

# Primary headache with onset in childhood and adolescence: natural history and prognostic factors in a Portuguese population

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**Introduction.** Headaches are the most frequent neurological disorder in the pediatric population, with great impact on quality of life. This study aims to characterize a cohort of patients followed at a pediatric neurology unit between January 1<sup>st</sup> 2013 and December 31<sup>st</sup>, 2021.

**Materials and methods.** We reviewed medical records and selected patients with primary headaches and a minimum follow-up of 12 months.

**Results.** A total of 226 patients were included, 54.4% female, with an average age at headache onset of  $9 \pm 3.5$  (3.1-16.5) years; 63.5% were prepubertal. A positive family history of headache was identified in 76.6% of cases and triggers in 63.6%. At first clinical assessment, 45.1% were classified as migraine without aura, 10.6% as migraine with aura, 3.5% tension-type, 8% mixed (tension and migraine), 1.3% other type and 31.4% were unclassifiable. The patients had a median follow-up of 2.4 (1.8-3.3) years. The diagnosis of tension-type headaches remained stable in 75% of the patients and resolved in 25%; 13% of the patients with migraine without aura changed into another type of headache and 17.4% resolved; 44.4% of the patients with migraine with aura turned into another type of headache and 11.1% resolved. Of the variables studied, only duration of headache episode had a significant association with headache remission, with odds ratio 0.16 ( $p = 0.03$ ; 95% confidence interval: 0.032-0.84).

**Conclusions.** Our study shows that headache type in pediatric population changes over time, especially in those with migraine with aura. The duration of each headache episode was presented as a predictor of headache remission over time.

**Key words.** Adolescence. Childhood. Headache. Natural history. Prognostic factors. Remission.

## Introduction

Headaches are the most frequent neurological disorder in the pediatric population, with a prevalence that can reach 75.7%-88% of children and adolescents, with migraine and tension-type headache being the most common forms of presentation [1, 2]. In addition to their high prevalence, they are also characterized by their impact on quality of life, with restrictions in daily life being reported in approximately 40% of cases [1,3].

Genizi et al studied a group of pediatric patients with headache and a 8-10 year follow-up after initial diagnosis, and found that, with regard to tension-type headache, the diagnosis remained stable in 36.7% of patients, changed to migraine in 18.3% of patients and resolved in 45%; in those with migraine, the diagnosis remained stable in 59.3% of patients, changed to tension-type headache in 16.9%

of patients and resolved in 23% [4]. Termine et al, in another similar study with a follow-up of 11 years, showed that migraine with aura remained in 44.1% of patients, changed to another headache diagnosis in 32.5% and resolved in 23.4% [5].

Factors such as female sex, older age, personal history of chronic migraine or migraine status, and low headache frequency have been identified as possible factors of clinical worsening over time [6]. Our study aims to characterize a cohort of pediatric patients with headaches followed at a pediatric neurology unit between January 1<sup>st</sup> 2013 and December 31<sup>st</sup>, 2021. We intended to identify and characterize primary headaches in children and adolescents; to characterize the evolution and natural history of tension-type headache and migraine headaches; finally, to assess predictors of persistence or remission of tension-type headache and migraine over time.

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This study was approved by the ethical committee of Centro Materno-Infantil do Norte Albino Aroso/Centro Hospitalar e Universitário do Porto, number 005-22 (005-DEFI/005-CE).

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**Table 1.** Characteristics of study population ( $n = 226$ ).

	Value
Sex - $n$ (%)	$n = 226$
Female	123 (54.4)
Age (years)	$n = 226$
Mean $\pm$ SD	$11.3 \pm 3.5$
Age of headache onset (years)	$n = 189$
Mean $\pm$ SD	$9.0 \pm 3.5$
Age group - $n$ (%)	
Prepubertal (<10 years)	120 (63.5)
Pubertal ( $\geq 10$ years)	69 (36.5)
Time of headache onset - first observation (months)	$n = 190$
Median (IQ)	12.0 (6.0-36.0)
Family history (years) - $n$ (%)	$n = 175$
Yes	134 (76.6)
Trigger factors - $n$ (%)	$n = 65$
Yes	41 (63.1)
Stress	20 (30.7)
Menstruation	5 (7.7)
Fatigue	4 (6.2)
Heat	4 (6.2)
Sleep disturbance	3 (4.6)
Others	5 (7.7)
Type of headache - T0	$n = 226$
MwA	102 (45.1)
MA	24 (10.6)
TTH	8 (3.5)
Mixed	18 (8.0)
Other	3 (1.3)
Unclassifiable	71 (31.4)
Headache duration - $n$ (%)	$n = 53$
Minutes-hours	32 (60.4)
Days	21 (39.6)

