

Primary headache in childhood associated with psychiatric disturbances: an update

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Abstract. – OBJECTIVE: Primary headache disorders in children are one of the most prominent topics in the pediatric neurology literature. However, there are many unsolved aspects, including the conditions associated with migraine. The present study aims to report on the frequency of behavioral comorbidities in the setting of primary headache in childhood.

PATIENTS AND METHODS: In this study, we enlisted 475 children (290 males and 185 females; ratio 1.6:1), aged 4 to 14 years, who were affected by primary headache. In direct interviews, children and parents gave information on the association of their headache with, attention-deficit/hyperactivity disorder, learning disabilities, tics, anxiety, depression, and obsessive-compulsive disorder. Other 475 children with no history of headache or recognized neurological conditions were matched for age, sex, race, and socioeconomic status and were used as controls.

RESULTS: A significant association of primary headache was found with anxiety and depression (p -value <0.001); overall, behavioral disorders were more common in children who experienced headache than in controls (p -value <0.001).

CONCLUSIONS: Primary headache in children is not associated with most of the common behavioral conditions. On the contrary, there was a significant association with anxiety and depression, as reported in adults.

Key Words:

Headache, Psychiatric disturbances, Migraine, Childhood, Movement disorders.

Introduction

Headache frequently occurs among children and adolescents and is one of the most common reasons for medical consultations in childhood. Headache is increasing in frequency from children of 3 years of age onwards, peaking in older children and adolescents. In children, secondary headache due to underlying etiologies are far more common than primary headache due to migraine.

Recognition of the temporal pattern of headache along with focused neurological examination will help in narrowing down the etiology. The key goal in urgent care assessment is to identify children with underlying serious illnesses that require stabilization and urgent referral¹.

Primary headache disorders in children have subdivided in migraine, cluster headache, tension-type headache (TTH), and other (uncommon) types in children. These are one of the most frequent and studied topics in the pediatric specialties, especially in the neurology literature, but some aspects need to be clarify, including the clinical distinction between migraine and TTH, the comorbidity and/or other conditions associated with migraine, and the efficacy of the treatments²⁻⁵. Differently from the childhood in adults, the comorbidity of primary headache disorders with several other conditions has been frequently reported, such as psychological or behavioral disorders or depressive disturbances⁶⁻¹⁵.

The present study aims to report the frequency of primary headache associated with emotional and behavioral disorders in children.

Patients and Methods

This is a case-control study conducted in the outpatient area at the Unit of Pediatrics and Pediatric Emergency at the University Hospital Policlinico-OVE in Catania, Italy, concerning children and adolescents (<18 years) coming from the Eastern provinces of Sicily (Italy) and sporadically from the Western areas. We followed the rule of our Ethics Committee (Ct 12537), as well as the Helsinki Declaration.

A total of 475 patients consecutively diagnosed with primary recurrent headaches from January 2011 to July 2019, according to the ICHD II criteria (International Classification of Headache Disorders, 2nd edition)¹⁰, were included in the case group.

The children's personal history was obtained, and general and neurological examinations were conducted, including blood pressure measurements and routine laboratory tests. Magnetic resonance imaging of the brain was performed in patients with anomalous clinical signs associated with headache. Children with single acute attack, increased intracranial pressure, previous trauma, fever, or other provocative causes of headache were excluded from our study.

A control group of other 475 children with no history of headache or recognized neurological conditions, matched for age, sex, race, and socioeconomic status, was randomly recruited from the same outpatient area.

Statistical Analysis

To establish the statistical significance of differences between groups, the Fisher's exact test and the Chi-square test for observed frequencies and the Student's *t*-test for continuous variables were used, as appropriate. A logistic regression model was used to assess comorbidities associated with headache.

Results

The headache group consisted of 475 children and adolescents comprising 290 males and 185 females. The diagnosis of primary headache was migraine in 114 patients, whereas 361 children

were affected by TTHs: any substantial differences were found between the two groups. Headache was found to be significantly associated with anxiety and depression (27% of children in the headache group vs. 8.3% of children in the control group, $p < 0.001$) but not with other behavioral disorders (Table I). Overall, psychiatric disorders were more common in children who experienced headache than in controls. Finally, the risk analysis showed that children in the headache group had 4.20 odds to have anxiety or depression compared with children in the control group (Figure 1).

Discussion

Primary headache disorders are one of the most common pathology in childhood and adolescence. Moreover, albeit the pathophysiologic mechanism of the headache is looks to be similar each in kids and in adults, the classification, the evolution and therefore the medical aid show great variations⁹⁻¹¹.

