

1 **Internalizing disorders rather than ADHD are risk factors for chronicity in**
2 **pediatric migraine patients**

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Abstract

Background/aim: Migraine is a prevalent neurological disorder that can lead to disability in children and adolescents. It is frequently accompanied by psychiatric comorbidities, both internalizing and externalizing disorders. While the relationship between migraine and internalizing disorders has been studied, there is limited research on the link between migraine and attention deficit hyperactivity disorder (ADHD).

Materials and methods: A total of 280 pediatric headache patients 107 with externalizing (ADHD) or 173 with internalizing disorders (depression and/or anxiety) were included. The data set was composed using the Turkish headache database, Mersin Branch. Pain characteristics, associated symptoms, and accompanying comorbidities were evaluated retrospectively.

Results: 204 patients were followed up with episodic migraine (EM) and 76 patients with chronic migraine (CM). 146 boys and 134 girls were evaluated, and internalizing disorders were more common in girls ($p < 0.001$). It was a much more prominent accompaniment in chronic migraine internalizing disorders ($p = 0.038$). EM, on the other hand, was more frequent in ADHD. Pain intensity and frequency were higher in those with internalizing disorders ($p = 0.007$), while photophobia was more prevalent in ADHD (OR; 0.555, $p = 0.044$). Moreover, we observed that individuals with internalizing disorders were predominantly female ($p = 0.003$) and had a higher mean age ($p < 0.001$) in comparison to those with externalizing disorders.

Conclusion: Internalizing disorders seem to be a risk factor for migraine chronification in pediatric migraine. ADHD is a prototypic externalizing disorder more associated with EM. This outcome provides an opportunity to follow our patients in terms of prognosis and offers us a better evaluation chance. Identifying factors that contribute to the

1 chronicity of migraine may lead to better management and a reduced disability for
2 migraine sufferers.

3 **Key words:** Migraine, childhood, chronification, internalizing, externalizing,
4 frontostriatal circuit

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1 **1. Introduction**

2 Primary headaches are the most common manifestation of pain in childhood and
3 adolescents and significantly impact on children's quality of life [1]. Migraine affects
4 9.1% of children and adolescents globally, making this condition a common concern for
5 many patients and their doctors [2]. Migraine in children has a high risk of chronification
6 and psychiatric comorbidities are an important risk factor for this chronification [3,4].
7 Psychiatric disorders can be classified as externalizing and internalizing disorders
8 although these terms are not used in the Diagnostic and Statistical Manual of Mental
9 Disorders (DSM) [5,6]. Externalizing behaviors and disorders are mainly identified by
10 actions in the outside world; such as hostility, aggression, acting out, and antisocial
11 behavior. On the other hand, internalizing behaviors and disorders are mainly identified
12 by processes that occur within oneself, such as depression, anxiety, and somatization.
13 Externalizing disorders are characterized by observable behaviors, such as attention-
14 deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, antisocial
15 personality disorder, and substance use disorders. Internalizing disorders, on the other
16 hand, are characterized by inward and non-observable processes, such as mood disorders
17 (e.g., major depressive disorder, dysthymia) and anxiety disorders (e.g., generalized
18 anxiety disorder, separation anxiety disorder, phobias, obsessive-compulsive disorder).
19 These terms are often used in research and clinical practice as a way to group similar
20 disorders and understand the underlying factors. Although internalizing and externalizing
21 psychopathology are separate based on their characteristic symptoms and behaviors, both
22 of them can be seen at the same time in the same person [7].
23 Again, the early maladaptive schemas (EMS) of these patients differ between
24 internalizing and externalizing disorders. EMS are deeply ingrained, self-defeating

1 patterns of thoughts, feelings, and behaviors that develop during childhood as a result of
2 negative experiences and innate temperament. These schemas are enduring and pervasive,
3 influencing the individual's perceptions of themselves, others, and the world around them.
4 They often lead to negative emotions, maladaptive behaviors, and interpersonal problems,
5 and can contribute to the development of various internalizing and externalizing
6 disorders. For example, two EMS, social isolation and vulnerability to harm/illness,
7 explained 45% of the variation in internalizing problems. Furthermore, the EMS of
8 entitlement/grandiosity and dependence/incompetence accounted for 19% of the variation
9 in externalizing problems, according to the same study [8]. EMS clearly illustrates our
10 thought patterns, such as coping strategies, and may be related to our temperament,
11 characteristics of headaches, and our prognosis. Since different schemas are defined in
12 internalizing and externalizing disorders and these schemas are considered to have an
13 effect on migraine, internalizing and externalizing disorders should be investigated in
14 detail in this respect [9]. Recent studies have also demonstrated that individuals with
15 migraine and comorbid internalizing disorders exhibit frontostriatal circuit dysfunction,
16 which plays a crucial role in the pathophysiology of these disorders [10,11]. Furthermore,
17 it was reported that individuals with migraine had significantly reduced striatal dopamine
18 transporter availability, indicating frontostriatal circuit dysfunction in migraine. It would
19 be useful to look at patients from this perspective [12].

