Physical–Mental Comorbidity of Pediatric Migraine in the Philadelphia Neurodevelopmental Cohort

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Objective To examine the associations between headaches and migraine with physical and mental disorders in a large pediatric registry.

Study design In total, 9329 youth aged 8-21 years from the Philadelphia Neurodevelopmental Cohort were included. Physical conditions, including headache, were ascertained from electronic medical records and in-person interviews. Modified *International Classification of Headache Disorders* (ICHD-II) criteria were used to classify migraine symptoms. Forty-two other physical conditions were classified into 14 classes of medical disorders. Mental disorders were assessed using an abbreviated version of the Kiddie-Schedule for Affective Disorders and Schizophrenia.

Results Lifetime prevalence of any headache was 45.5%, and of migraine was 22.6%. Any headache was associated with a broad range of physical disorders, attention-deficit/hyperactivity disorder (OR 1.2 [95% CI 1.1-1.4]), and behavior disorders (1.3 [1.1-1.5]). Youth with migraine had greater odds of specific physical conditions and mental disorders, including respiratory, neurologic/central nervous system, developmental, anxiety, behavior, and mood disorders than those with nonmigraine headache (OR ranged from 1.3 to 1.9).

Conclusions Comorbidity between headaches with a range of physical conditions that have been associated with adult migraine demonstrates that multimorbidity occurs early in development. Comorbidity may be an important index of heterogeneity of migraine that can guide clinical management, genetic investigation, and future research on shared pathophysiology with other disorders. *(J Pediatr 2019;205:210-7).*

Headache is a common neurologic complaint in childhood and adolescence that has substantial impact on both educational and social functioning. Population-based data from the National Health and Nutrition Examination Survey indicate that more than 1 in 4 American adolescents aged 16-18 years suffer from frequent or severe headache, including migraine.[1] Recurrent headaches in childhood can be as disabling as other chronic conditions such as arthritis or cancer.[2] The widespread comorbidity of migraine with several physical and mental conditions has been documented in both clinical and community samples.[3,4] Headache-related disability among adults in the US can be largely attributed to physical and mental comorbidity that lead to greater severity and impairment.[5]

Medical conditions reported with increased frequency among children with migraine or headache include asthma and atopic disorders,[1,6,7] stroke[8] and cardiovascular risk factors,[9,10] sleep problems,[11] motion sickness,[12] epilepsy,[13,14] epistaxis[15] and, in girls of reproductive age, menorrhagia[16] and pre-eclampsia.[17] Previous work on comorbidity of headache/migraine and physical disorders in US population-based studies revealed that adolescent migraine is associated with inflammatory conditions such as asthma and seasonal allergies, whereas headache in general is associated with neurologic conditions such as epilepsy, persistent nightmares, and motion sickness, as well as abdominal complaints.[18] Likewise, rates of psychiatric symptoms and disorders are elevated among youth with headache and migraine.[19-24] Youths with migraine and comorbid conditions exhibit more general impairment, school absences,[25] and greater continuity of headache over time.[26]

To date, few studies have investigated the full range of mental and physical conditions associated with headache subtypes defined by the *International Classification of Headache Disorders, second edition* [ICHD-II]).[27] Most earlier research was either based on clinical samples or on a limited number of physical conditions. The objectives of this study are to examine the associations between headache and a comprehensive set of physical and mental conditions in youth identified in a large, systematically obtained pediatric registry; to determine the specificity

ADHD	Attention-deficit/hyperactivity disorder
CGAS	Children's Global Assessment of Functioning
CHOP	Children's Hospital of Philadelphia
EMR	Electronic medical record
ICHD-II	*International Classification of Headache Disorders, second edition*
PNC	Philadelphia Neurodevelopmental Cohort

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of patterns of physical and mental comorbidity with migraine; and to evaluate the extent to which comorbidity is associated with functional impairment.

Methods

Our sample is from the Philadelphia Neurodevelopmental Cohort (PNC), a collaborative National Institute of Mental Health–funded Grand Opportunity Study between the Brain Behavior Laboratory at the University of Pennsylvania and the Center for Applied Genomics at Children's Hospital of Philadelphia (CHOP). The participants from PNC were recruited from a pool (N = 50 293) of youth previously genotyped as part of a genomic study through pediatric outpatient medicine or preoperative surgery clinics within the CHOP network to characterize clinical, neurobehavioral phenotypes, and genotypes.[28] Enrollment criteria included the following: (1) aged 8-21 years, (2) ambulatory in stable health, (3) proficient in English, (4) physically and cognitively capable of participating in an interview and performing the neurocognitive assessment, and (5) absence of a disorder that impaired mortality or cognition (eg, paresis or palsy, intellectual disability).

