dual-frame design that included 904 adolescent residents of the households that participated in the National Comorbidity Replication Survey Replication (response rate 85.9%) and 9,244 adolescent students selected from a representative sample of 320 schools in the same nationally representative sample of counties as the National Comorbidity Survey Replication (response rate 74.7%) (24). Once the survey was completed, cases were weighted for variation in within-household probability of selection (in the household sub-sample) and for residual discrepancies between the sample and the US population on the basis of socio-demographic and geographic variables. These weighting procedures are discussed in more detail elsewhere (25, 26).

Definition of migraine and nonmigraine headaches

The NCS-A included an interview of physical conditions based on the chronic conditions assessed in the US National Health Interview Survey (27). Respondents were asked whether they ever in their life experienced each of the symptom-based conditions in this checklist and, if so, whether they experienced them at any time in the past 12 months. Symptoms of the ICHD-II. (28) criteria for migraine with aura, migraine without aura and tension-type headache were utilized in extracting data from the diagnostic module for somatic conditions and for the analyses. The interview included all of the criteria for migraine with the exception of the number of attacks, and aggravation by, or causing avoidance of, routine physical activity. Migraine with aura was defined by the presence of spots, lines or heat waves and a partial loss of vision before the headache. Probable migraine was defined as headache fulfilling all but one criterion for migraine with or without aura.

Comorbid Chronic Physical Conditions

One parent or parent surrogate of each participating adolescent was asked to complete a Parent Self-Administered Questionnaire (SAQ) that contained informant questions about the adolescent's physical and mental health. The overall response rate for completion of the SAQ was 83.3%. The abbreviated version of the SAQ was administered to parents when completion of the full SAQ was not feasible. The full SAQ was completed by 6,491 parents and the abbreviated form by 1,994 parents, yielding a total of 8,485 parent reports. The Physical Health section included lifetime questions about a wide range of problems including neurologic disorders (epilepsy, developmental disorders "such as autism, Asperger's, or pervasive developmental disorder", persistent nightmares learning disability), heart problems, inflammatory conditions (asthma, allergies), skin problems, motion sickness, vision, speech or hearing impairment, and stomach "trouble (such as gastritis, ulcers)".

Data Analysis

Logistic regression analyses were used to evaluate the association between specific headache types (e.g., migraine with aura, migraine without aura, and other headaches) and physical disorders while controlling for sex, age, and ethnicity. Subgroup comparisons included migraine with aura versus migraine without aura, migraine (with or without aura) versus other headache, migraine (with or without aura) versus no headache, and headache versus no headache. Significance tests were calculated using Wald chi-squared tests based on design-corrected coefficient variance-covariance matrices. Statistical significance was evaluated based on two-sided design-based 0.05 level tests. Significance tests, standard errors (s.e.), and 95% confidence intervals (95% CI) were estimated using the Taylor Series method to adjust for the weighting and clustering. All analyses were implemented in SUDAAN (RTI, Research Triangle Park, NC) because it takes into account the complex survey design when yielding findings that generalize to the U.S. adolescent population.

RESULTS

Among the 6,843 adolescents aged 13 to 18, 8.0% were reported to have experienced migraine without aura and 0.9% had migraine with aura in the previous 12 months. Adolescents who suffered from migraine without aura were more than twice as likely to be female [68.7% (s.e. 2.9) versus 31.3% (s.e. 2.9)], while migraine with aura was more equally distributed among males and females [48.2% and 51.8% (s.e. 7.5)] (Table 1).