20 Internalizing and externalizing symptoms are important in chronicity associated with
21 psychiatric comorbidities. A high level of internalizing and externalizing symptoms was
22 found to be associated with a lower chance for remission in headache syndromes [13].
23 Internalizing disorder is focused on the own self, externalizing disorder particularly
24 occurs in interaction with the social environment. Internalizing symptoms primarily

1 include anxiety and depressive symptoms, while externalizing symptoms include
2 aggressive behavior, anger and hyperactivity correlated with headache in children and
3 adolescents [14]. We know that there is a bidirectional relationship between headaches
4 and psychopathology in children and adolescents. Headache leading to psychiatric
5 symptoms contributes to missed school days, poor cognitive functioning, and
6 family/friend relationships, conversely, the presence of psychopathology, especially
7 internalizing disorders leads to somatic complaints and headache [3]. Children with
8 internalizing disorders are more stressed and introverted by nature. Therefore, it is
9 thought that these children will have more somatic complaints and headaches, so its
10 relationship with headaches has been studied more. Whereas previous research has
11 reported associations between headaches and internalizing disorders, particularly
12 depression and anxiety, recent research has shown that headaches are also common in
13 externalizing disorders [15,16]. For example, migraine was found to be approximately
14 2.5 times more common in ADHD, which is one of the externalizing disorders [17]. The
15 EPICPAC-T (Epidemiology of Childhood Psychopathology in Turkey), the largest
16 epidemiologic face-to-face survey of school-age children in Turkey, found ADHD is the
17 most common disorder with (19.5%) and without impairment (16.7%) among 6- to 13-
18 year-old school children. Again, oppositional defiant disorder (ODD) and conduct
19 disorder (CD), types of disruptive behavior disorders, are frequently seen in children and
20 adolescents with the rate of 3.44% and 0.36% respectively [18]. Likewise, depression and
21 anxiety are common in children with a prevalence of 6.2% and 3.2%, respectively [19].
22 Due to the high incidence of these diseases and the high correlation between migraine
23 and these diseases, it becomes important to investigate the characteristics of migraine in
24 these diseases. Since migraine has a high disease burden and causes severe disability, we

1 thought that determining the characteristics of migraine would contribute to the
2 management of headaches in these diseases and give an idea about its possible course.
3 Based on this, we searched for possible clinical clues to migraine differences in
4 internalizing and externalizing disorders. To add evidence to the preexisting research,
5 here we aimed to describe the migraine characteristics in externalizing and internalizing
6 disorders.

7 **2. Materials and methods**

8 **2.1. Study design and data collection**

9 This study was planned as a single-center, retrospective, observational, comparative case
10 series. In this study, we included 173 patients with internalizing disorders and 107 patients
11 with externalizing disorders among the headache patients, a total of 280 children and
12 adolescents, we followed together between 2018 - 2022. The data set was composed using
13 the Turkish headache database, Mersin Branch. All patients' information was in this
14 database in detail.

15 In this study, a child and adolescent psychiatrist conducted face-to-face psychiatric
16 interviews with all patients and their parents. She asked for teacher observation forms to
17 elaborate on psychiatric anamnesis if necessary. All psychiatric disorders were diagnosed
18 according to DSM - IV diagnostic criteria by the same child and adolescent psychiatrist.
19 According to the DSM - IV diagnostic criteria, patients with ADHD, oppositional and/or
20 conduct disorder were classified as having externalizing disorder, while those with
21 depression and/or anxiety disorders (generalized anxiety disorder, social phobia, panic
22 disorder, and obsessive-compulsive disorder) were evaluated as having internalizing
23 disorders. The study included 173 patients with internalizing disorders, including
24 depression (n = 47), anxiety disorder (n = 68), obsessive-compulsive disorder (n = 32),

1 and depression with anxiety (n = 26). The study also involved 107 patients with
2 externalizing disorders, including ADHD (n = 77), ADHD with ODD (n = 23), and
3 ADHD with conduct disorder (n = 7). We excluded the patients who had both
4 internalizing and externalizing disorders from the study. Patients with mental retardation,
5 psychotic disorder, bipolar disorder, pervasive developmental disorder, alcohol and
6 substance abuse, and tic disorder were excluded.

