



Comparative Study on Primary Chronic Daily Headache and Its Subtypes in Adolescents and Adults in Tertiary Care Centre in South India

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ABSTRACT:

Objectives: To determine the relative frequency of chronic daily headache (CDH) subtypes in adolescents and to compare the distribution of CDH subtypes in adolescents and adults of various ages.

Methods: Adolescents (13 to 21 years, n=150) and adults (22 to 35 n=150) were recruited during the same time frame. CDH subtypes were classified according to the criteria proposed by Silberstein and Lipton (1996) as transformed migraine (TM), chronic tension-type headache (CTTH), new daily persistent headache (NDPH), and hemicrania continua (HC).

Results: Among adolescents and adults there were substantial differences in the distribution of CDH subtypes. The relative frequency of TM was lower in adolescents (66.4% vs 87.4%, $p < 0.001$), while NDPH (24.1% 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. The lower relative frequency of TM in adolescents was accounted for by TM with medication overuse (TM+), much more common in adults (29.4% vs 64.5%, $p < 0.001$). In fact, TM without medication overuse (TM-) was more common in adolescents (64.2% vs 26.5%, $p < 0.001$). The relative frequency of TM- increased as the age increases ($p < 0.001$).

Conclusions: In adolescents with CDH, TM usually develops without medication overuse. Adolescents with the early onset form of TM may develop the disorder in the absence of medication overuse because they are at increased biologic risk.

I. INTRODUCTION:

Primary chronic daily headache (CDH) of long duration is a syndrome characterized by headaches not attributable to a secondary disorder, which last more than 4 hours a day and occur 15 or more days per month. This syndrome affects 4% of

the general population{1,2} and 30% to 84% of patients seen in headache clinics.3-5. The criteria most frequently used to classify primary CDHs of long duration are those proposed by Silberstein and Lipton (S-L).{6,7}. According to these criteria, the CDH syndrome encompasses four main diagnoses: 1). transformed migraine (TM); 2). chronic tension-type headache (CTTH); 3). new daily persistent headache (NDPH); 4). hemicrania continua (HC). These subgroups are further divided into those with medication overuse and without medication overuse.

The most recent version of the International Headache Society criteria (ICHD-II), published in 2004 by the International Headache Society (IHS), includes all four types of CDH of long duration, although the term chronic migraine (CM) is used instead of TM, and the definition of CM is much more restrictive, requiring 15 or more migraine days (not headache days) per month. In this article we will use the TM criteria{9}. Although most previous research focused on adults, CDH is also a major problem in children and adolescents{10}. According to this study, using the first edition of the IHS criteria (ICHD- 1), the authors could not classify 64% of patients. Using a restrictive version of the S-L criteria they were able to classify twice as many patients{11}. This study classified TM just in patients with a history of transformation. The S-L criteria allow the classification of TM even when a history of transformation is not obtained, if another link with migraine can be demonstrated{7}.

Migraine begins before the age of 20 in most adults with the disorder{12}. The differences between CDH in the pediatric and adult populations are poorly studied. It is possible that biologic and environmental influences play different roles in adults and adolescents. Accordingly, the aims of this study are 1) to determine the relative frequency of CDH subtypes



in adolescents, using a large clinical series from a headache clinic, and 2) to contrast the distribution of the CDH subtypes and the influence of medication overuse in adolescents and adults, overall and stratified by sex and age.

II. METHODS:

Adolescents (13 to 21 years of age) and adults (22-35 years or older) with CDH were recruited from a headache clinic between november 2019 to august 2021. All patients had primary CDH according to the S-L criteria,{7} and were classified into TM with (TM+) and without (TM_) medication overuse, CTTH, NDPH, and HC. All subjects were assessed using standardized intake forms and daily headache calendars. Adolescents and adults were assessed by the same physicians.To be included in this study, patients had to have been followed in the clinic for more than 3 months with one of the subtypes of CDH, providing headache calendars for this time period. During the entire study period, the clinic used a uniform clinical intake form and standardized headache calendars. Information was collected by the same physician using standardized questionnaires, regarding the following: 1)

intensity of pain (fourpoint scale indicating severe, moderate, mild, or no pain); 2) frequency of pain at the time of the first visit (reported to all intensities of pain) and at onset; 3) location of pain (unilateral, bilateral, alternating sides); 4) quality of pain (throbbing, squeezing, steady, knife-like, or other); 5) duration of pain; 6) premonitory features; 7) aura (description and frequency); 8) associated symptoms (nausea, anorexia, vomiting, photophobia, phonophobia, osmophobia, dizziness, red eye, ptosis, tearing, miosis, or other); 9) relationship between pain and physical activity and description of the patient's behavior during the headache. The questionnaire has been described in detail elsewhere{5}.

