

Migraine at All Ages

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Although the influence of age on the prevalence of migraine is well known, the clinical characterization of migraine across the lifespan remains poorly studied. Limited evidence suggests that migraine attacks get shorter and less typical with advancing age. Similar results were found for transformed migraine at different ages. In this article, we first discuss the prevalence and clinical features of episodic migraine. We then discuss the epidemiology and profile of transformed migraine across the lifespan. Clarifying the influence of age on migraine is of importance for clinical diagnosis and treatment. It also may contain clues to evolving disease biology.

Introduction

Migraine is a prevalent disease that affects approximately 12% of the adults in occidental countries [1,2]. Although migraine is common at all ages, the effects of age on the prevalence of migraine are dramatic. Before puberty, migraine prevalence is slightly higher in boys than in girls; as adolescence approaches, incidence and prevalence increase more rapidly in girls than in boys. The prevalence increases throughout childhood and early adult life until the approximate age of 40 years. In most studies, the prevalence is highest from the age of 25 to 55 years, the peak years from economic productivity, dramatically declining after that [1,2,3••,4••].

Although the age influence on the prevalence of migraine is well known, the clinical characterization of migraine at different ages is poorly described. Most studies that focus on the clinical characterization of migraine do not specifically address migraine at particular age ranges [5,6,7••]. Some evidence suggests that migraine attacks get shorter [8] and less typical [9] with advancing age. On the other hand, clinic-based studies show that, at least for transformed migraine, there are important

phenotypical differences between adolescents and adults, and that attacks become less typical with age [10••].

Herein, we review the prevalence and symptom profile of migraine across the lifespan. We discuss separately episodic migraine and transformed migraine (TM) because of their important age-dependent clinical particularities. We first discuss the prevalence and clinical features of episodic migraine and then discuss the epidemiology and profile of TM across the lifespan. Clarifying the influence of age on migraine is of importance for clinical diagnosis and treatment; it also may contain clues to evolving disease biology. A better comprehension of migraine over the lifespan is particularly important if we view migraine as a progressive disorder.

The Epidemiology of Migraine at Different Ages

The incidence of migraine

The incidence of migraine is far less studied than its prevalence. In a study that used reported age of migraine onset to indirectly estimate incidence, Stewart et al. [11] found that the incidence of migraine with aura peaked between the ages of 12 and 13 years in women (14.1/1000 person-years), whereas migraine without aura peaked between the ages of 14 and 17 years (18.9/1000 person-years). In men, the incidence of migraine with aura peaked several years earlier (5 years of age at 6.6/1000 person-years). This earlier age of onset helps to explain the higher prevalence of migraine in boys than in girls; the peak for migraine without aura was 10/1000 person-years between the ages of 10 and 11 years (Fig. 1). New cases of migraine were uncommon in men in their twenties. This study supported the concept that migraine begins earlier in men than in women and that migraine with aura begins earlier than migraine without aura.

A study assessing the incidence of migraine in a random sample of young adults (21–30 years) found that the incidence of migraine was 5.0 per 1,000 person years in men and 22.0 in women [12], lower than the incidence in younger ages. A lower incidence of migraine also was found in a study using a linked medical records system [13•]. In this study, the average annual incidence rate per 1000 person-years was 3.4 (4.8 in women and 1.9 in men). In women, incidence rates were low at the extremes of age and higher among those aged between 10 and 49 years, with a striking peak at the age of 20 to 29 years.