7 The study subjects were younger than 18 years of age and had migraine, including 46
8 cases migraine with aura (MwA), 158 cases migraine without aura (MwoA), and 76 cases
9 chronic migraine (CM). The classification of migraine was based on The International
10 Classification of Headache Disorders, 3rd edition (Headache Classification Committee,
11 2018) [20]. Patients with "headache-plus" diagnosis (e.g., migraine plus tension type
12 headache) were excluded from the study. All patients underwent a neurological
13 examination following a complete psychiatric evaluation. During face-to-face interviews,
14 we noted the presence of migrainous features (nausea, vomiting, photophobia,
15 phonophobia, and aggravation by physical activity), osmophobia, headache frequency,
16 presence of aura, localization, intensity of pain according to the visual analog scale
17 (VAS), and attack duration. In addition to demographic data, we recorded the presence
18 of psychiatric illness in their parents, the presence of stress, and the duration of education
19 of the subjects.

20 **2.2. Statistical analysis**

21 For data entry and analysis, we used the TIBCO Statistica version.13.5.0.17 program. The
22 results are given as 95% confidence intervals, and $p < 0.05$ was considered significant.
23 We used the Shapiro-Wilk test to assess the normality of continuous variables. Non-

1 parametric methods were used because continuous variables were not normally
2 distributed. We used the Mann Whitney U test for comparing two independent groups
3 and the Chi-square test in the analysis of categorical data. Multiple logistic regression
4 backward elimination method was used for variables that may influence internalizing and
5 externalizing disorders.

6 **3. Results**

7 Our study evaluated a total of 280 participants, including 146 boys (52.1%) and 134 girls
8 (47.8%). There were differences between the patient groups regarding age and gender
9 distribution for both boys and girls. Participants in the internalizing group were
10 significantly older than those in the externalizing group ($p < 0.001$). Moreover, there was
11 a higher proportion of girls in the internalizing group ($p = 0.003$). Additionally,
12 participants in the externalizing group had slightly lower levels of education than those
13 in the internalizing group ($p = 0.015$).

14 Regarding the presence of psychiatric disorders in parents, 164 patients had data on this
15 matter. The mother and/or father of 53 patients had a history of psychiatric disorder and
16 were significantly higher in externalizing disorders ($p = 0.041$). Further details on the
17 demographic and headache characteristics of the patients is shown below (Table 1).

18 When examining the characteristics of headaches, we found that participants with
19 internalizing disorders had significantly higher levels of pain severity and headache
20 frequency ($p = 0.001$, $p = 0.007$) in comparison to those with externalizing disorders as
21 shown in Table 2. However, there was no significant difference between the two groups
22 in terms of pain duration ($p = 0.097$) and aura. The prevalence of MwoA was significantly
23 higher in the externalizing group, while CM was significantly higher in the internalizing

1 group ($p = 0.038$). The migraine characteristics and related factors are summarized below
2 (Table 2).

3 Our results indicated that there was no significant difference in the distribution of most
4 symptoms between the two groups, including nausea, vomiting, light, sound, and smell
5 sensitivity, as well as physical activity. Similarly, there was no significant difference in
6 pain quality ($p = 0.169$) or in the distribution of pain (unilateral or bilateral headache, p
7 $= 0.602$) between the two groups. Stress and physical activity, which are among the most
8 common triggers, did not differ significantly between the groups ($p = 0.074$ and $p = 0.492$,
9 respectively).

10 Age, gender, nausea, vomiting, photophobia, phonophobia, osmophobia, stress, physical
11 activity, pain frequency, pain duration, pain intensity, localization, and throbbing pattern
12 were included in the multiple regression model to investigate the relationship between
13 internalizing and externalizing disorders. By removing the non-significant variables
14 according to the backward elimination, a meaningful model was formed with the
15 remaining variables in Table 3.