Table 2 presents the prevalence of comorbid disorders by headache subtypes among adolescents. Significant main effects for associations between headache subtypes emerged for epilepsy or seizures, persistent nightmares, developmental disorders, serious hearing, vision or speech problems, allergies or hay fever and serious abdominal problems. Pairwise comparisons between headache subtypes and somatic conditions based on logistic regression models that controlled for sex, age and ethnicity are presented in Table 3. Youth with headaches had greater rates of epilepsy or seizures (OR 2.02 [95% CI: 1.04–3.94]) and persistent nightmares (OR 2.28 [95% CI: 1.34–3.87]) than those without headaches. Allergies and asthma were more frequently reported by adolescents with migraine compared to those with other headache subtypes or no headache. In particular youth who endorsed migraine without aura were much more likely than those with other headache types to also report allergies (OR 1.71 [95% CI: 1.13–2.58]) and asthma (OR 2.29 [95%CI: 1.27–4.14]). Finally, adolescents with headaches had significantly elevated rates of motion sickness, and abdominal complaints than those without headaches.

DISCUSSION

While many prior studies have demonstrated the currently described comorbidity in migraineurs, this is the first study to evaluate these associations in a population-based study of adolescents assessed with the ICHD-II criteria. The results confirm those of previous clinical studies that have reported increased frequencies of allergies, and asthma among youth with migraine (7–12, 31–33), and are generally consistent with the results of our parallel study of adults in the U.S. general population (6). Non-specific headaches in youth were associated with epilepsy/seizures, persistent nightmares, allergies and abdominal

problems. These patterns of comorbidity may provide insight into sources of clinical and etiologic heterogeneity of migraine, and may have important relevance to the treatment of youth with headaches.

Allergies, Asthma and Hay Fever

Several population-based and clinical studies have established an association between migraine and asthma or allergic disorders in adults and children (7–12, 30). In studies from referral clinics, a variety of atopic disorders including rhinitis, conjunctivitis, food and drug allergy, as well as a family history of atopic disorders, has been noted in more patients with than without migraine (8). Likewise, patients in treatment for allergic rhinitis were significantly more likely to suffer from migraine headaches than those without allergic rhinitis (10). Support for these associations in population surveys of adults in Norway (11), England and Wales (12), and the United States (30) confirm that the association of asthma, hay fever and chronic bronchitis with headache is not an artifact of treatment seeking bias, and that the potential mechanisms for these non-random associations requires further investigation.

Clinical (9) and community surveys of youth (7) have also confirmed an elevation of allergies among youth with migraine. In a previous study of a nationally representative sample of U.S. children, we reported a strong association between asthma, allergies and ear infections with frequent severe headaches, particularly in the younger children (ages 4–11 years) (1). More than 40% of children with headache had at least one the following three conditions: asthma, hay fever, or frequent ear infection) compared to 25.0% of headache-free children ($p<.0001$) (1). However, the present study is the first study to examine this association for I.H.S.-defined headache subtypes in a population sample of U.S. youth.

Comorbidity between migraine with allergic conditions could be attributed to inflammatory mediators particularly mast cells, underlying atopic disorders, that may also underlie the development of headaches (31). Alternatively, headaches could be a secondary manifestation of allergies, or a side effect of its treatment. The cross sectional design of the present study did not permit evaluation of these alternative explanations.

Seizures/Epilepsy

The association between seizures or epilepsy and migraine has been less consistent. Only two of the dozen systematic (39–44) and controlled (39, 41, 45–49] studies of this association reported a significant association between these two conditions (41,45). Likewise, the two controlled studies of sufficiently large samples of children found no systematic association between convulsions and migraine (7). In the present study, adolescents with headache or migraine more often reported a diagnosis of epilepsy than their non-migraine headache counterparts.

Migraine and epilepsy are both paroxysmal disorders, characterized by temporary cerebral dysfunction and share several clinical similarities. Both disorders may share a common origin in cortical hyperexcitability – in one case leading to seizure phenomena characterized by hypersynchronous firing and on the other hand culminating in migraine headache caused by cortical spreading depression. Attacks of migraine or epilepsy can be triggered by

hormonal changes, sleep disturbances or head trauma. Associations between migraine and certain epilepsy syndromes, such as occipital lobe epilepsy, rolandic epilepsy, adult onset myoclonus epilepsy, absence epilepsy and temporal lobe epilepsy, have been previously reported (32). However, our study design did not permit differentiation into which type of epilepsy is particularly associated with migraine.