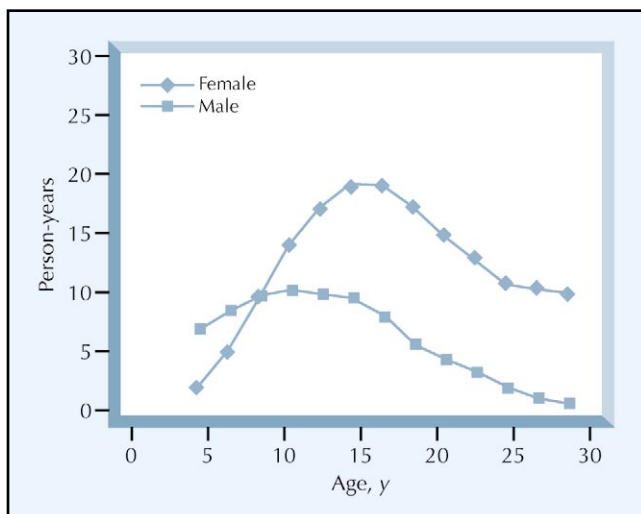


Figure 1: Incidence of migraine, by age and sex (Data modified from Stewart et al. [11], with permission).

A European study showed that in the Danish population, the annual incidence of migraine in those aged 25 to 64 years was 8/1000, being 15/1000 in men and 3/1000 in women. Prevalence peaked in younger women (20/1000) [14].

The prevalence of migraine

The prevalence of migraine has been extensively studied (for reviews, see references [15] and [16••]). It is known that migraine is more common in boys than in girls before puberty. As adolescence approaches, incidence and prevalence increase more rapidly in girls than in boys. The prevalence increases throughout childhood and early adult life until the approximate age of 40 years, after which it declines [2] (Fig. 2). Overall, prevalence is highest between the ages of 25 and 55 years, the peak years from economic productivity, which at least partially explains the substantial influence of migraine on lost work time (see next section).

Several studies assessed the prevalence of migraine in the pediatric population. In Italy, Raieli et al. [17] assessed the prevalence of migraine headache in an epidemiologic survey of 11- to 14-year-old students. Overall migraine prevalence was 3.0%, with a slight female preponderance. Other studies found higher prevalence. A study performed in the United Kingdom showed that migraine prevalence was higher in boys than in girls at 3 to 5 years of age and at 5 to 7 years of age. Prevalence was equal in boys and girls between the ages of 7 and 11 years and was higher in girls after age 11 [18].

Two studies reported on the prevalence of pediatric migraine in the Asian middle-east. The first one, performed in southern Iran, found that the prevalence rate for migraine was 6.1% (95% CI, 5.0–7.2) [19]. The second study, in Saudi Arabia, found a sharp increase in the prevalence rate (from approximately 2% to approximately

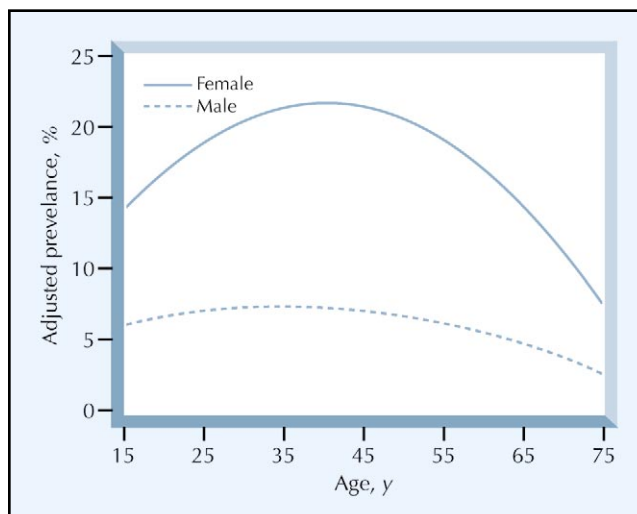


Figure 2: Adjusted prevalence of migraine by age from a meta-analysis of studies using IHS criteria.

9%) at the ages of 10 to 11 years for both boys and girls. Age-adjusted prevalence for migraine between the ages of 6 and 15 years was 6.2% [20].

In adults, estimates of migraine prevalence range from 3.3% to 21.9% for women and 0.7% to 16.1% for men [15,16••].

The phenotype of migraine at different ages

Little is known about the clinical differences of migraine according to the phase of life. This is important for a better comprehension of the natural history of migraine, as well as for a more sophisticated clinical characterization of this disease.