16 The results revealed that photophobia had an odds ratio (OR) of 0.555 (95% CI: 0.313 -
17 0.984) and a p -value of 0.044 for having internalizing disorders. This suggests that
18 individuals with externalizing disorders were more likely to experience photophobia than
19 those with internalizing disorders. Additionally, the severity of pain and headache
20 frequency had positive associations with internalizing disorders, with ORs of 1.370 (95%
21 CI: 1.124 - 1.670) and 1.036 (95% CI: 1.003 - 1.071), respectively ($p = 0.002$; $p = 0.033$).
22 The results also indicated that being female and increasing age were associated with
23 internalizing disorders ($p = 0.008$; $p = 0.009$). These variables, which differed

1 significantly as a result of our study, are summarized in the figure The figure displays
2 clinical clues regarding the course of migraine in internalizing or externalizing disorders
3 (Figure).

4 Our study findings suggest that internalizing disorders may be a risk factor for
5 chronification in pediatric migraine. Being female and increasing age also seem to be risk
6 factors for this chronification.

7 **4. Discussion**

8 Migraine is a common neurological disorder that affects children and adolescents, often
9 causing significant disability. Individuals with migraine may also experience comorbid
10 psychiatric conditions, such as internalizing and externalizing disorders. While research
11 has explored the association between migraine and internalizing disorders, there is limited
12 understanding of the relationship between migraine and externalizing disorders, including
13 ADHD. To address this gap, we conducted a study aiming to better understand the
14 characteristics of migraine in these conditions and identify factors contributing to
15 migraine chronification. Our study findings shed light on the associations between
16 migraine and internalizing and externalizing disorders, providing important insights for
17 the coping with and treatment of migraine in these patients.

18 Most of the cross-sectional studies conducted to date have revealed an association
19 between migraine and many diseases, such as anxiety disorders and depression [21].
20 However, the underlying mechanisms of the relationship between migraine and
21 psychiatric disorders are still unclear. In recent years, the relationship between migraine
22 and externalizing disorders has started to attract attention [16,17].

1 In our study, we investigated whether there was a difference between internalizing and
2 externalizing disorders in terms of migraine characteristics. We found that CM was more
3 common in individuals with internalizing disorders, while EM especially migraine
4 without aura was more common in those with externalizing disorders ($p = 0.038$). From
5 the literature, it is apparent that psychiatric disorders are more common in patients with
6 CM than those with EM, and they increase the risk of chronic headaches and transformed
7 migraine [21]. Similarly, CM was common in our study group (27.1%). The estimated
8 prevalence of chronic daily headaches in children and adolescents ranges from 0.9% to
9 7.8% in studies conducted in several countries [22]. The high prevalence of CM in our
10 study may be due to the fact that we are a specialized headache clinic or comorbid
11 psychiatric disorders.

12 Previous studies have shown that internalizing disorders, in particular, lead to somatic
13 complaints and headaches [3]. In our study, the pain intensity and frequency were found
14 to be riskier in individuals with internalizing disorders than in those with externalizing
15 disorders, as per multiple regression analysis. This suggests that the course of pain is more
16 severe in internalizing disorders and that these disorders contribute to chronicity.
17 Additionally, our study found that the prevalence of female gender was higher in
18 individuals with internalizing disorders, which is consistent with the literature [6].
19 Although there was no difference in terms of migraine characteristics when they were
20 compared individually, photophobia was higher in individuals with externalizing
21 disorders when multiple regression analysis was performed.

22 When the genetic load is considered in terms of biological origin, externalizing disorders
23 are more hereditary, while the genetic load of depression and anxiety is relatively less.
24 Externalizing disorders ADHD, ODD, CD are more long-term disorders with congenital

1 features, while the behavioral aspect predominates, while internalizing disorders are
2 disorders with a predominant cognitive aspect that develop later due to cognitive
3 distortions [23]. The fact that the history of psychiatric disorder in the parents was
4 significantly higher in the externalizing group in our study also supports these data ($p =$
5 0.041).

6 Externalizing disorders are chronic problems that negatively affect school life, home life
7 and peer relations for the child and family, and are unnoticed but create great stress. It is
8 known that as a result of this chronic stress, internalizing disorders such as depression
9 and anxiety disorders are added to the process in the long term, and the frequency of
10 comorbidity increases, especially in adolescence [24]. In this study, it was noteworthy
11 that the age and the frequency of CM were higher in the internalizing disorder group (p
12 $= 0.009$ and $p = 0.038$, respectively). Although we excluded the diagnosis of externalizing
13 disorder in the group with internalizing disorder in the study, longitudinal follow-up
14 studies of individuals with migraine and externalizing disorder at a young age may be
15 informative in terms of defining the determinants of CM.