Based on electronic medical records (EMRs) screen and consent to recontact, 13 598 youth met eligibility criteria were invited, and 9498 youth enrolled consecutively from November 2009 and November 2011 and consented to a face-to-face interview either on campus or in their homes. The reasons for those noninterviewed were our inability to locate (43%), declined (18%), repeated no-shows (9%), moved out of study area (10%), or ineligibility due to age change or medical reasons or cognitive disturbance (5%); another 15% were still in the process of potential enrollment at the time of this work. The interview (GOASSESS) included demographics, medical history, an abbreviated structured interview on the full range of mental disorders, as well as the Children's Global Assessment of Functioning (CGAS) Scale,[29] and incorporated a timeline of life events to enhance the accuracy of recall. Of 9498 participants, 9329 with complete information on headache information, comorbidity, CGAS, and demographic characteristics were available for analysis in the study. These study procedures were approved by the institutional review boards of University of Pennsylvania and CHOP. The PNC study is described in detail elsewhere.[28,30]

Physical Conditions Classifications

Forty-two physical conditions were identified via electronic searches of the CHOP EMRs and youth (18-21 years) or parent (for 8-17 years participating youth) GOASSESS interviews. EMRs were reviewed manually for those youth with insufficient diagnostic information from electronic searches. Conditions were coded by the *International Classification of Diseases, Ninth Revision* by nurses and other qualified medical staff. Discrepant information that occurred in approximately 5% of the cases was reconciled by physician review. Parent report also was used to identify disorders that were diagnosed after the last evaluation at CHOP. An individual physical condition was considered as present if the condition required standing medications, monitoring, and procedures or absent if there was no condition or the condition was mild in severity (ie, symptoms of disorders that are clearly evident but do not impair function or require chronic treatment or medication or hospitalization). In total, 42 conditions in the study were classified into 14 groups by a group of clinical experts at CHOP who collaborated on the PNC study. The categories were intended to group disorders based on physiologic symptoms and/or medical specialties. These 14 groups included (1-3) allergy/immunologic (severe allergies, asthma/respiratory, autoimmune/inflammatory), (4) cardiologic, (5) endocrine/metabolic, (6) eye/ear/nose/throat, (7) gastrointestinal, (8) hematologic, (9) nephrology/urologic, (10-12) neurologic (birth anomalies, central nervous system, developmental), (13) oncologic, (14) orthopedic.

Headache Subtype Ascertainment

Participants were interviewed about lifetime headache symptoms ("Have you ever had headache?") in the medical history section of the GOASSESS. Subsequent questions were asked whether his/her headache was accompanied by the presence of other symptoms such as (1) sensitivity to light/noise, (2) gastrointestinal symptoms, (3) unilateral pain, (4) throbbing/pulsation pain, and (5) interference at school/work. Among those who endorsed headache, modified ICHD-II diagnostic criteria were used to ascertain whether his/her headache met the criteria for migraine. The criteria for migraine require endorsement of any 3 of the aforementioned 5 symptoms that were accompanied by headache. Participants also were asked whether their migraine had either been diagnosed or treated by a doctor. In analyzing these 2 migraine groups, we did not find different patterns of comorbidity, so they were combined. The headache status was therefore categorized into 3 mutually exclusive levels: migraine, nonmigraine, and no headache in the analyses.

Mental Disorder Assessment

An abbreviated version of the Kiddie-Schedule for Affective Disorders and Schizophrenia with a structured screener was used in the GOASSESS to collect psychiatric diagnostic information on lifetime anxiety (agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social anxiety, and specific phobia), mood (major depression, mania), behavior (conduct, oppositional/defiant disorder), attention-deficit/hyperactivity disorder (ADHD), and eating disorders (anorexia, bulimia). Details regarding interviewer training and supervision are presented elsewhere.[28,30] The dimensional indices of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* mental disorders were generated by computerized diagnostic algorithms that incorporated endorsement of screen questions, symptom count, duration, distress, and impairment. For this study, each mental disorder was binary coded as 1 (present) if the participant met the threshold disorder criteria or 0 (absent) if met subthreshold or symptom free. The CGAS Scale was rated for all youth who completed the GOASSESS, and functional impairment was defined by a CGAS scored ≤70.

Demographic covariates included sex, age group (8-12 years, 13-18 years, 19-21 years), race/ethnic group (non-Hispanic white, non-Hispanic black, Hispanic, other race), and maternal education (less than high school, high school graduation, some college, college graduation, or higher).

Statistical Analyses

Statistical analyses were conducted with the SAS software package, version 9.3 (SAS Inc, Cary NC). Lifetime prevalence rates of migraine with or without medical diagnosis/treatment and nonmigraine headache were estimated for the total sample and by demographic characteristics.