Several possible mechanisms have been proposed to explain the comorbidity of migraine and epilepsy. These include serotonergic dysfunction, disturbances of neurotransmitters such as glutamate, norepinephrine, gamma aminobutyic acid and dopamine, or abnormalities in a single gene or a group of functionally linked genes (33). Established literature suggests the possibility that genetic polymorphisms in ion channels and other excitability molecules contribute to epilepsy susceptibility. Sporadic migraine susceptibility may be related to polymorphisms in the same or different excitability molecules (34). It has been observed that mutations in the same genes can cause either migraine or epilepsy or both. The syndrome of familial hemiplegic migraine can be caused by mutation in *CACNA1A*, *ATP1A2*, and *SCN1A*. Mutations in *CACNA1A* can also cause idiopathic generalized epilepsy and mutations in *SCN1A* may cause generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (or SMEI). The neurotransmitter, glutamate acting on ionotropic glutamate receptors is known to play a significant role in most, if not all, forms of interictal and ictal epileptiform activity. Similarly, there is strong evidence that glutamate release contributes to the triggering of cortical spreading depression (34). It is notable that anti-epileptic drugs including valproate, topiramate and gabapentin can also be effective at migraine prophylaxis.

In our study epilepsy was more commonly found in sufferers of all headache subtypes compared to those who did not suffer from headache. It is possible that there is a subset of patients with migraine who share this predisposition to epilepsy and future research should examine whether manifestations or treatment of migraine among those with seizures/epilepsy differs from that of migraine alone.

Sleep Disturbances

Our finding of an association between frequent nightmares and headache in youth partially confirms prior research documenting an association between migraine and a range of sleep problems such as nightmares, sleep walking, and sleep difficulties (19). For example, Vgontzas et al (35) reported that adults with migraine were more than four times as likely to report nightmares of childhood onset compared to those without migraine. Small clinical studies have suggested that dreams, especially those characterized by a strong negative effect, can sometimes predict attacks of migraine particularly those characterized by a strong negative effect (36, 37).

Other Physical Correlates

The association between stomach/abdominal problems and headache in the present study confirms the results of previous studies including a classic school-based sample of youth in Finland (38). Abdominal complaints in youth could represent the initial harbinger of adult onset bowel problems. In our parallel study of U.S. adults, we found a three-fold increased

rate of Irritable Bowel Syndrome among those with migraine compared to those with no headache Saunders et al (6). Although various gastrointestinal conditions have been linked with migraine, it is difficult to distinguish whether these conditions are truly independent or whether they represent gastrointestinal manifestations of migraine, especially in children. Chronic headache sufferers may require the use of a long-term prophylactic medication, in addition to abortive pharmacologic agents. It is vital that treating physicians prescribe such medications after careful review of associated physical conditions. For example - Beta-blockers, commonly used for migraine prophylaxis, must be avoided in patients who have asthma. On the other hand an antihistamine such as cyproheptadine may be an ideal prophylactic agent for some one suffering from both migraine and seasonal allergies. Knowledge of comorbidity thus should inform and influence ideal clinical management of headaches.

Strengths and Limitations

The strengths of this study include the large and nationally representative sample of adolescents and the breadth of correlates of chronic conditions included in the survey. Moreover, few population-based studies of headache have investigated co-morbidity with a range of medical disorders, in this age group. Limitations of this study include its cross-sectional nature with the result that our data are necessarily correlative and cannot address causality. The diagnostic criteria for migraine and migraine with aura are an approximation of the ICHD-II criteria, as built into the pre-determined interview. Migraine with aura in this study did not include all visual, sensory and dysphasic phenomena and this may underestimate the prevalence of migraine with aura. It would be interesting to assess the temporal sequence of the associated disorders in order to permit the design of better strategies for prevention and management.