IQ: interquartile range; MA: migraine with aura; MwA: migraine without aura; SD: standard deviation; TTH: tension-type headache.

## Material and methods

### Study design

Cross-sectional study, based on data collection from the electronic clinical records carried out in the Pediatric Neurology Service of the Centro Materno-Infantil do Norte Albino Aroso/Centro Hospitalar Universitário do Porto, Portugal.

### Sample

The study included all children and adolescents complaining of headaches referred and observed at the Pediatric Neurology Service, between January 1<sup>st</sup> 2013 and December 31<sup>st</sup>, 2021. The sample included all patients with primary headaches, according to the International Classification of Headache Disorders, 3<sup>rd</sup> edition, with a minimum follow-up of 12 months.

### Design

To assess the natural course in each patient, headaches were classified in the first visit (T0) as unclassifiable, tension-type headache, migraine with aura, migraine without aura, mixed (tension-type headache and migraine) or other type headache. Then, the clinical evolution of headache was assessed at 12 months (T1) and at discharge or last visit (T2), whichever was applicable, and classified as remission, persistence, or transformation. Persistent headaches were defined as those that still presented as tension-type headache, migraine with aura, migraine without aura or mixed at follow-up. Transformed headaches were those that changed over time into a different classification. Remission was considered when the patient reported absence of episodes at the follow-up visits.

### Study variables

The following variables were collected: sex, age (years), age at and onset of headache and at first visit (years), prepubertal or pubertal stage (<10 versus  $\geq 10$  years) at diagnosis, family history of headache (positive versus negative), type of headache (unclassifiable, tension-type headache, migraine with aura, migraine without aura, mixed or other type), aura (presence versus absence), duration of each headache episode (minutes-hours versus days), triggering factors (presence versus absence) and headache clinical evolution (remission, persistence or transformation).

### Statistical method

Categorical variables are presented as frequencies, and percentages and continuous variables as means and standard deviations or medians and interquartile ranges for variables with skewed distributions. Normal distribution was checked using Shapiro-Wilk test of skewness and kurtosis. Categorical variables were compared using Fisher's ex-

act test or  $\chi^2$  test as appropriate and continuous variables with Student's *t* test or Mann-Whitney U test for independent samples. All reported *p* values are two-tailed, with *p* value of 0.05 indicating statistical significance.

Binary logistic regression was adjusted considering as independent variables sex and duration of each headache episode. The variables were included as predictors if they were selected from bivariate analysis (*p* < 0.05). Analyses were performed with Statistical Package for the Social Sciences (SPSS) software version 27.0.

## Results

### Characterization of the sample

Our sample included 226 children and adolescents with primary headache, 54.4%, females with an average age of  $11.3 \pm 3.5$  years (minimum, 2.7, and maximum, 17.5). Mean age of headache onset was  $9.0 \pm 3.5$  years (minimum, 3.1, and maximum, 16.5) and 63.5% (120/189) were prepubertal. A positive family history of headache was identified in 76.6% (134/175) and triggers were reported in 63.1% (41/65) of the cases.

The median time from headache onset onto first observation (T0) was 12 (6-36) months. At first clinical assessment, 45.1% were classified as migraine without aura, 10.6% as migraine with aura, 3.5% as tension-type headache, 8% as mixed, 1.3% as other type and 31.4% were unclassifiable. The duration of each headache episode was short in most cases, with 60.4%, lasting from minutes to hours. Table I shows the clinical and demographic characteristics of our study population.