Data were analysed using SPSS software.Means were compared using the unpaired t-test with Welch correction after the KS normality test. Proportions were compared using the χ^2 test in tables of contingency. When the expected value of a cell was small or null, we used the Fisher exact test for proportions. The proportions of the CDH subtypes by age were analyzed with the χ^2 tests for trends.A p value of <0.05 was considered stastically significant.

Table 1 : Demographics and clinical characteristics of adolescents and adults with primary headache

Characteristics	Adolescents, n =150	Adults, n=150	p Value
Age at onset of episodic headache, y, mean (SD)	13.4 (2.9)	25.2 (16.2)	<0.0001
Age at onset of CDH, y, mean (SD)	14.5 (3.2)	27.2 (13.1)	<0.0001
Interval from onset of episodic headache to onset of CDH, y, mean (SD)	2 (0.9)	8.5 (4.2)	<0.0001
Duration of CDH, y, mean (SD)	2.2 (3.1)	16.9 (13.3)	<0.0001
Percentage female	59	62	<0.04
Medication overuse, % of subjects	34.6	64.7	<0.0001
Headache days per month, mean (SD)	22.1 (7.0)	27.5 (6.1)	<0.0001



III. RESULTS :

Our sample consisted of 150 adolescents and 150 adults with primary CDH of long duration. The detailed demographic characteristics of the adolescent and adult populations were reviewed elsewhere{13}. While most adults with CDH were female (61%), the female predominance was not as evident in the adolescent group (50%) ($p < 0.05$). The mean age in the adult group was 30.2 years; in the adolescent group it was 15.2 years. Compared to adults, adolescents reported an earlier age at episodic headache onset (at age 13.4 vs 25.5, $p < 0.0001$). CDH itself also began earlier in adolescents than in adults (14.5 vs 27.2 years, $p < 0.0001$). Adolescents also had fewer days of headache per month than adults (22.1 vs 27.5, $p < 0.0001$), and medication overuse was much less common in adolescents than adults (34.5% vs 64.7%, $p < 0.0001$) (table 1).

We were able to classify all adolescents and adults using the S-L criteria. The majority of the adolescents had TM (66.4%), mainly TM₋ (57.4% of the TM). NDPH (24.1%) was the second most common form of CDH in adolescents and, again, it was usually not associated with medication overuse; only 23% of the NDPH patients overused medication. CTTH was diagnosed in only 12.3% of the adolescents (not associated with medication overuse in all cases). We did not find any cases of HC in the adolescent group.

Among adults, TM with overuse was the most frequent diagnosis (64.2%), followed by TM without overuse (26.5%). NDPH without overuse was diagnosed in 49 (7.6%) subjects, while NDPH with overuse occurred in 28 (3.6%). CTTH was diagnosed in 9 (0.9%), while HC occurred in 6 (0.7%). Therefore, differences in the relative frequency of TM were accounted for by TM₊ (29.4% vs 64.5%, $p < 0.001$). In fact, TM₋ was more common in adolescents than in adults (42.5% vs 26.9%, $p < 0.0001$)

(table 2).

These relationships held true after stratifying by sex. The relative frequency of TM₋ was greater in female adolescents than in female adults (41.5% vs 25.5%, $p < 0.001$), and in male adolescents than in male adults (36.5% vs 23.5%, $p < 0.02$). The relative frequency of TM₊ was lower in female adolescents than in female adults (24.2% vs 68.3%, $p < 0.001$), and in male adolescents than in male adults (34.3% vs 55.8%, $p < 0.001$). NDPH with medication overuse was also more common in male adolescents (figure 1). We also compared both groups stratified by age (figure 2). The proportion of TM₊ sufferers increased in every single age assessed until the age of 50 years, while the proportion of TM₋ decreased with age ($p < 0.0001$, test for trends). The prevalence of NDPH also decreased with age ($p < 0.01$, test for trends). We did not assess trends for CTTH and HC due to our small sample.