In 2013, Costa et al¹¹ hypothesized that mutation in a calcium gene channel renders the individual more sensitive to environmental factors, resulting in a wave of cortical spreading depression when the attack starts. Shah and Kalra³ suggest that the pathophysiology of primary headache involves the neurovascular system and is based on the concept of cortical spreading depression and trigeminovascular activation, followed by transmission through the thalamus to higher cortical structures. On the other hand, Alp et al⁴ have speculated that oxidants play an important role in the genesis of this disorder(s) founding high levels of total oxidants and the oxidative stress index in patients with migraine.

In kids, primary headache disorders have typically been associated to giddiness, childhood periodic syndromes, incontinence and travel illness¹² and this is in contrast to what is seen at adult age¹².

Table I. Sample composition of our patients.

Patients	N = 475
Males	N = 290 (61%)
Females	N = 185 (39%)
Age	4-14 years
Enrolling time	January 2011 to July 2019
Migraine	N = 114
TTHS	N = 361

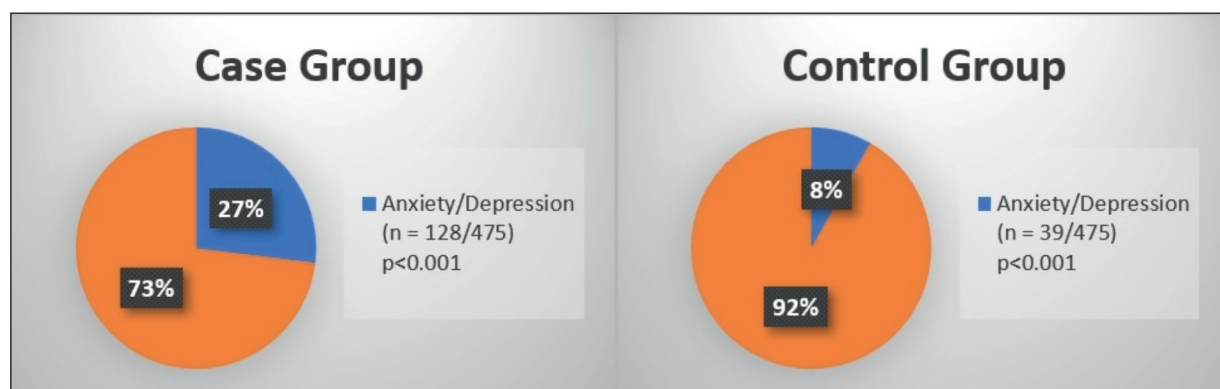


Figure 1. Results in our patients. Differences from the case and control group. Results in our patients' risk analysis showed that children in the headache group had 4.20 odds to have anxiety or depression compared with children in the control group.

One major purpose of discussion, in the literature, is the comorbidity of headache with behavioral and emotional disorders in kids. In the present study, there was no significant difference between the primary headache and control groups in the prevalence of attention-deficit/hyperactivity disorder, tics, obsessive-compulsive disorder, and learning disabilities. On the contrary, there was a significant association with anxiety and depression.

Bruijn et al⁹ found that healthy children had the same percentage to develop thought problems or withdrawn behavior, or social problems, or delinquent or aggressive behavior of children with migraine in a clinical setting. Somatic complaints and internalizing behaviors could also be additional disorders related to headache rather than different psychological or behavioral disorders. These authors concluded that healthy controls children do not exhibit psychological dysfunctions and psychiatric comorbidity compared to children with migraine. In contrast, Pakalnis et al¹³ found significant comorbidity of migraines with signs of an oppositional defiant disorder.

Data from our cluster confirm the above results⁹. However, we showed a big association with internalizing disorders, particularly anxiety and depression. The multiplied risk of depression in adults with headache has been well documented by many authors^{7,8} and Fuh et al¹⁴ found that the association between depressive disturbances and headache are frequent however with freelance impact. Antonaci et al¹⁵, in a study of young and adult patients, reported an increased risk of affective and anxiety disorders in patients with migraines compared with subjects without migraine, especially in patients affected by daily

chronic headache. Psychiatric comorbidity may indeed influence migraine evolution, leading to the chronic use of illicit substances. Isik et al¹⁶ reported that headache is more common and disabling in children who have a lower socioeconomic status. Thus, these children, can have other behavioral problems, or have parents or other relatives with psychiatric or somatic disorders. Isik et al¹⁶ also observed that the incidence of headache could increase for the stress, the poor diet, and/or for restricted access to medical care due to a low socioeconomic status¹⁶.

A lot of studies have linked childhood maltreatment to headache, specially to severity of illness, and also to migraine. Anda et al¹⁷ found a relationship between frequent headache during adulthood and adverse childhood experiences (ACEs). Childhood maltreatment, physical, sexual, and emotional abuse, emotional and physical neglect were significantly associated with chronic migraine and transformed migraine¹⁷. Fearon and Hotopf⁶ concluded that headache in children could have a future negative course in adulthood with a high risk of chronic headache or other different physical and psychiatric symptoms. Their study was a population-based birth cohort and the results obtained showed that headache in childhood are associated with several psychosocial factors. In the same way, Jette et al⁷ asserted that migraine is related to major emotional disorder and bipolar and panic disorders.