It is well established that migraine attacks tend to be shorter in children than in adults [21••,22••]. The International Classification of Headache Disorders (ICHD) require that untreated migraine attacks typically last for a minimum of 4 hours in adults, but accept a shorter duration (> 1 hour) in children [23]. It also has been suggested that children have unilateral and throbbing pain less frequently than in adults, although this may be a result of age-specific difficulties in reporting the symptoms [24].

Although less frequently discussed, it also may be suggested that, similar to what is seen in children, migraine attacks are less typical in the elderly than in middle-aged. A prospective study found that in individuals older than 70 years, probable migraine (PM; a migraine subtype missing just one migraine feature) with and without aura was more common than respectively migraine with and without aura. Most of those who filled criteria for PM when enrolled in the study had strict migraine in the past. Furthermore, many who did not have a migraine attack in the year before the study had experienced migraine attacks in the past, with clinical improvement after the age of 60 years [8].

A second study retrospectively assessed subjects seen in an outpatient headache clinic. In that service, migraine occurred in 25% of the elderly and 29% of younger headache sufferers (NS). Migraine attacks were less typical in the elderly than in younger individuals. A lower proportion of migraine attacks in the elderly were unilateral (38% vs 57%; $P < 0.01$). The prevalence of associated symptoms also was lower in the elderly than in younger people (nausea, 75% vs 86%, $P < 0.05$; vomiting, 30% vs 54%, $P < 0.05$; photophobia and phonophobia, 83% vs 94%, $P < 0.05$). Some premonitory or other accompanying symptoms, such as paleness, dry mouth, and anorexia, were more common in the elderly. Based on this retrospective review, the authors concluded that migraine attacks are less typical in the elderly [9].

To better assess the clinical differences of migraine according to the age, we recently used a validated computer-assisted telephone interview to identify a population sample in three urban centers in the United States [25•]. Eligible participants were older than 18 years of age. We hypothesized that if migraine gets less typical in particular ages, the prevalence of PM (a migraine subtype missing just one migraine feature), relative to migraine, gets higher.

The peak of prevalence for migraine occurred between the ages of 30 and 39 years (prevalence, 20.1%). The prevalence of migraine declined subsequently in every age range to a minimum of 3.9% in those older than 70 years of age (Table 1). For PM, the peak of prevalence occurred at younger ages (18–29 years; 17.5%) and also declined subsequently to a prevalence of 6.4% at the age of 70 years or older. Across the lifespan, migraine was more common than PM between the ages of 30 and 49 years. The proportion of subjects with migraine and PM was nearly the same as in those between the ages of 50 and 59 years, and PM was more common than migraine in younger and older ages.

Clinical features of migraine by age

We also assessed the proportion of individuals with the distinguishing migraine features (the criteria proposed by the ICHD-2 as the migraine diagnostic features) by age range [15]. Severe pain and unilateral pain was most common between the ages of 30 and 59 years (Table 2). In contrast, the proportion of subjects reporting that most of their attacks were throbbing declined between age group from those between the ages of 18 and 29 years to those older than 70 years of age (65.7%). Using the ages between 18 and 29 years as a reference, whereas 83% of this group had throbbing pain, 79.1% of those between the ages of 40 and 49 years (OR, 0.61; 95% CI, 0.51–0.73), 75% of those between the ages of 60 and 69 years (OR, 0.59; 95% CI, 0.49–0.7), and just 65% of those 70 years of age or older (OR, 0.37; 95% CI, 0.25–0.86) had it (Table 2). The odds ratio and confidence intervals for each pain feature by age group are shown in Table 2.