### Natural history of headache

Table II shows the distribution of unclassifiable, tension-type headache, migraine without aura, migraine with aura, mixed and other headache at baseline and their clinical evolution over time. The results are presented at T1 (follow-up 12 months) and at T2 (follow-up at discharge or last visit). The median follow-up at T1 was 1.3 (1.1-1.4) years and the median follow-up at T2 was 2,4 (1,8-3,3) years. In our study population, 22.4% and 21.3% of patients were headache-free at T1 and T2, respectively. Tension-type headache appears to be the type of headache that remains more stable over time, persisting in 75% of the patients at T1 and T2.

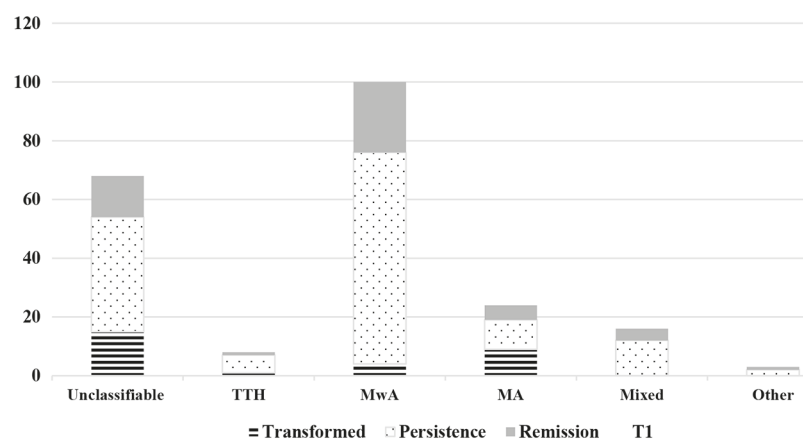
**Table II.** Headache diagnosis at the first consultation and clinical evolution: at 12 months (T1) and at discharge or last visit (T2).

	Time	Total	Headache clinical evolution						
			No headache	Unclassifiable	CT	TTH	MwA	Mixed	Other
Unclassifiable - n = 71	T1	68	14 (20.6)	39 (57.4)	3 (4.4)	11 (16.2)	0 (0)	1 (1.5)	0 (0)
	T2	37	10 (27)	13 (35.1)	3 (8.1)	7 (18.9)	0 (0)	4 (10.8)	0 (0)
TTH - n = 8	T1	8	1 (12.5)	0 (0)	6 (75)	0 (0)	0 (0)	1 (12.5)	0 (0)
	T2	4	1 (25)	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)	0 (0)
MwA - n = 102	T1	100	24 (24)	2 (2)	1 (1)	72 (72)	0 (0)	1 (1)	0 (0)
	T2	46	8 (17.4)	0 (0)	2 (4.3)	32 (69.6)	0 (0)	4 (8.7)	0 (0)
MA - n = 24	T1	24	5 (20.8)	2 (8.3)	0 (0)	7 (29.2)	10 (41.7)	0 (0)	0 (0)
	T2	9	1 (11.1)	0 (0)	0 (0)	4 (44.4)	4 (44.4)	0 (0)	0 (0)
Mixed - n = 18	T1	16	4 (25)	0 (0)	0 (0)	0 (0)	0 (0)	12 (75)	0 (0)
	T2	9	2 (22.2)	0 (0)	0 (0)	0 (0)	0 (0)	7 (77.8)	0 (0)
Other - n = 3	T1	3	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (66.7)
	T2	3	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (66.7)
Total - n = 226	T1	219	49 (22.4)	43 (19.6)	10 (4.6)	90 (41.1)	10 (4.6)	15 (6.8)	2 (0.9)
	T2	108	23 (21.3)	13 (12)	8 (7.4)	43 (39.8)	4 (3.7)	15 (13.9)	2 (0.9)

MA: migraine with aura; MwA: migraine without aura; TTH: tension-type headache.