Cross-tabulations were used to examine the associations of headache with the 14 medical specialty/system physical conditions, 4 major classes of mental disorders (eating disorder was not included because of small numbers), and functional impairment (CGAS ≤70). The analytical sample n = 9329 consisted of 8764 unique families, with 565 families having multiple children and adolescent participants, with sibling size ranging from 2 to 8. We applied a generalized estimating equation approach to accommodate clustered multiple sibling observations within the same families. The logit link function and exchangeable correlation structure were used. The associations of 3-level headache status and dichotomously scored physical conditions, mental disorders, and functional impairment score were estimated using multivariate generalized estimating equation models. Each model included headache status as the main exposure variable and was adjusted for demographic covariates (sex, age, race/ethnicity, and maternal education). The physical conditions, mental disorders, and functional impairment were treated as the outcome variables, one at a time, entered separate models. The final models were further adjusted for other physical conditions and mental disorders. Ad hoc group comparisons were made to examine the associations of headache vs no headache as well as migraine vs nonmigraine headache. Regression coefficients and SEs were exponentiated and are reported as ORs and 95% CIs. The Benjamini–Hochberg false discovery rate procedure[31] was applied to account for false positives due to multiple significance testing. Significance tests were evaluated using 2-sided P values < .05.

Results

Among the 9329 participants aged 8-21 years, 22.6% met criteria for migraine headache and 23.0% reported nonmigraine headache during their lifetime (**Table I**). Migraine sufferers were significantly more likely to be female, older in age, and from families with lower levels of maternal education. The race/ethnic distribution of youth with nonmigraine headache was similar to that of migraine headache. Migraine prevalence among male subjects was 19.4% and among female subjects was 25.5%.

Table II and **Table III** present the prevalence of comorbid disorders by headache subtypes. We compared physical conditions across 3 headache groups: migraine, nonmigraine headache, and no headache. Compared with those with nonmigraine headache, we found that youth with migraine suffered more frequently from other neurologic/central nervous system disorders (OR 1.7; 95% CI 1.4-2.0), developmental conditions (OR 1.3; 95% CI 1.1-1.6), respiratory problems (OR 1.3; 95% CI 1.1-1.6), anxiety (OR 1.6; 95% CI 1.3-2.0), mood (OR 2.0; 95% CI 1.6-2.3), and behavioral (OR 1.3; 95% CI 1.1-1.6) disorders, after adjusting for demographic characteristics (age, sex, race/ethnicity, and maternal education) and other mental and physical conditions. Children with any headache type were more likely to have cardiovascular (OR 1.4; 95% CI 1.1-1.7) and gastrointestinal (OR 1.2; 95% CI 1.1-1.4) problems, as well as ADHD (OR 1.2; 95% CI 1.1-1.4) than those without

Table I. Prevalence of migraine by demographic characteristics in youth (n = 9329)

Sociodemographic characteristics	n	Migraine n = 2104 %	Nonmigraine headache n = 2144 %	No headache n = 5081 %	*P* value
Total	9329	22.6	23.0	54.5	
Sex					
Male	4497	41.5	47.2	51.4	<.0001
Female	4832	58.5	52.8	48.6	
Age, y					
<13	3736	25.1	37.3	47.4	<.0001
13-18	3832	38.5	44.8	40.6	
>18	1761	36.5	17.9	12.0	
Race/ethnicity					
Hispanic	627	7.0	7.0	6.5	.665
NH black	2968	31.6	33.2	31.3	
Other	653	7.0	6.9	7.1	
NH white	5081	54.4	52.9	55.2	
Maternal education					
Less than HS	406	4.7	4.2	4.3	<.0001
HS graduate	2514	29.3	27.9	25.6	
Some college	2303	27.7	25.8	23.0	
College+	3965	36.9	40.5	45.7	

HS, high school; *NH*, non-Hispanic.
P value based on Wald χ^2 tests; unknown maternal education not shown.

Table II. Association between physical conditions/specialty and headache subgroup