Hena et al¹⁸ found the association of depressive symptoms, pain (headache and stomachache), related to analgesic consumption, in addition to the association between depressive symptoms and analgesic consumption among adolescents. Just et al¹⁹ asserted that children and adolescents

with primary headache suffer more often from depression, anxiety, internalizing problems, and somatization than controls. They steered that comorbidity is an important risk factor for chronic primary headache in adulthood.

A robust association between migraine, in patients between the ages of 18 and 65 years, and mood and anxiety disorders, together with depression, dysthymia, manic depression, panic attacks, phobic neurosis and specific anxiety disorder, was observed by Ratcliffle et al⁸. Tension-type headache (TTH) is a frequent type of headache disorder and imposes a significant burden, and there is scant information about the prevalence and impact of comorbid anxiety and depression among individuals with TTH²⁰. Song et al²⁰ reported that the prevalence of anxiety (9.5% vs. 5.3%, $p=0.001$) and depression (4.2% vs. 1.8%, $p=0.001$) was significantly higher than that of non-headache participants. Anxiety and depression were more prevalent in participants with TTH than in non-headache participants. In children with TTH these two conditions become more evident in correspondence of an exacerbation of headache symptoms²⁰. Arruda and Bigal²¹, in their population-based study, confirmed a higher prevalence of anxious symptoms in children and adolescents with migraine. A study of a large sample of schoolchildren in Taiwan reported by Wang et al²², showed that children affected by chronic headache had one or more psychiatric disorders, primarily mood or anxiety disorders, nearly the 47% of the sample of 122 children²². Two years later, the same authors identified a higher frequency of suicidal ideation in younger adolescents with migraine with aura or high headache frequency. These associations were independent of depressive symptoms²³, and Parisi²⁴ stressed that increasing suicide risk was probably related to medication and medicine usage in adolescents with headache. Slater et al²⁵ assessed comorbid psychiatric diagnoses in youth with CDH and showed that 29.6% of CDH patients met the criteria for at least one psychiatric diagnosis. Of those, anxiety disorders were the most common (16.6% of the sample). The most common anxiety diagnoses were specific phobia, generalized anxiety disorder, and obsessive-compulsive disorder. Mood disorders, on the other hand, were less prevalent (9.5%)²⁵.

In addition, Merikangas et al²⁶, found a powerful correlation between migraine, anxiety, and depression, which was also the same for the Young-HUNT Study²⁷. Contrary to what we have

reported. Kowal and Pritchard²⁸ and Laurell et al²⁹ showed a predominance of comorbidity with alternative pains instead of psychological problems issues. For children in the headache group, we recorded a significant association between primary headache, anxiety, and depression, as has been reported in adults. The nature of this relationship is still unknown, as well as if the relationship is specific to migraine or related to attack frequency. However, anxiety, more than depression, predicts the long-term persistence of migraine, TTH, and headache-related disability and reduces perceptions of efficacy with acute treatment³⁰. Some authors recommend that psychiatric disorders may not specifically relate to migraine but to chronic illness, in general, finding no distinction in anxiety and depression levels between migraine and chronic non-headache pain samples³¹. Other scholars³² suggest that common genetic and/or environmental risk factors may underlie both migraine and psychiatric disorders. Children with migraine seem to be characterized by a higher prevalence of familial headache recurrence and parents' psychiatric disorders than children with another headache subtypes³³. Oelkers-Ax and Resh³⁴ found that the transmission could also be environmental instead of genetic, with somatization representing a form of family "style". On the other hand, anxiety and migraine, as well as depression and migraine, are associated with a specific gene polymorphism, supporting the hypothesis of a shared genetic linkage between these conditions³⁵. In the last decades, new genetic risk variants have been identified and associated to psychiatric disorders and to common forms of migraine, but so far, little is known about the possible shared genetic risk factors for psychopathological comorbidities in headache³⁶.

Identification and treatment of comorbid psychiatric conditions are essential to management and prognostication in pediatric headache³⁷. An integrated, medical, and psychological approach in taking care of these young patients and their families is necessary³⁰⁻³⁹. Holroyd et al³⁸ demonstrated that patients with chronic TTH were more likely to experience a clinically significant reduction (50% or more) in headache index scores from psychotherapy (stress management, relaxation training, and cognitive coping therapy) combined with medication than medication alone (64% vs. 38%). These data suggest that a multidisciplinary treatment approach is recommended, and different treatment guidelines should

be implemented for patients with these comorbid psychiatric conditions⁴⁰.

Conclusions

The results we have detected demonstrated that primary headache is a frequent disease in pediatric age and frequently in the literature it is not associated with most of the common behavioral conditions.