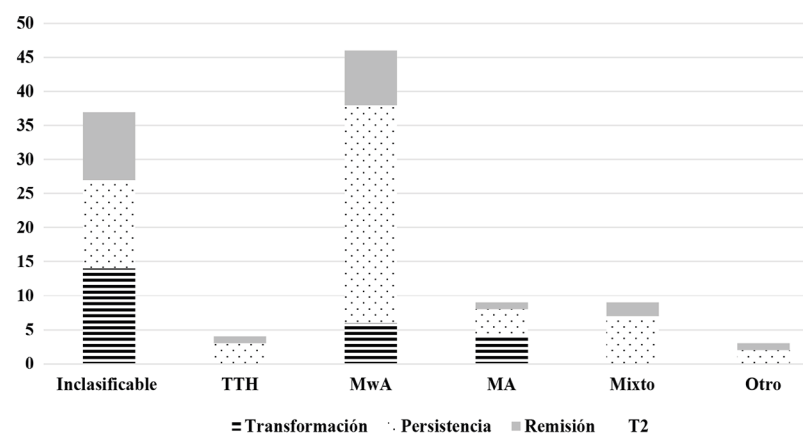
Regarding migraine without aura, in the longest follow-up, it reached remission in 17.4% of the cases, remained similar in 69.6% and changed to another type in 13%, namely into tension-type headache or mixed headache. On the contrary, migraine with aura showed the same tendency to persist as to change to migraine without aura, with 44.4% cases for each of the situations; only 11.1% of the patients were headache free. Mixed headaches (tension-type headache and migraine) resolved in approximately one quarter of patients and remain similar in three quarters, with no change into another type of headache. Figures 1 and 2 show headache clinical evolution and classification as remission (no headache), persistence (same type of headache) or transformation (into another type of headache) at T1 and T2.

**Figure 1.** Headache clinical evolution and classification as remission, persistence or transformed at T1.



MA: migraine with aura; MwA: migraine without aura; TTH: tension-type headache.

**Figure 2.** Headache clinical evolution and classification as remission, persistence or transformed at T2.



MA: migraine with aura; MwA: migraine without aura; TTH: tension-type headache.

### Prognostic factors

#### Univariate analysis

When comparing variables between groups who achieved headache remission (in T1 or T2) versus those who did not, we found a statistically significant difference regarding sex (female versus male) and duration of each headache episode (minutes-

hours versus days),  $p = 0.02$ . The results are shown in table III.

#### Multivariate analysis

Considering the variables described as statistically significant in the univariate analysis and applying binary logistic regression, only duration of each headache episode described in first consultation had a significant association with headache remission, with odds ratio 0.16 ( $p = 0.03$ ; 95% confidence interval: 0.03-0.84), as summarized in table III. The presence of short episodes of headache had 84% lower odds of headache persistence over time.

### Discussion

The present study shows the epidemiological reality of headache and its natural history in a part of the Portuguese pediatric population.

Our study suggests that headaches in pediatric patients may have a favorable long-term outcome with almost 25% achieving headache-free status, which is in line with other studies [4].

Tension-type headache appears to be the type of headache that remains most stable over time, persisting with the same classification in 75% of patients. Genizi et al described a different pattern of evolution in their study, with 36.7% of the patients where this diagnosis remaining with the same diagnosis, 18.3% changing into migraine and 45% resolving [4]. This difference can be explained by a longer follow-up and a larger sample of patients with tension-type headache.

The clinical evolution of migraine with aura, showed an equal tendency to persist or to change into another type of headache, which is in line according to what was found in the study of Termine et al [5].

About migraine without aura, in the longest follow-up, it reached remission in 17.4% of the cases, remained similar in 69.6% and changed into another type in 13%, findings that are also in line with what has been described. Genizi et al describe in their manuscript that the diagnosis of migraine remained stable in 59.3% of patients, changed to tension-type headache in 16.9% and resolved in 23%. This data is similar to ours, but refers to the natural history of all migraines (with and without aura) [4]. The natural history of migraine without aura is not described in previous articles.

Multiple factors have been described as possible factors for clinical worsening over time such as fe-

male gender, older age, personal history of chronic migraine or migraine status, and depressive symptoms [6]. In our study, among the factors evaluated, only the short duration of each headache episode was presented as a predictor of headache remission over time. This association had not yet been described and it can be useful in the clinical setting in establishing the prognosis of the child with headache.