Diagnoses	Adolescents N=150 (%)	Adults N=150 (%)	P-value
Transformed Migraine	100 (66.4)	131 (87.4)	<0.001
With medication overuse	35 (29.4)	94 (64.5)	
Without medication overuse	65 (64.2)	37 (26.5)	
NDPH	35 (24.1)	16 (10.8)	<0.001
With medication overuse	8 (3.5)	5 (3.3)	
Without medication overuse	27 (15.8)	11 (7.5)	
Chronic tension type headache	15 (10.1)	2 (0.9)	<0.001



With medication overuse	Without medication overuse	0 15 (10.1)	1 (0.5) 1 (0.4)	
Hemicrania continua		0	1 (0.8)	NS

Table 2 :Diagnoses for primary chronic daily headache in adolescents and adults in our sample

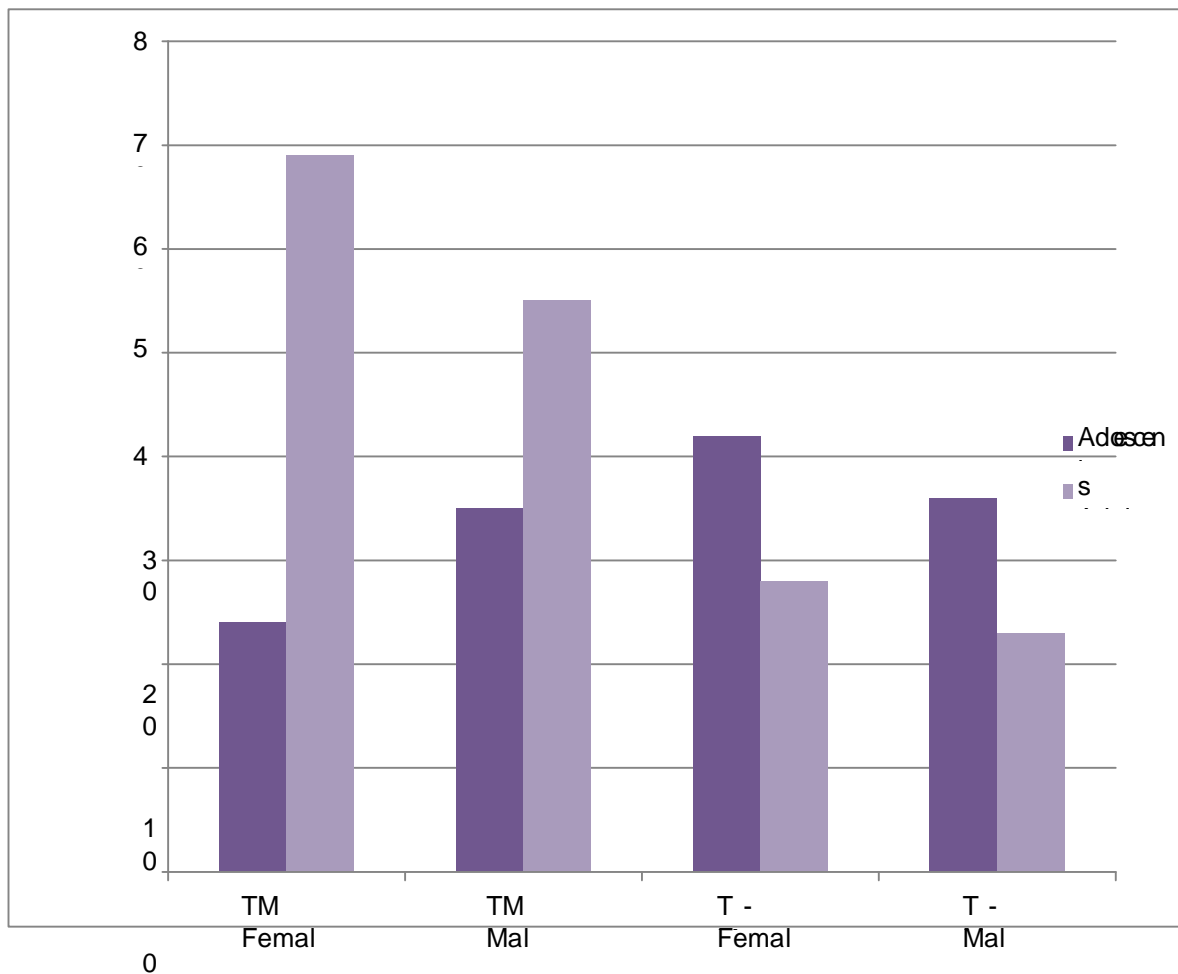


Figure 1. Relative frequency of transformed migraine, among adolescent and adult chronic daily headache sufferers, stratified by sex. TM+ transformed migraine with medication overuse; TM- transformed migraine without medication overuse; $p < 0.001$.



Royal bars = adolescents; Grey bars = adults.

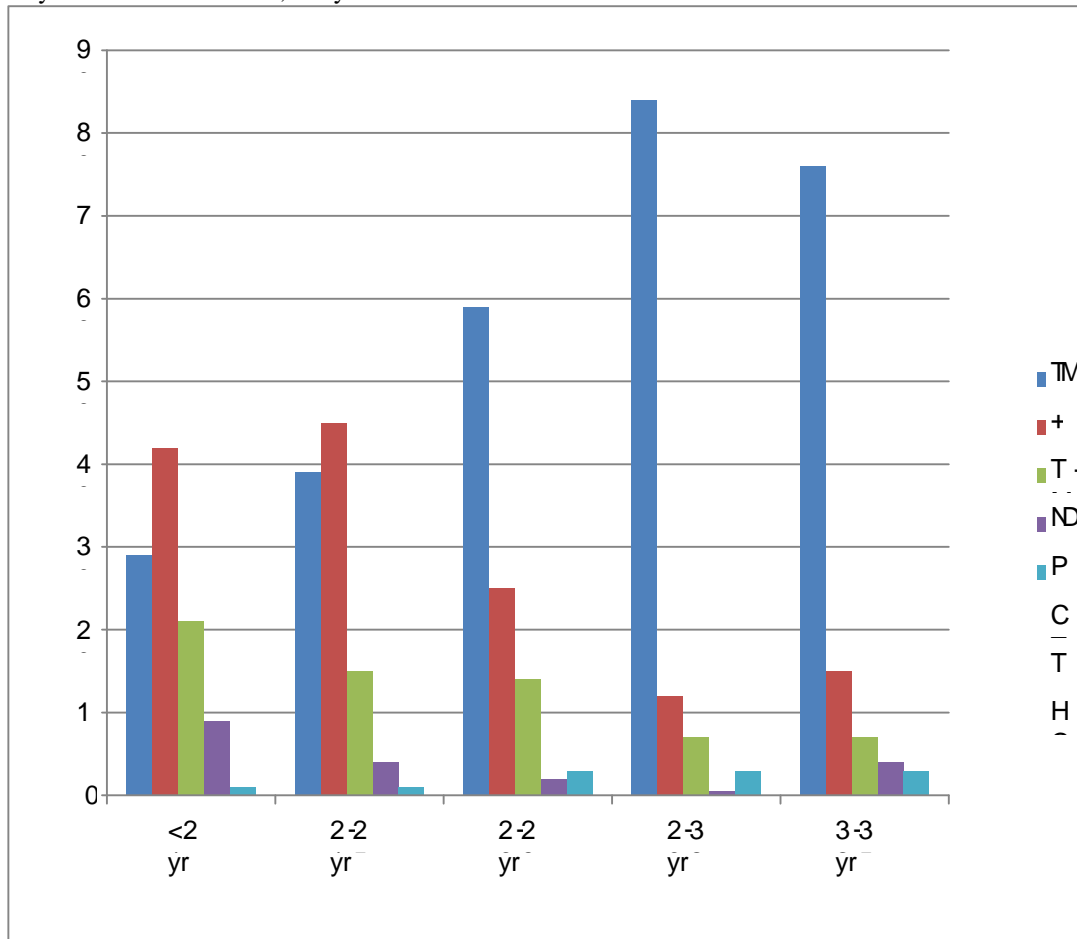


Figure 2. Chronic daily headache subtypes stratified by age. The p values of the chisquare for trends are presented in the text.