CONCLUSIONS

Migraine among American youth is common and can be associated with a variety of other physical conditions which can further exacerbate headache-related disability. The associations between headaches with a range of physical conditions that have been associated with adult migraine, might suggest that the onset of these conditions may precede that of migraine. Follow up of this sample could elucidate the temporal order of presentation of these conditions with adult migraine subtypes. Patterns of co morbidity may be an important index of heterogeneity of migraine that can guide clinical management, genetic investigation, and future research on shared pathophysiology with the specific other disorders.

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Table 1

Sociodemographic Characteristics of the NCS-A Adolescent Sample (N=6483) % (s.e.)

		N	Migraine with Aura	Migraine w/o aura	Other Headache	None	*p-value*
		6,483	**65**	**480**	**276**	**5662**	
Sex	Male	**3,150**	48.2 (7.5)	31.3 (2.9)	35.7 (3)	53.9 (1.1)	
	Female	**3,333**	51.8 (7.5)	68.7 (2.9)	64.3 (3)	46.1 (1.1)	<0.0001
Age	13–14	**2,611**	31.0 (7.0)	34.4(3.7)	35.4(4.7)	36.2(2.5)	
	15–16	**2,528**	42.4(10.0)	39.4(3.4)	51.3(4.1)	41.6(2.0)	
	17–18	**1,344**	26.6(10.5)	26.2(3.7)	13.3(3.7)	22.2(1.2)	n.s.
Race	Non hispanic white	**4,257**	65.6(7.7)	69.4(3)	58.3(4.1)	65.6(1.9)	
	Non hispanic black	**1,097**	10.4(5.9)	13.7(1.9)	16.9(3.2)	15.2(1.2	
	Hispanic	**758**	12.9(6)	10.4(1.8)	20.6(5.7)	14.4(1.4)	
	Other	**371**	11.1(5.2)	6.5(2.4)	4.2(1.3)	4.8(0.5)	n.s.
Income/Poverty Line	IPL <1.5	**925**	6.9(3.4)	13.4(2.2)	13.1(3.4)	14.8(1.2)	
	1.5<= IPL <= 3	**1,218**	18.7(6.2)	21.4(3.1)	22.3(4.2)	18.9(0.8)	
	3 < IPL <= 6	**2,139**	33(7.3)	34.7(3.5)	28.1(3)	32.7(1.3)	
	IPL > 6	**2,201**	41.4(9.7)	30.5(3.1)	36.6(4.6)	33.6(1.6)	n.s.

Table 2

Physical Comorbidity by Headache Subtypes in the U.S. Adolescents (NCS-A) (N=6483) %(s.e.)

	N	Migraine with Aura	Migraine w/o Aura	Other Headache	No Headache	*p-value*
		65	480	276	5662	
Neurological Disorders						
Epilepsy or seizures	148	0.8 (0.79)	4.5 (1.51)	2.9 (1.15)	2.0 (0.4)	0.0291
Persistent nightmares	265	18.2 (5.41)	8.0 (1.82)	4.2 (2.29)	3.5 (0.43)	0.0144
Learning disability	929	13.8 (6.65)	14.8 (2.57)	13.0 (3.34)	13.9 (0.79)	n.s.
Developmental disorders	51	0 (0)	0.8 (0.22)	0.2 (0.2)	0.7 (0.15)	0.0264
Serious hearing, vision, or speech problem	681	2.3 (1.43)	13.2 (1.77)	6.8 (2.14)	10.4 (0.81)	0.0035
Motion sickness	621	10.2 (3.47)	15.1 (3.05)	13.3 (3.09)	8.9 (0.63)	n.s.
Somatic Disorders						
Allergies or hay fever	1975	36.8 (8.94)	43.4 (3.4)	29.8 (4.31)	29.8 (0.95)	0.001
Asthma	1027	15.9 (5.76)	20.2 (2.98)	10.1 (2.32)	16.4 (0.74)	n.s.
Frequent high fevers	230	1.6 (1.2)	4.8 (1.51)	1.3 (0.76)	3.0 (0.27)	n.s.
Serious stomach trouble	270	10.3 (4.69)	10.1 (2.56)	3.7 (1.65)	3.5 (0.34)	0.0007
Severe acne	519	10.6 (5.69)	11.7 (2.39)	6.8 (2.46)	9.0 (0.51)	n.s.
Skin problems other than acne	588	15.4 (7.09)	10.1 (2.27)	11.9 (3.59)	7.5 (0.49)	n.s.
Heart problems	161	1.1 (0.77)	4.0 (1.3)	3.2 (2.06)	2.9 (0.39)	n.s.
Other life-threatening/impairing illness	311	10.3 (3.21)	5.8 (1.57)	2.8 (1.55)	5 (0.54)	n.s.