This study has some limitations such as being a retrospective study carried out in a specialized pediatric headache consultation in a single pediatric hospital which may explain some variations found in the epidemiology. However, most of our results are in line with data previously found in other international studies which seems to suggest that it is a good sample. In conclusion, our study shows that patient type of headache changes over time, especially in those with migraine. The short duration of each headache episode was presented as a predictor of headache remission over time.

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**Table III.** Univariate analysis and binary logistic regression.

	Headache remission (T1 o T2)		p value
	No	Yes	
Sex - n (%)			
Female	99 (59.3)	24 (42.1)	p = 0.02
Male	68 (40.7)	33 (57.9)	
Age at diagnosis (years)			
Mean ± SD	8.9 ± 3.6	9.2 ± 3.6	p = 0.65
Age at diagnosis (years)			
Prepubertal (<10 years)	90 (64.3)	29 (61.7)	p = 0.75
Pubertal (≥10 years)	50 (35.7)	18 (38.3)	
Family history (years) - n (%)			
No	27 (21.4)	12 (25.5)	p = 0.57
Yes	99 (78.6)	35 (74.5)	
Trigger factors - n (%)			
No	20 (40.8)	4 (23.5)	p = 0.2
Yes	29 (59.2)	13 (76.5)	
Headache duration - n (%)			
Minutes-hours	19 (50)	12 (85.7)	p = 0.02
Days	19 (50)	2 (14.3)	
Presence of aura - n (%)			
No	142 (85)	52 (91.2)	p = 0.24
Yes	25 (15)	5 (8.8)	
Independent variables	p value	OR	95% CI
Sex	0.79	1.20	0.32-4.49
Headache duration	0.03	0.16	0.03-0.84

CI: confidence interval; OR: odds ratio; SD: standard deviation.

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## Cefaleas primarias con inicio en la infancia y la adolescencia: historia natural y factores pronósticos en una población portuguesa

**Introducción.** Las cefaleas son el trastorno neurológico más habitual en la población pediátrica e influyen notablemente en su calidad de vida. La finalidad de este estudio es caracterizar una cohorte de pacientes en seguimiento en una unidad de neurología pediátrica entre el 1 de enero de 2013 y el 31 de diciembre de 2021.

**Materiales y métodos.** Hemos revisado informes médicos y seleccionado a pacientes con cefaleas primarias y un seguimiento mínimo de 12 meses.

**Resultados.** Se incluyó a un total de 226 pacientes, el 54,4% mujeres, con una media de edad al comenzar las cefaleas de 9 ± 3,5 (3,1-16,5) años; el 63,5% eran prepuberales. Se identificó un historial familiar positivo de cefalea en el 76,6% de los casos y factores desencadenantes en el 63,6%. En una primera evaluación clínica, el 45,1% se identificó como migrañas sin aura; el 10,6%, como migrañas con aura; el 3,5%, como cefalea tensional; el 8%, como de tipo mixto (cefalea tensional y migraña); el 1,3%, de otro tipo; y el 31,4% resultó clasificable. Los pacientes se sometieron a un seguimiento

promedio de 2,4 (1,8-3,3) años. El diagnóstico de cefalea tensional se mantuvo estable en el 75% de los pacientes y se solucionó en un 25%; para el 13% de los pacientes con migraña sin aura, el diagnóstico cambió a otro tipo de cefalea, y para el 17,4%, se solucionó; para el 44,4% de los pacientes sin migraña con aura, el diagnóstico cambió por el de otro tipo de cefalea, y para el 11,1%, se resolvió. De las variables estudiadas, sólo la duración del episodio de cefalea tuvo una asociación significativa con la remisión de la cefalea, con una *odds ratio* de 0,16 ( $p = 0,03$ ; intervalo de confianza al 95%: 0,032-0,84).

**Conclusiones.** Nuestro estudio muestra que el tipo de cefalea en la población pediátrica cambia con el paso del tiempo, especialmente en los pacientes con migraña con aura. La duración de cada uno de los episodios de cefalea se presentó como un predictor de la remisión de la cefalea con el paso del tiempo.

**Palabras clave.** Adolescencia. Antecedentes naturales. Cefalea. Factores de pronóstico. Infancia. Remisión.