IV. DISCUSSION :

CDH, a major problem in children and adolescents, is often not effectively treated{14,15} in part because diagnostic criteria remain controversial{16-19}.The present study shows that the S-L criteria can be used to classify adolescents with CDH. Not surprisingly, in comparison with adults, there were some important differences in CDH in adolescents. Adolescents with CDH report earlier ages at onset for both episodic and chronic daily headache (see table 1). Adolescents with CDH also have fewer days with headache per month; however, both groups present with near-daily headaches. There are important differences in the relative frequency of CDH subtypes among adolescents and adults. Our study showed that TM accounts for 70% of CDH in the adolescent population, in comparison with 89% in adults.

While medication overuse was present in 108 of 150 adults with TM (72.5%), it occurred in

only 64 of 150 adolescents with TM (42.6%). In other words, the minority of adolescents with TM overuse medication.

There are several possible explanations for this observation. One possibility is that medication overuse is largely a consequence of frequent headache, a treatment taken in response to pain. Perhaps there is less medication overuse in adolescents because they have less access to medications than adults. Alternatively, for a range of neurologic disorders, early onset cases have the highest level of biologic or genetic risk{22,23}.Under this hypothesis, adolescents with CDH, by virtue of greater genetic risk, may be less likely to require an environmental exacerbating factor such as medication overuse. A third hypothesis is that environmental risk factors for CDH other than medication overuse play a major role{24}.For example,there is some evidence that stressful life events during childhood are risk



factors for CDH in adolescents{25}, although these events also operate in adults{24}.

These three explanations are neither exhaustive nor mutually exclusive. As a first step toward exploring them we examined the relative frequency of TM_ as a function of age. If medication overuse is low in adolescents solely because of limited access, the relative frequency of TM_ should be uniformly elevated through adult life. Similarly, if some special environmental risk factor operates in adolescence, the relative frequency of TM_ should be flat in adult life. If there is a gradient of age-associated biologic risk, and medication overuse plays an increasingly important role as biologic risk decreases with age, we would predict that the relative frequency of TM_ would increase across the life span. As figure 2 illustrates, the data are compatible with the last hypothesis.

An alternative explanation for these data is that medication overuse is associated not with the onset of CDH, but with the persistence of CDH. As a consequence, CDH would persist into older ages among those who overuse medication. NDPH was the second most common CDH within our adolescent sample. It was relatively more common than in adults. This is supported by the literature data. A prior study assessing the relative frequency of CDH subtypes in adolescents found that 36% of them were classified with NDPH{26}. A retrospective chart review carried out from a computerized database to identify patients with NDPH using the S-L criteria showed that the age at onset of NDPH ranged from 12 to 76 years. The peak age at onset was the second and third decade in women and the fifth decade in men. In our sample most of the adolescents with NDPH were female (mean age 14.5){27}.

While most studies of adults show that CDH is more common in women{18-21}, we found a less prominent female predominance in adolescents. Most cases of overusing medication were in male adolescents. Other studies have reported a higher relative frequency in adolescents. In this study, as in ours, medication overuse was not present in most cases (reported by 42% of patients). Interestingly, male sex was associated with a higher degree of reported disability in the study{11}. These results should be interpreted cautiously. Because this is a clinic-based study, we refer to the relative frequency, not the prevalence of disorders under study, because the population denominator is not known. Further, factors that lead to subspecialty consultation, particularly factors that may operate differentially in

adolescents and adults, may influence study results. Additionally, because adults were requested to provide information on a chronic disorder beginning several years before, recall bias is more likely in this group. Finally, we did not assess headache-related disability in our current study. Different disability profiles could at least partially explain different findings. However, in a previous study we showed that the vast majority of adolescents (82%) and adults (78%) presenting in a headache clinic with CDH were severely disabled{13}. CDH in the adolescent population has several particularities.

NDPH and CTTH are more common than in adults and medication overuse is less common. We found that the relative frequency of TM_ increases with age in the adult population. We suggest that adolescents with the early onset form of the disease may be at increased biologic risk, and so less dependent on environmental risk factors such as medication overuse for CDH to develop. This hypothesis requires further testing in representative samples. Finally, the S-L criteria, when used with detailed headache histories and headache diaries, are adequate to classify CDH in adolescents

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