Table 3

Associations between Headache Subtypes and Somatic Conditions in U.S. Adolescents (n=6,483)

	N	Migraine Aura vs Migraine, No Aura	Migraine vs. Other Headache	Migraine vs. No Headache	Headache vs. No Headache
Neurological Disorders		Adjusted Odds Ratios (95% confidence intervals)[1]			
Epilepsy or seizures	148	0.15 (0.03, 0.86)	1.51 (0.5, 4.57)	1.51 (0.6, 3.84)	**2.02 (1.04, 3.94)**
Persistent nightmares	265	2.45 (0.99, 6.06)	2.17 (0.68, 6.89)	1.28 (0.4, 4.11)	**2.28 (1.34, 3.87)**
Learning disability	929	0.78 (0.22, 2.77)	1.17 (0.55, 2.47)	1.07 (0.56, 2.04)	1.19 (0.83, 1.71)
Developmental disorders	51	N/A	3.27 (0.38, 28.16)	0.34 (0.04, 2.82)	0.87 (0.45, 1.67)
Serious hearing, vision, or speech problem	681	**0.14 (0.04, 0.56)**	1.91 (0.83, 4.37)	0.71 (0.35, 1.42)	1.12 (0.81, 1.55)
Motion sickness	621	0.66 (0.24, 1.82)	0.97 (0.43, 2.18)	1.63 (0.83, 3.19)	**1.6 (1.07, 2.4)**
Somatic Disorders					
Allergies or hay fever	1975	0.76 (0.3, 1.90)	**1.66 (1.12, 2.48)**	1.06 (0.72, 1.57)	**1.5 (1.17, 1.92)**
Asthma	1027	0.72 (0.28, 1.84)	**2.22 (1.26, 3.92)**	0.59 (0.33, 1.03)	1.04 (0.73, 1.49)
Frequent high fevers	230	0.31 (0.06, 1.67)	3.79 (0.95, 15.20)	0.43 (0.13, 1.45)	1.21 (0.68, 2.14)
Serious stomach trouble	270	0.95 (0.22, 4.15)	2.78 (0.94, 8.21)	1.09 (0.42, 2.83)	**2.36 (1.59, 3.51)**
Severe acne	519	0.84 (0.18, 3.85)	1.72 (0.67, 4.42)	0.80 (0.37, 1.71)	1.18 (0.82, 1.7)
Skin problems other than acne	588	1.67 (0.44, 6.34)	0.81 (0.41, 1.61)	1.69 (0.89, 3.22)	1.48 (0.96, 2.27)
Heart problems	161	0.24 (0.04, 1.36)	1.17 (0.25, 5.5)	1.28 (0.33, 4.95)	1.42 (0.79, 2.56)
Other life-threatening/impairing illness	311	1.94 (0.68, 5.6)	2.09 (0.66, 6.69)	0.55 (0.18, 1.71)	0.96 (0.65, 1.40)

[1]Logistic regression models adjusted for age, sex and ethnicity