For the associated symptoms, nausea was most common for those subjects between the ages of 40 and 59 years [25•]. The proportion of subjects reporting phonophobia and photophobia trended downward with age. Finally, as expected, the proportion of subjects with aura increased by every single age range, from 12.9% for those between the ages of 18 and 29 years, to 18.2% for those aged 30 to 39 years (OR, 1.37; 95% CI, 1.23–1.52), 20.1% for those aged 40 to 49 years (OR, 1.7; 95% CI, 1.5–1.8), 32% in those aged 50 to 59 years (OR, 2.2; 95% CI, 2–2.5), 46% in those aged 60 to 69 years (OR, 3.1; 95% CI, 2.6–3.7), and 69.3% in those aged 70 years or older (OR, 4.6; 95% CI, 3.1–6.8).

Frequency of migraine attacks by age

Finally, we assessed the proportion of migraine sufferers who had between 10 and 14 headache days per month, as a function of age, and found a direct relationship (Fig. 3). Whereas 12.5% of those between the ages of 18 and 29 years had 10 to 14 headache days per month, the proportion was significantly higher in every other age range, peaking in those aged 70 years or older (41%; OR, 4.8; 95% CI, 3.9–7.12) [25•].

Chronic Daily Headaches at Different Ages

Chronic daily headache subtypes

Chronic daily headache (CDH) also is a significant problem in children and adolescents [26,27••,28]. In a study of 189 consecutive patients younger than 18 years of age, who presented for initial evaluation at one of nine tertiary headache clinics with CDH, the mean age of onset of CDH was 13.0 ± 3.1 years. The differences between the distribution of CDH in adults and adolescents are poorly understood. Previous studies suggest that chronic tension-type headache (CTTH) is more common in adolescents than in adults [26,27••].

Similarly, we conducted a clinic-based study assessing adolescents (13–17 years; $n = 170$) and adults (≥ 18 years; $n = 638$) recruited during the same time frame. CDH subtypes were classified as TM, CTTH, new daily persistent headache (NDPH), and hemicrania continua (HC) [29••].

Among adolescents and adults, there were substantial differences in the distribution of CDH subtypes. The relative frequency of TM was lower in adolescents (68.8% vs 87.4%; $P < 0.001$), whereas NDPH (21.1% vs 10.8%; $P < 0.001$) and CTTH (10.1% vs 0.9%; $P < 0.0001$) were more common. HC (0 vs. 0.9%, NS) was equally rare [19] (Table 3).

The lower relative frequency of TM in adolescents was accounted for by TM with medication overuse (TM+), which is much more common in adults (28.2% vs 62.5%; $P < 0.001$). In fact, TM without medication overuse (TM-) was more common in adolescents (40.5% vs 24.9%; $P < 0.001$). The relative frequency of TM+ increased until the age of 50 years ($P < 0.001$).

Table 1. Prevalence of migraine, probable migraine, and all migraine according to the demographic characteristics

	Respondents, n	Migraine			Probable migraine			All migraine		
		Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	
Age overall, y										
18–29	31,168	5049	16.2	5447	17.48	10,496	33.68			
30–39	39,388	7927	20.13	6252	15.87	14,179	36			
40–49	38,985	6156	15.79	5584	14.32	11,740	30.11			
50–59	23,256	2945	12.66	2921	12.56	5866	25.22			
60–69	9885	735	7.44	855	8.65	1590	16.08			
70+	2653	105	3.96	169	6.37	274	10.33			
Total	145,335	21,843	15.03	21,228	14.61	43,071	29.64			
Gender by age, y (male)										
18–29	11,609	1048	9.03	1631	14.05	2679	23.08			
30–39	13,959	1420	10.17	1750	12.54	3170	22.71			
40–49	12,627	1063	8.42	1438	11.39	2501	19.81			
50–59	7185	462	6.43	705	9.81	1167	16.24			
60–69	2895	97	3.35	181	6.25	278	9.6			
70+	706	15	2.12	35	4.96	50	7.08			
Total	48,981	4105	8.38	5740	11.72	9845	20.1			
Gender by age, y (female)										
18–29	19,559	4001	20.46	3816	19.51	7817	39.97			
30–39	25,429	6507	25.59	4502	17.7	11,009	43.29			
40–49	26,358	5093	19.32	4146	15.73	9239	35.05			
50–59	16,671	2483	14.89	2216	13.29	4699	28.19			
60–69	6090	638	10.48	674	11.07	1312	21.54			
70+	1855	90	4.85	134	7.22	224	12.08			
Total	96,262	17,738	18.43	15,488	16.09	33,226	34.52			