16 There is limited research exploring the relationship between migraine and externalizing
17 disorders such as ADHD, although promising developments have been identified with
18 regards to their association with frontostriatal circuit dysfunction [25]. Identifying the
19 neurobiological mechanisms underlying these comorbidities and understanding the
20 association between frontostriatal circuit dysfunction and migraine comorbidities are
21 essential for optimal management and treatment of these conditions [10]. In this context,
22 evaluating migraine characteristics in externalizing and internalizing disorders and
23 identifying the factors that contribute to the chronicity of migraine disorders is a crucial

1 step towards better understanding the neurobiological mechanisms of these conditions
2 [26].

3 Although our study shed light on the differences in migraine characteristics between
4 individuals with internalizing and externalizing disorders, there are some limitations that
5 need to be considered. The study only included a relatively small sample size of 280
6 participants, which may not be representative of the entire population of children and
7 adolescents with migraine and comorbid psychiatric disorders. Also, the study was
8 conducted at a specialized headache clinic, which may have resulted in a selection bias
9 towards more severe or chronic cases of migraine. We also did not include a control group
10 of children and adolescents without migraine or psychiatric disorders, which would have
11 allowed for a better comparison of migraine characteristics between the different groups.
12 Finally, the study did not investigate the potential impact of medication use on migraine
13 characteristics in the different groups, which may have influenced the results.

14 The implications of this study highlight the importance of understanding the
15 characteristics of migraine in both internalizing and externalizing disorders, which can
16 aid in the management and treatment of these comorbidities. It is worth noting that the
17 multidisciplinary approach used in this study, which involved both neurology and child-
18 adolescent psychiatry departments, allowed for a more comprehensive evaluation of
19 migraine patients with comorbid psychiatric disorders. Furthermore, the comprehensive
20 dataset used in this study, which included detailed medical histories, physical exams, and
21 neuroimaging studies, provided a more thorough understanding of the characteristics of
22 migraine in individuals with both internalizing and externalizing disorders. This
23 highlights the importance of utilizing a multidisciplinary and comprehensive approach in
24 future studies on migraine and psychiatric comorbidities. Additionally, the design of this

1 study focused on the frontostriatal circuit, a neural network that is known to be involved
2 in a wide range of cognitive and emotional functions, including reward processing,
3 decision-making, and impulse control. By considering the frontostriatal circuit in the
4 context of migraine comorbidities, our study provides a more comprehensive
5 understanding of the neurobiological mechanisms underlying these conditions.

6 In conclusion, the high prevalence of psychiatric disorders in children and adolescents
7 with migraine highlights the need for understanding the headache characteristics and
8 assessing the risk of chronicity in terms of treatment and prognosis, particularly for
9 children and adolescents. This study provides insights into the differences in migraine
10 characteristics between internalizing and externalizing disorders and emphasizes the
11 necessity for further research in this field. Furthermore, the association between
12 frontostriatal circuit dysfunction and migraine comorbidities underscores the importance
13 of investigating the underlying neurobiological mechanisms to enhance the management
14 and outcomes of patients with these conditions. Our study is important in that it is the first
15 to address the characteristics of migraine in internalizing and externalizing disorders.
16 These findings may lead to a reduction in disability and an improvement in the quality of
17 life of affected individuals.

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21 **Conflict of interest**

22 On behalf of all authors, the corresponding author states that there is no conflict of
23 interest.

24 **Informed consent**

1 This study was approved by the local ethical committee of Mersin University (decision
2 number: 9/161, decision date: 12.05.2016) and the procedures were by ethical standards,
3 as well as in accordance with the principles stated in the Declaration of Helsinki. There
4 is no data collected that could potentially identify individual patients. Written informed
5 consent was obtained from the patient themselves who participated in the study and
6 their families.

7 **Author contributions**

8 Conception and design of the study: A.Ö., N.Ö. and G.G.A. Data collection: A.Ö., N.Ö.,
9 G.G.A. Analysis and interpretation of results: N.Ö., A.A.Ö, A.Ö. Writing the first draft:
10 N.Ö. Supervision: A.Ö., G.G.A. All authors approved the final version of the manuscript.