	Total	Migraine	Nonmigraine headache	No headache	Headache vs no headache	Migraine vs nonmigraine headache	Headache vs no headache	Migraine vs nonmigraine headache
		n = 2104	n = 2144	n = 5081				
	n = 9329	(1)	(2)	(3)	(1 and 2) vs (3)	(1) vs (2)	(1 and 2) vs (3)	(1) vs (2)
Physical conditions/specialties*	%	%	%	%	aOR (95% CI)†	aOR (95% CI)†	aOR (95% CI)‡	aOR (95% CI)‡
Allergy/immunology								
Allergies	0.9	1.0	1.0	0.8	1.40 (0.90-2.18)	1.13 (0.61-2.10)	1.31 (0.83-2.06)	0.97 (0.52-1.82)
Asthma/respiratory	19.0	21.5	18.1	18.3	1.22 (1.10-1.36)§	1.40 (1.20-1.63)¶	1.18 (1.06-1.31)¶	1.32 (1.13-1.55)¶
Autoimmune/iflammation	8.6	10.6	8.0	8.1	1.10 (0.94-1.28)	1.28 (1.03-1.58)	1.04 (0.89-1.21)	1.18 (0.95-1.46)
Cardiology	4.3	6.0	4.3	3.6	1.41 (1.15-1.74)¶	1.35 (1.02-1.79)	1.38 (1.12-1.69)¶	1.29 (0.97-1.72)
Endocrine/metabolism	5.9	6.6	6.2	5.5	1.12 (0.94-1.34)	1.05 (0.81-1.35)	1.10 (0.92-1.31)	1.01 (0.78-1.30)
Eye/ear/nose/throat	3.2	3.6	3.3	2.9	1.23 (0.97-1.56)	1.11 (0.79-1.55)	1.17 (0.92-1.49)	1.03 (0.73-1.44)
Gastroenterology	11.0	14.1	10.7	9.8	1.25 (1.09-1.43)¶	1.30 (1.07-1.57)**	1.21 (1.05-1.38)**	1.21 (1.00-1.47)
Hematology	3.8	4.9	3.6	3.3	1.21 (0.98-1.51)	1.38 (1.02-1.85)	1.19 (0.96-1.49)	1.35 (1.00-1.81)
Nephrology/urology	2.5	3.0	2.3	2.3	1.05 (0.80-1.36)	1.23 (0.83-1.81)	0.99 (0.76-1.29)	1.11 (0.75-1.65)
Neurology								
Birth anomalies	14.3	15.0	14.7	13.9	1.16 (1.03-1.30)	1.06 (0.89-1.26)	1.09 (0.96-1.23)	0.95 (0.80-1.13)
Central nervous system	11.7	18.5	10.6	9.3	1.50 (1.31-1.72)§	1.78 (1.49-2.13)§	1.46 (1.28-1.67)§	1.68 (1.40-2.02)§
Developmental	15.1	17.9	14.2	14.2	1.28 (1.14-1.44)§	1.47 (1.24-1.75)§	1.22 (1.08-1.37)¶	1.34 (1.13-1.59)¶
Oncology	3.1	3.2	2.9	3.1	0.90 (0.70-1.15)	0.94 (0.67-1.34)	0.89 (0.70-1.14)	0.95 (0.67-1.34)
Orthopedics	7.6	9.0	7.3	7.1	1.12 (0.95-1.31)	1.23 (0.98-1.54)	1.09 (0.92-1.28)	1.18 (0.94-1.48)

*Medical conditions based on medical chart review and parent informant report (or proband report for age 18 and older); OR (95% CI) based on generalized estimating equation models.
†Adjusted for demographics (sex, age, race/ethnicity, maternal education).
‡Adjusted for physical conditions and mental disorders that were shown significant in univariate analysis.
§$P < .0001$.
¶$P < .01$.
**$P < .05$ (all P values adjusted for false discovery rate).

Table III. Association between mental disorders and headache subtypes

Mental disorder classes*	Total n = 9329 %	Migraine n = 2104 (1) %	Nonmigraine headache n = 2144 (2) %	No headache n = 5081 (3) %	Headache vs no headache (1 and 2) vs (3) aOR (95% CI)†	Migraine vs nonmigraine headache (1) vs (2) aOR (95% CI)†	Headache vs no headache (1 and 2) vs (3) aOR (95% CI)‡	Migraine vs nonmigraine headache (1) vs (2) aOR (95% CI)‡
Anxiety disorder	12.0	17.2	10.0	10.7	1.24 (1.09-1.42)§	1.88 (1.57-2.26)¶	1.13 (0.99-1.30)	1.62 (1.34-1.96)¶
ADHD	17.6	18.3	18.0	17.0	1.35 (1.21-1.51)¶	1.31 (1.12-1.54)§	1.22 (1.08-1.36)§	1.08 (0.91-1.28)
Behavior disorder	15.0	19.5	14.6	13.3	1.36 (1.21-1.54)¶	1.55 (1.31-1.83)§	1.29 (1.14-1.46)¶	1.32 (1.10-1.57)§
Mood disorder	12.5	21.6	9.8	10.0	1.26 (1.11-1.44)§	2.20 (1.83-2.63)¶	1.18 (1.03-1.35)	1.93 (1.59-2.33)¶