Table 2. Migraine pain features according to the age range

	Number	Percentage	Odds ratio	Lower limit, CI	Upper limit, CI
Unilateral (age range in years)					
18–29	3111	60.3	1*		
30–39	4149	61.5	1.04	0.96	1.12
40–49	3979	64.6	1.19	1.1	1.28
50–59	1988	67	1.35	1.22	1.44
60–69	434	59.5	0.93	0.8	1.1
70+	59	54	0.78	0.5	0.9
Throbbing (age range in years)					
18–29	4266	83.1	1*		
30–39	5534	82	0.96	0.87	1.06
40–49	4867	79.1	0.74	0.67	0.81
50–59	2291	77.8	0.69	0.61	0.73
60–69	551	75	0.59	0.49	0.7
70+	71	65.7	0.37	0.25	0.86
Severe (age range in years)					
18–29	4020	78.3	1*		
30–39	5512	81.7	1.24	1.13	1.35
40–49	5061	82.2	1.28	1.16	1.4
50–59	2375	80.6	1.15	1.03	1.29
60–69	563	76	0.9	0.7	1
70+	68	63	0.47	0.31	0.7
Worsened by physical activity (age range in years)					
18–29	2972	57.9	1*		
30–39	4081	60.5	1.11	1.03	1.2
40–49	3640	59.1	1.05	0.97	1.13
50–59	1646	55.9	0.96	0.87	1.05
60–69	360	49	0.69	0.59	0.81
70+	39	36	0.41	0.27	0.6

*Number and proportion of those who had the feature in more than 50% of the attacks.

Transformed migraine in adolescents and adults

It is well known that in most patients with TM, as attack frequency increases, the number of migraine features diminish during the transformation period. If that is so, it may be hypothesized that adolescents with TM have more migraine days compared with adults. We also hypothesize that as the duration of CDH (interval from the onset of CDH to the current assessment) and duration of migraine (interval from the onset of migraine to the current assessment) increase, the proportion of migraine attacks decreases [30].

To test this hypothesis, we assessed the proportion of subjects with TM who have 15 or more migraine days per month as a function of duration of CDH in an adolescent sample. We included 267 adolescents (13–17 years) seen

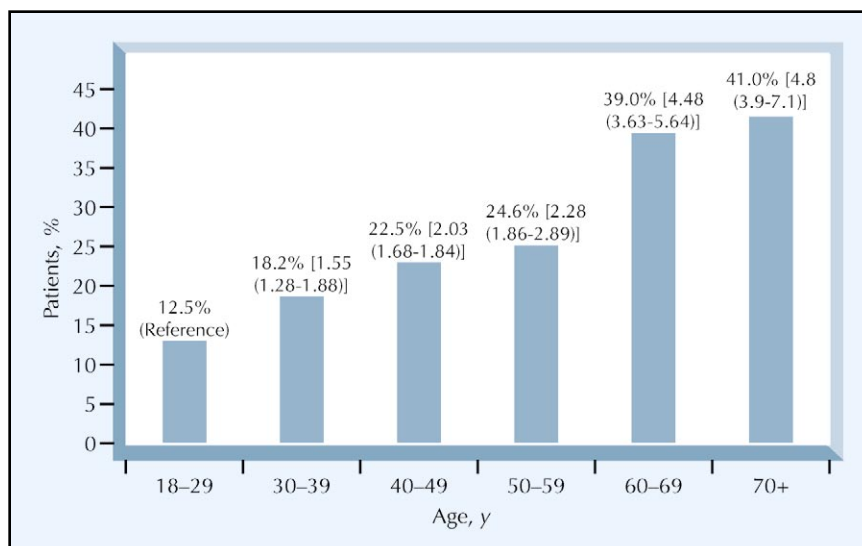
in a headache center to identify 117 with TM. We divided subjects with TM into those with recent onset (< 1 year) versus longer duration (> 1 year) and examined the number of migraine days per month and demographic features. We modeled predictors of CM (> 15 migraine days per month) using logistic regression.