11 **References**

- 12 1. Ozge A, Sasmaz T, Cakmak SE, Kaleagasi H, Siva A. Epidemiological-based
13 childhood headache natural history study: after an interval of six years. *Cephalalgia*
14 2010; 30 (6): 703-712. <https://doi.org/10.1177/0333102409351797>
- 15 2. Wöber-Bingöl C. Epidemiology of migraine and headache in children and
16 adolescents. *Current Pain Headache Reports* 2013; 17 (6): 341. <https://doi.org/10.1007/s11916-013-0341-z>
- 18 3. Fearon P, Hotopf M. Relation between headache in childhood and physical and
19 psychiatric symptoms in adulthood: national birth cohort study. *BMJ* 2001; 322
20 (7295): 1145. <https://doi.org/10.1136/bmj.322.7295.1145>
- 21 4. Guidetti V, Galli F, Fabrizi P, Giannantoni AS, Napoli, L et al. Headache and
22 psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study.
23 *Cephalalgia* 1998; 18 (7): 455-462. [https://doi.org/10.1046/j.1468-](https://doi.org/10.1046/j.1468-2982.1998.1807455.x)
24 2982.1998.1807455.x

- 1 5. Cicchetti D, Sheree LT. Internalizing and Externalizing Expression of Dysfunction.
2 1st ed. New York, NY, USA: Taylor and Francis Group; 2014.
3 <https://doi.org/10.4324/9781315807256>
- 4 6. Babicka-Wirkus A, Kozlowski P, Wirkus L, Stasiak K. Internalizing and
5 externalizing disorder levels among adolescents: Data from Poland. *International*
6 *Journal of Environmental Research and Public Health* 2023; 20 (3): 2752
7 <https://doi.org/10.3390/ijerph20032752>
- 8 7. Cosgrove VE, Rhee SH, Gelhorn HL, Boeldt D, Corley RC et al. Structure and
9 Etiology of Co-occurring Internalizing and Externalizing Disorders in Adolescents.
10 *Journal of Abnormal Child Psychology* 2011; 39 (1): 109-123.
11 <https://doi.org/10.1007/s10802-010-9444-8>
- 12 8. Van Vlierbege L, Braet C. Dysfunctional schemas and psychopathology in referred
13 obese adolescents. *Clinical Psychology and Psychotherapy* 2007; 14 (5): 342-351.
14 <https://doi.org/10.1002/cpp.546>
- 15 9. Aksu GG, Kayar O, Tufan AE, Acarlı AO, Sucu DH et al. A. Early maladaptive
16 schemas in episodic and chronic migraine in adolescents. *Frontiers in Neurology*
17 2023; 14: 1128953. <https://doi.org/10.3389/fneur.2023.1128953>
- 18 10. Coppola G, Di Renzo A, Tinelli E, Lepre C, Lorenzo C et al. Thalamo-cortical
19 network activity between migraine attacks: Insights from MRI-based microstructural
20 and functional resting-state network correlation analysis. *The Journal of Headache*
21 *and Pain* 2016; 17 (1): 100. <https://doi.org/10.1186/s10194-016-0693-y>
- 22 11. Tietjen GE, Brandes JL, Peterlin BL, Eloff A, Dafer RM et al. Childhood
23 maltreatment and migraine (part II). Emotional abuse as a risk factor for headache

- 1 chronification. *Headache* 2010; 50 (1): 32-41. [https://doi.org/10.1111/j.1526-](https://doi.org/10.1111/j.1526-4610.2009.01557.x)
2 4610.2009.01557.x
- 3 12. Dresler T, Caratozzolo S, Guldolf K, Huhn JI, Loiacono C et al. Understanding the
4 nature of psychiatric comorbidity in migraine: A systematic review focused on
5 interactions and treatment implications. *The Journal of Headache and Pain* 2019; 20
6 (1): 51. <https://doi.org/10.1186/s10194-019-0988-x>
- 7 13. KrönerHerwig B, Gassmann J. Headache disorders in children and adolescents: their
8 association with psychological, behavioral, and socio environmental factors.
9 *Headache* 2012; 52 (9): 1387–1401. [https://doi.org/10.1111/j.1526-](https://doi.org/10.1111/j.1526-4610.2012.02210.x)
10 4610.2012.02210.x
- 11 14. Carasco M, Kröner-Herwig B. Psychological predictors of headache remission in
12 children and adolescents. *Adolescent Health Medicine and Therapeutics* 2016; 7: 59-
13 66. <https://doi.org/10.2147/AHMT.S97925>
- 14 15. Pitrou I, Shojaei T, Chan-Chee C, Wazana A, Boyd A et al. The associations between
15 headaches and psychopathology: A survey in School Children. *Headache* 2010; 50
16 (10): 1537-1548. <https://doi.org/10.1111/j.1526-4610.2010.01781.x>
- 17 16. Salem H, Vivas D, Cao, F, Kazimi, IF, Teixeira AL et al. ADHD is associated with
18 migraine: a systematic review and meta-analysis. *European Child and Adolescent*
19 *Psychiatry* 2018; 27 (3): 267-277. <https://doi.org/10.1007/s00787-017-1045-4>
- 20 17. Kutuk MO, Tufan AE, Güler G, Yalin, OO, Altintas E et al. Migraine and associated
21 comorbidities are three times more frequent in children with ADHD and their
22 mothers. *Brain and Development* 2018; 40 (10): 857-864.
23 <https://doi.org/10.1016/j.braindev.2018.06.001>