All *P* values adjusted for false discovery rate.
*Diagnosis algorithms for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* indices of mental disorders considered endorsement of screen question, symptom count, duration, distress and impairment; anxiety = agoraphobia, generalized anxiety disorder, panic disorder, separation anxiety disorder; ADHD = attention-deficit hyperactivity disorder; behavior = oppositional defiant disorder (requiring ≥4 symptoms), conduct disorder; mood = major depressive disorder and mania; OR (95% CI) based on generalized estimating equation models.
†Adjusted for demographics (sex, age, race/ethnicity, maternal education).
‡Adjusted for physical conditions and mental disorders that were shown as significant in univariate analysis.
§$P < .01$.
¶$P < .0001$.

headache. There were no significant associations between nonmigraine headaches relative to no headache with any of the physical or mental disorders investigated in this study.

The **Figure** shows the mean CGAS scores among youth with migraine, subdivided by the presence of other physical conditions and mental disorders. Comorbid mental disorders were associated with a significant decrease in CGAS scores compared with those with migraine only ($P < .001$), after adjustment for age, sex, race/ethnicity, and maternal education.

Discussion

Although there is abundant information on patterns of comorbidity in clinical samples of youth with migraine, our study sought to evaluate comprehensive patterns of physical and mental comorbidity with both headache in general, and ICHD-II–defined migraine, specifically in a large pediatric sample. Our results demonstrate that headache, particularly migraine, is associated with respiratory and other neurologic and developmental disorders, as well as with anxiety and mood disorders in this sample. The specificity of these patterns of comorbidity may provide clues regarding multisystem etiology and/or risk factors that may index the heterogeneity of migraine. The emergence of comorbidity early in development also suggests that future studies should track not only the course and outcome of migraine but also its longitudinal interrelationship with other central nervous system, immunologic, and mental disorders. Our findings also highlight the

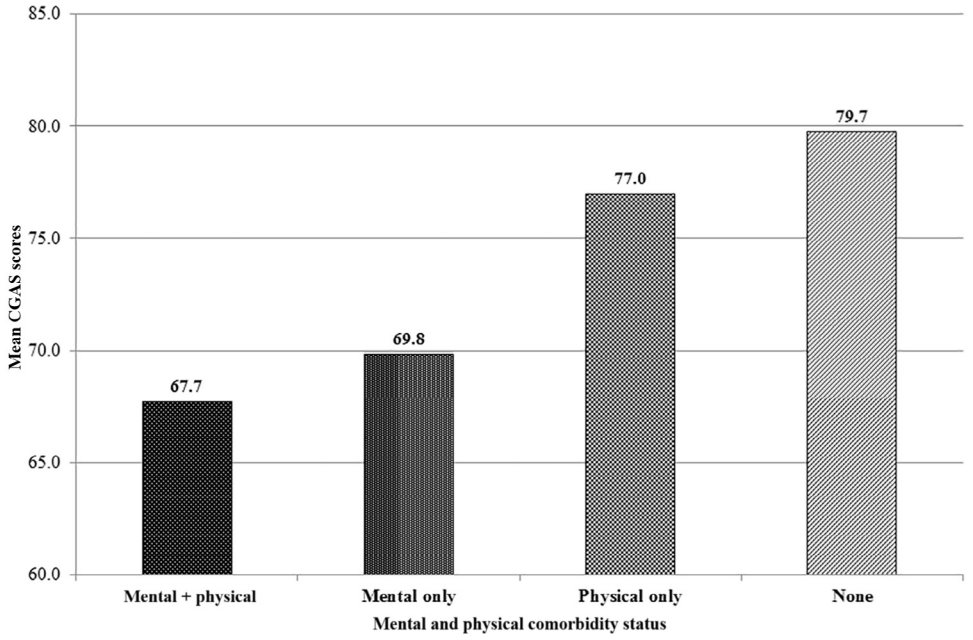

Figure. Mean CGAS among respondents with migraine. Group comparisons after adjusted for age, sex, race/ethnicity, maternal education: mental + physical vs mental only $P = .0036$, all other pairwise comparisons $P < .0001$.

importance of comprehensive evaluation of both physical and mental disorders in youth with migraine in both treatment and research.

The association between asthma with migraine in the present study is consistent with our earlier findings of comorbid respiratory conditions in general in young migraineurs, as well as several earlier population-based and clinical studies of both adults and children.[1,6,7] The lack of an association with allergies in this sample is likely attributable to the high threshold of severe allergies imposed in the medical record classification. Several hypotheses have been described previously for the comorbidity of asthma and headache, including a common genetic disposition, mast cell activation, functional abnormality in smooth muscle in blood vessels and airways, vasoactive mediator, and abnormal arachidonic acid metabolism.[32] Future studies that specifically examine immune and inflammatory markers may provide insight into explanations for this now well-documented association.