Of 117 adolescents with TM, 55 (47%) had recent onset (< 1 year) and 62 (53%) had long-duration TM. Those with recent-onset TM were much more likely to also meet criteria for CM (74.5% vs 25.8%; $P < 0.001$). This was verified in the subgroup of subjects with TM with medication overuse (recent-onset, 66.7% vs long-duration, 37%; $P = 0.01$) and in the subgroup of those with TM without medication overuse (62.2% vs 19.2%;

Table 3. Diagnoses for primary chronic daily headache in adolescents and adults

	Adolescents, n (%)	Adults, n (%)	P value
Transformed migraine	117 (68.8)	558 (87.4)	$P < 0.001$
With medication overuse	48 (28.2)	399 (62.5)	$P < 0.001$
Without medication overuse	69 (40.5)	159 (24.9)	
New daily persistent headache	36 (21.1)	69 (10.8)	$P < 0.001$
With medication overuse	9 (3.5)	21 (3.3)	NS
Without medication overuse	27 (15.8)	48 (7.5)	
Chronic tension-type headache	17 (10.1)	6 (0.9)	$P < 0.001$
With medication overuse	0	2 (0.3)	$P = 0.05$
Without medication overuse	17 (10.1)	4 (0.6)	
Hemicrania continua	0	5 (0.8)	NS

NS—not significant.

**Figure 3:** Proportion of subjects with more than 10 headache days per month within the all migraine group, according to the age.

$P = 0.001$) [31]. Modeling the dichotomous outcome of CM (> 15 days of migraine/month) in logistic regression, CM was predicted by recent onset of CDH, recent onset of migraine (< 36 months), and younger ages (< 15 years), but not gender or use of migraine-preventive drugs or medication overuse [20,21••].

Conclusions

The prevalence of both migraine and PM decrease with age past 40 years, suggesting remission in a fraction of migraine sufferers. More subjects have migraine than PM at intermediate ages, whereas the opposite is true for the extremes of ages assessed in this study. This also suggests that migraine is less typical in the extremes of ages and flourishes between the ages of 30 and 49 years. In those with ICHD-2 migraine, attacks tend to be more typical in the younger subjects than in the elderly. Higher proportion of young individuals have the hallmarks of migraine, such as unilateral pain, pain aggravated by exercises, photophobia, and phonophobia. As

expected, aura shows the opposite pattern and is more common with age. The frequency of headache attacks increases with age in the migraine and PM group.

The profile of migraine changes over the lifespan, and suggests three non-exclusive profiles. In a subgroup of subjects, migraine remits. In some sufferers, migraine gets less typical, resembling PM rather than full migraine. Finally, migraine progresses in some individuals. Future research should focus on predictors of these profiles. Our findings also have clinical implications. Migraine, its less typical subtype (PM), and one of its complications (CDH) may be missed more often at specific ages, and a lower proportion of these subjects may receive adequate treatment.

There are important differences in the profile of CDH in adolescents and adults. CTTH and NDPH are more common in adolescents than in adults; TM is more common in adults than in adolescents; and HC is equally rare. Medication overuse is associated more commonly with TM in adults than in adolescents. It is possible that those with a higher biologic predisposition develop TM earlier

and with less environmental influence (adolescents). The lower proportion of adolescents overusing medication also may reflect the higher difficulty in obtaining analgesics at this age. Adolescents with TM have a higher frequency of migraine attacks than adults with TM. In adolescents and in adults, migraine is more likely in individuals who are young, whose episodic headache began recently, and who have CDH of recent onset. These findings suggest that early in the process of transformation, migraine is more frequent and that as CDH evolves, fewer typical attacks of migraine occur.

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