- 1 18. Ercan, ES, Polanczyk, G, Ardic, UA, Yuce, D, Karacetin G et al. The prevalence of
2 childhood psychopathology in Turkey: a cross-sectional multicenter nationwide study
3 (EPICPAT-T). *Nordic Journal of Psychiatry* 2019; 73 (2): 132-140.
4 <https://doi.org/10.1080/08039488.2019.1574892>
- 5 19. Erskine HE, Baxter AJ, Patton G, Moffitt TE, Patel V et al. The global coverage of
6 prevalence data for mental disorders in children and adolescents. *Epidemiology and
7 Psychiatric Sciences* 2017; 26 (4): 395-402.
8 <https://doi.org/10.1017/S2045796015001158>
- 9 20. Headache Classification Committee of the International Headache Society (IHS). The
10 International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38
11 (1): 1-211. <https://doi.org/10.1177/0333102417738202>
- 12 21. Antonaci, F, Nappi G, Galli F, Manzoni GC, Calabresi P et al. Migraine and
13 psychiatric comorbidity: a review of clinical findings. *The Journal of Headache and
14 Pain* 2011; 12 (2): 115-125. <https://doi.org/10.1007/s10194-010-0282-4>
- 15 22. Seshia SS. Chronic daily headache in children and adolescents. *Current Pain and
16 Headache Reports* 2012; 16 (1): 60-72. <https://doi.org/10.1007/s11916-011-0228-9>
- 17 23. Mikolajewski AJ, Allan NP, Hart SA, Lonigan CJ, Taylor J. Negative affect shares
18 genetic and environmental influences with symptoms of childhood internalizing and
19 externalizing disorders. *Journal of Abnormal Child Psychology* 2013; 41 (3): 411-
20 423. <https://doi.org/10.1007/s10802-012-9681-0>
- 21 24. Loth AK, Drabick DAG, Leibenluft E, Hulvershorn LA. Do childhood externalizing
22 disorders predict adult depression? A meta-analysis. *Journal of Abnormal Child
23 Psychology* 2014; 42 (7): 1103-1113. <https://doi.org/10.1007/s10802-014-9867-8>

- 1 25. Ozge A, Genç H, Aksu GG, Uludüz D. Migraine and frontostriatal circuit disorders:
2 What have we learned until now? *Neurological Sciences and Neurophysiology* 2021;
3 38 (2): 81-89. https://doi.org/10.4103/nsn.nsn_9_21
- 4 26. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric
5 comorbidities of episodic and chronic migraine. *Journal of Neurology* 2013; 260 (8):
6 1960-1969. <https://doi.org/10.1007/s00415-012-6725-x>

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1 **Table 1.** Clinical and demographic characteristics of the study patients.

		Internalizing disorders (n:173)		Externalizing disorders (n:107)		
		Mean±SD (Min-Max)	Median [IQR]	Mean±SD (Min-Max)	Median [IQR]	p
Age		14.52 ± 2.82 (4-18)	15 [13-17]	13.2 ± 2.79 (6-18)	13 [12-15]	< 0.001^a
Education period (year)		6.68 ± 3.3 (0-12)	7 [4-9]	5.81 ± 2.76 (0-11)	6 [4-7]	0.015^a
Gender	Male	78	45.1	68	63.6	0.003^b
	Female	95	54.9	39	36.4	
Psychiatric disorder in parents		12	21.8	41	37.6	0.041^b

2 *a: Mann Whitney U test, b: Chi-Squared test*

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1 **Table 2.** Migraine phenotypic features of the study patients.