Youth with migraine also had greater rates of neurologic disorders besides migraine. Although we could not assess the specific neurologic conditions from the electronic records, an ambulatory sample without cognitive difficulties was likely to yield youth with milder disorders, such as intermittent seizures or tics, rather than more severe disabling conditions such as stroke, cerebral palsy, or genetic encephalopathies. Although the evidence has been inconsistent,[13,18] our earlier research, and that of others, has shown that epilepsy is more common in adolescents with headache or migraine than in those without headache. This association could be confounded by neurologic manifestations of migraine with aura, or could be a true association as comprehensively described in earlier research that compares the similarities between migraine and epilepsy, such as paroxysmal nature, temporary cerebral dysfunction, and other shared clinical features. Cortical hyperexcitability could lead to seizure phenomena characterized by hypersynchronous firing or culminate in migraine headache caused by cortical spreading depression. Notably, antiepileptic drugs, including valproate, topiramate, and gabapentin, can be effective at migraine prophylaxis.

Our findings also confirm the results of previous studies of comorbidity of mental disorders with headache in general and migraine in particular. We found that headache in general was associated with a range of mental disorders, particularly ADHD, thereby confirming our previous findings in 2 population-based studies.[1,33] The specificity of the association between migraine with anxiety and mood disorders confirms findings from earlier community samples.[22,23,26] The emergence of comorbidity early in development suggests that many of these conditions may actually comprise risk factors for migraine or may be common manifestations of its underlying diathesis.[26] Potential explanations for the specific associations with mood and anxiety should be explored in future research. For example, the strong association between anxiety symptoms and disorders and migraine in childhood could reflect increased autonomic reactivity that has been postulated to underlie migraine.[6]

We also noted an association between headaches in general and cardiovascular and abdominal disorders. The association between stomach/abdominal problems and headache in the present study confirms the results of our previous population-based study of US adolescents, which showed that headaches were more than twice as likely to be concomitant with gastrointestinal complaints.[18] In our parallel study of US adults, we found a 3-fold increased rate of irritable bowel syndrome among those with migraine compared with those with no headache.[5] Abdominal complaints in youth could represent the initial harbinger of adult-onset bowel problems. It is difficult to distinguish whether these conditions are truly independent or whether they represent gastrointestinal manifestations of headache or migraine, especially in children.

Several previous studies of adults have examined the relationship between cardiovascular disease and migraine, with contradictory results.[34] Clinic-based studies have shown that there is an increased incidence of structural cardiac lesions, such as patent foramen ovale, atrial septal aneurysm, and mitral valve prolapse, among patients with migraine.[35] The nature of data retrieval from the EMR did not permit a clear understanding of which specific cardiovascular complaints were associated with headaches in this sample.

Our findings have broad implications for identifying sources of heterogeneity of headache and migraine. The pervasive comorbidity of migraine with other developmental, neuropsychiatric, and immunologic conditions may reflect shared aspects of pathophysiology. Documentation of comorbidity also can inform effective clinical management of headaches. Selection of single pharmacologic agents that treat both migraine and comorbid conditions could minimize polypharmacy that may actually exacerbate migraine. Whereas some pharmacologic agents, such as anticonvulsants and antidepressants, may treat both headache and comorbid conditions, other headache prophylactic medications, such as beta blockers, may actually exacerbate asthma. Likewise, serotonin-reuptake inhibitors may actually induce or increase migraine attacks.[36] Thus, consideration of comorbidity in treatment of children with recurrent headache is critical to provide optimal care. These findings also have major relevance to systematic clinical trials of migraine that often fail to consider comorbidity in the design and analysis.[37]

Given the specificity of the association between migraine with anxiety and mood disorders, comorbid psychopathology also may influence the prognosis and progression of migraine headache. This is especially relevant, because behavioral and psychological risk factors may be implicated in the increase in severity and chronicity of headaches.[38-40] Incorporation of comorbid disorders into treatment of children with migraine may facilitate modification of the trajectories of both conditions across the lifespan.

The strengths of our study include the large, systematic sample of youth and the breadth of correlates of chronic conditions included in the survey. Few population-based studies of headache have investigated comorbidity with a range of medical disorders in this age group. Nonetheless, our study has limitations, including its cross-sectional nature with the result that our data are necessarily correlative and cannot address causality. Evaluation of the temporal sequence of the associated

disorders could inform strategies for prevention and management. Another limitation is the diagnostic criteria for migraine and migraine with aura are an approximation of the ICHD-II criteria. Migraine with aura in this study did not include all visual, sensory, and dysphasic phenomena which may underestimate its prevalence. The generally greater prevalence rates of migraine and other physical disorders also reflect that this is not a true population-based sample. However, patterns of comorbidity are likely to be comparable because we did not find differences in comorbidity by a treatment history among those youth with migraine in the present study. Future follow-up of subsets of this sample will be informative in confirming the classification of physical and mental disorders and examining the longitudinal stability and directional links of these associations.

Migraine among youth is common and is associated with a variety of other physical conditions that can further exacerbate headache-related disability. Comorbidity between headaches with a range of physical conditions that have been associated with adult migraine demonstrates that multimorbidity occurs early in development. Prospective data are needed to elucidate the temporal presentation of these conditions with migraine subtypes. Comorbidity 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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References

1. Lateef TM, Merikangas KR, He J, Kalaydjian A, Khoromi S, Knight E et al. Headache in a national sample of American children: prevalence and comorbidity. J Child Neurol 2009;24:536-43.
2. Powers S, Patton S, Hommel KA, Hershey AD. Quality of life in childhood migraine: clinical impact and comparison to other chronic illnesses. Pediatrics 2003;112:1-5.
3. Scher A, Bigal M, Lipton RB. Comorbidity of migraine. Curr Opin Neurol 2005;18:305-10.
4. Radat F, Swendsen J. Psychiatric comorbidity in migraine: a review. Cephalalgia 2005;25:165-78.
5. Saunders K, Merikangas K, Low NCP, Von Korff M, Kessler RC. Impact of comorbidity on headache-related disability. Neurology 2008;70:538-47.
6. Bille B. Migraine on school children. Acta Paediatr Scand 1962;51(suppl 136):3-151.
7. Mortimer MJ, Kay J, Gawkrodger DJ, Jaron A, Barker DC. The prevalence of headache and migraine in atopic children: an epidemiologic study in general practice. Headache 1993;33:427-31.
8. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, et al. Is migraine a risk factor for pediatric stroke? Cephalalgia 2015;35:1252-60.
9. Nelson KB, Richardson AK, He J, Lateef TM, Khoromi S, Merikangas KR. Headache and biomarkers predictive of vascular disease in a representative sample of US children. Arch Pediatr Adolesc Med 2010;164:358-62.
10. Vanmolkot FH, de Hoon JN. Increased C reactive protein in young adult patients with migraine. Cephalalgia 2007;27:843-6.
11. Rains JC, Poceta JS. Headache and sleep disorders: review and clinical implications for headache management. Headache 2006;46:1344-61.
12. Barabas G, Matthews WS, Ferrari M. Childhood migraine and motion sickness. Pediatrics 1983;72:188-90.
13. Haan J, Terwindt GM, Van Den Maagdenberg AMJM, Stam AH, Ferrari MD. A review of the genetic relation between migraine and epilepsy. Cephalalgia 2007;28:105-13.
14. Winawer MR, Hesdorffer DC. Migraine, epilepsy and psychiatric comorbidity: partners in crime. Neurology 2010;74:1166-8.
15. Jarour IT, Jarour KJ. Migraine and recurrent epistaxis in children. Pediatr Neurol 2005;33:94-7.
16. Tietjen G, Conway A, Utley C, Gunning WT, Herial NA. Migraine is associated with menorrhagia and endometriosis. Headache 2006;46:422-8.
17. Adeney KL, Williams LA. Migraine headaches and preeclampsia: and epidemiological overview. Headache 2006;46:794-803.
18. Lateef TM, Cui L, Nelson KB, Nakamura EF, Merikangas KR. Physical comorbidity of migraine and other headache in United States adolescents. J Pediatr 2012;161:308-13.
19. Merikangas KR, Merikangas JR, Angst J. Headache syndromes and psychiatric disorders: association and familial transmission. J Psychiatr Res 1993;27:197-210.
20. Bruijn J, Locher H, Passchier J, Dijkstra N, Arts WF. Psychopathology in children and adolescents with migraine in clinical studies: a systematic review. Pediatrics 2010;126:323-32.
21. Balottin U, Fusar Poli P, Termine C, Molteni S, Galli F. Psychopathological symptoms in child and adolescent migraine and tension-type headache: a meta-analysis. Cephalalgia 2013;33:112-22.
22. Arruda MA, Bigal ME. Behavioral and emotional symptoms and primary headaches in children: a population-based study. Cephalalgia 2012;32:1093-100.
23. Anttila P, Sourander A, Metsähonkala L, Aromaa M, Helenius H, Sillanpää M. Psychiatric symptoms in children with primary headache. J Am Acad Child Adolesc Psychiatry 2004;43:412-9.
24. Milde-Busch A, Boneberger A, Heinrich S, Thomas S, Kühnlein A, Radon K, et al. Higher prevalence of psychopathological symptoms in adolescents with headache. A population-based cross-sectional study. Headache 2010;50:738-48.
25. Brna P, Gordon K, Dooley J. Canadian adolescents with migraine: impaired health-related quality of life. J Child Neurol 2008;23:39-43.
26. Guidetti V, Galli F. Evolution of headache in childhood and adolescence: an 8 year follow-up. Cephalalgia 1998;18:449-54.
27. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. Cephalalgia 2004;24(S1):S24-101.
28. Merikangas KR, Calkins ME, Burstein M, He JP, Chiavacci R, Lateef T, et al. Comorbidity of physical and mental disorders in the neurodevelopmental genomics cohort study. Pediatrics 2015;135:e927-38.
29. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983;40:1228-31.
30. Calkins ME, Moore TM, Merikangas KR, Burstein M, Satterthwaite TD, Bilker WB, et al. The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neurodevelopmental Cohort. World Psychiatry 2014;13:296-305.
31. Benjamini Y, Horhberg Y. Controlling for false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser A Stat Soc 1995;B57:289-300.
32. Aamodt AGH, Stovner LJ, Langhammer A, Hagen K, Zwart JA. Is headache related to asthma, hay fever, and chronic bronchitis: the Head-HUNT study. Headache 2007;47:204-12.
33. Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical comorbidity of Attention-Deficit Hyperactivity Disorder in US adolescents. J Child Neurol 2016;31:1282-9.
34. Hu X, Zhou Y, Zhao H, Peng C. Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies. Neurol Sci 2017;38:33-40.
35. McCandless RT, Arrington CB, Nielsen DC, Bale JF Jr, Minich LL. Patent foramen ovale in children with migraine headaches. J Pediatr 2011;159:243-7.