		Internalizing disorders (n:173)		Externalizing disorders (n:107)		p
		Mean±SD (Min-Max)	Median [IQR]	Mean±SD (Min-Max)	Median [IQR]	
Headache frequency (day/month)		12.76 ± 8.64 (1-30)	10 [6-16.5]	10.11 ± 7.75 (1-30)	8 [4-15]	0.007^a
Attack duration (minutes)		296.07 ± 351.91 (30-1800)	150 [60-360]	222.24 ± 264.83 (30-1440)	120 [60-240]	0.097 ^a
VAS		7.51 ± 1.41 (4-10)	7 [7-9]	6.96 ± 1.27 (3-10)	7 [6-8]	0.001^a
		n	%	n	%	p
Subtypes	MwA	28	16.2	18	16.8	0.038^b
	MwoA	89	51.4	69	64.5*	
	CM	56	32.4*	20	18.7	
Headache quality	Pressing	39	22.5	32	29.9	0.169 ^b
	Throbbing	134	77.5	75	70.1	
Localization	Unilateral	98	56.6	64	59.8	0.602 ^b
	Bilateral	75	43.4	43	40.2	

Aura	47	27.2	19	17.8	0.071 ^b
Nausea	114	65.9	71	66.4	0.937 ^b
Vomiting	49	28.3	21	19.6	0.102 ^b
Photophobia	109	63.0	71	66.4	0.570 ^b
Phonophobia	91	52.6	58	54.2	0.794 ^b
Osmophobia	63	36.4	30	28.0	0.148 ^b

1 * represents a significantly higher rate, a: Mann Whitney U test, b: Chi-Squared test,
2 MwA: migraine with aura, MwoA: migraine without aura, CM: chronic migraine, VAS:
3 visual analogue scale

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1 **Table 3.** Predictor variables and their association with internalizing disorders.

	Odds Ratio	95% C.I.		p
		Lower	Upper	
Gender	2.058	1.210	3.499	0.008
Age	1.131	1.032	1.240	0.009
Photophobia	0.555	0.313	0.984	0.044
Headache frequency (day/month)	1.036	1.003	1.071	0.033
VAS	1.370	1.124	1.670	0.002
Constant	0.022			0.000

2 *p: Multiple Logistic Regression*

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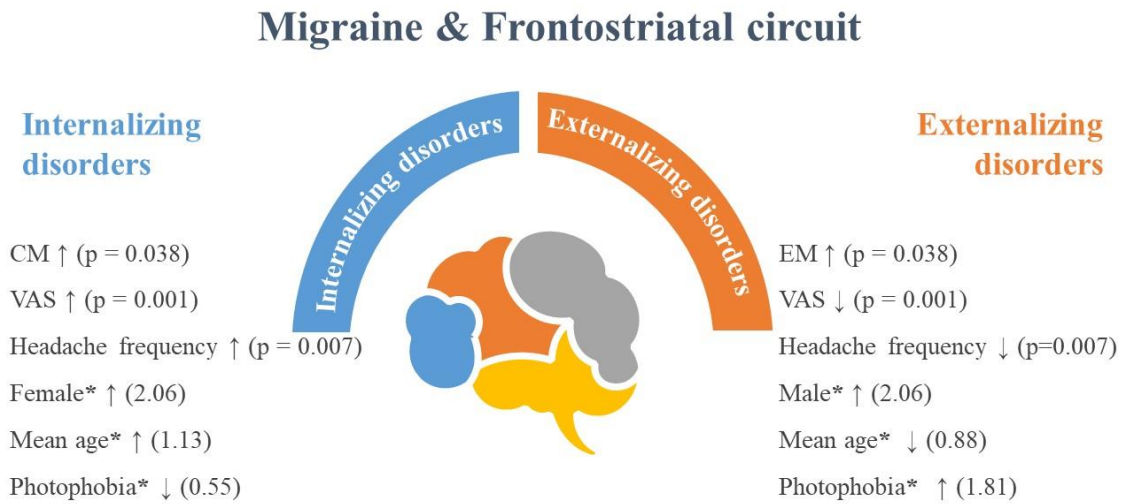
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1 **Figure. Clinical clues of migraine in internalizing or externalizing disorders.**



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3 *CM: chronic migraine, EM: episodic migraine, VAS: visual analogue scale. *Risk*

4 *coefficients were determined by multiple regression analysis*

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