36. Munera P, Goldstein AJ. Migraine and sertraline. J Am Acad Child Adolesc Psychiatry 2001;10:1125-6.
37. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. N Engl J Med 2017;376:115-24.
38. Lipton RB, Pan J. Is migraine a progressive disease? JAMA 2004;291:493-4.
39. Scher AI, Lipton RB, Stewart W. Risk factors for chronic daily headache. Curr Pain Headache Rep 2002;6:486-91.
40. Lipchik GL, Penzien DB. Psychiatric comorbidities in patients with headache. Sem Pain Med 2004;2:93-105.

50 Years Ago in *The Journal of Pediatrics*

The Effect of Arginine Infusion on Plasma Growth Hormone and Insulin in Children

Root AW, Saenz-Rodriguez C, Bongiovanni AM, Eberlein WR. J Pediatr 1969;74:187-97.

Growth hormone (GH) deficiency (GHD) is the primary indication for GH therapy, with an estimated incidence of 1 in 3500 children.[1] Many advancements have been made in the treatment of GHD; however, the diagnosis of GHD remains difficult owing to the inability to measure directly GH hormone secretion.

In 1969, Root et al described the effects of arginine infusion on levels of plasma GH and insulin in children. This study was undertaken to verify the clinical utility of arginine as a provocative stimulus to assess GH reserve in children. Owing to the pulsatile nature of GH release, random serum GH concentration is an inadequate measure of GH secretion, and thus provocative testing with insulin-induced hypoglycemia was the standard method of assessing GH secretion before these data were available. This study proved that arginine stimulation did indeed increase concentrations of plasma GH in children.

Since the publication of this study, arginine has become one of the standards used for provocative testing, along with clonidine and glucagon. Insulin-induced hypoglycemia has fallen out of favor because of concerns about hypoglycemia. Centers choosing to use GH stimulation testing generally use 2 agents to assess GH response. The threshold for an appropriate response remains controversial and varies among institutions and agents used. Another confounder of GH stimulation tests is the presence of sex hormones, which can facilitate an adequate GH response in normal children. This was seen in the study by Root et al, when 4 of the male patients without a response were treated with diethylstilbestrol (DES) and subsequently had an appropriate response to arginine. Today, many centers choose to do "priming" with sex steroids on prepubescent children before GH stimulation tests.[2] Although other forms of estrogen are now used for priming, DES has been banned in the US since the 1970s owing to the long-term side effects, such as birth defects and cancer in women exposed to DES and their offspring.

Today we also have other indirect markers of GH secretion, including insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). The concentrations of IGF-1 and IGFBP-3 are dependent on GH secretion and remain stable during the day, making them useful tools for assessing GHD. The combination of auxology, physical examination, measures of IGF-1 and IGFBP-3, and sex steroid-primed GH stimulation tests continues to be the foundation for establishing the diagnosis of GHD in children.

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References

1. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994;125:29-35.
2. Marin G, Domene HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB Jr. The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. J Clin Endocrinol Metab 1994;79:537-41.