The pathophysiology of the headache is presumed to be similar to that in adults, although classification, clinical course, comorbidity, prognosis and therapy show wide differences. In our series, we found an association between headache and anxiety/depression (27% of children in the headache group vs. 8.3% of children in the control group, $p < 0.001$). Moreover, psychiatric disorders were more common in children who experienced headache than in control group. Finally, the risk analysis showed that odds of anxiety and depression in children in the headache group is 4.20 times more frequent than in children in the control group.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

A. F., C. M., R. T., R. F., C. M., F. G., R. F., A. F., P. S., S. M. reviewed the literature, critically discussed various aspects of epilepsy in pediatric patients and read the manuscript; C. R., P. P., D.K. J., R. R., S.Y. C., and S. M., E. P., V. V., A. F. wrote the manuscript and prepared table and figure.

References

- 1) LAKSHMIKANTHA KM, NALLASAMY K. Child with headache. *Indian J Pediatr* 2018; 85: 66-70.
- 2) PAVONE P, RIZZO R, CONTI I, VERROTTI A, MISTRETTA A, FALSAPERLA R, PRATICO AD, GROSSO G, PAVONE L. Primary headaches in children: clinical findings on the association with other conditions. *Int J Immunopathol Pharmacol* 2012; 25: 1083-1091.
- 3) SHAH UH, KALRA V. Pediatric migraine. *Int J Pediatr* 2009; 2009: 424-192.
- 4) ALP R, SELEK S, ALP SI, TAŞKIN A, KOÇYİĞİT A. Oxidative and antioxidative balance in patients of migraine. *Eur Rev Med Pharmacol Sci* 2010; 14: 877-882.
- 5) WINNER P, HERSHEY AD. Epidemiology and diagnosis of migraine in children. *Curr Pain Headache Rep* 2007; 11: 375-382.
- 6) FEARON P, HOTOPF M. Relation between headache in childhood and physical and psychiatric symptoms in adulthood: national birth cohort study. *BMJ* 2001; 322: 1145.
- 7) JETTE N, PATTEN S, WILLIAM J, BECKER W, WIEBE S. Comorbidity of migraine and psychiatric disorders a national population based-study. *Headache* 2008; 48: 501-516.
- 8) RATCLIFFLE GE, ENNS MW, JACOBI F, BELIK SL, SAREEN J. The relationship between migraine and mental disorders in a population based sample. *Gen Hospit Psychiat* 2009; 31: 14-19.
- 9) BRUIJN J, LOCHER H, PASSCHIER J, DIJKSTRA N, ARTS WF. Psychopathology in children and adolescents with migraine in clinical studies: a systematic review. *Pediatrics* 2010; 126: 323-332.
- 10) HEADACHE CLASSIFICATION SUBCOMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY. The international classification of headache disorders. *Cephalalgia* 2004; 24: 1-160.
- 11) COSTA C, TOZZI A, RAINERO I, CUPINI LM, CALABRESI P, AYATA C, SARCHIELLI P. Cortical spreading depression as a target for anti-migraine agents. *J Headache Pain* 2013; 14: 62-69.
- 12) CAROTENUTO M, ESPOSITO M, PASCOTTO A. Migraine and enuresis in children: an unusual correlation? *Med Hypotheses* 2010; 75: 120-122.
- 13) PAKALNIS A, GIBSON MS, COLVIN A. Comorbidity of psychiatric and behavioral disorders in pediatric migraine. *Headache* 2005; 45: 590-596.
- 14) FUH JL, WANG SJ, LU SR, LIAO YC, CHEN SP, YANG CY. Headache disability among adolescents: a student population-based study. *Headache* 2010; 50: 210-218.
- 15) ANTONACI F, NAPPI G, GALLI F, MANZONI GC, CALABRESI P, COSTA A. Migraine and psychiatric comorbidity: a review of clinical finding. *J Headache Pain* 2011; 12: 115-125.
- 16) IŞIK U, TOPUZOĞLU A, AY P, ERSU RH, ARMAN AR, ÖNSÜZ MF, KARAVUŞ M, DAĞLI E. The prevalence of headache and its association with socioeconomic status among schoolchildren in Istanbul, Turkey. *Headache* 2009; 49: 697-703.
- 17) ANDA R, TIETJEN G, SCHULMAN E, FELITTI V, CROFT J. Adverse childhood experiences and frequent headaches in adults. *Headache* 2010; 50: 1473-1481.
- 18) HENA M, LEUNG C, CLAUSSON EK, GARMY P. Association of depressive symptoms with consumption

- of analgesics among adolescents. *J Pediatr Nurs* 2019; 45: e19-e23.
- 19) JUST U, OELKERS R, BENDER S, PARZER P, EBINGER F, WEISBROD M, RESCH F. Emotional and behavioral problems in children and adolescence with primary headache. *Cephalalgia* 2003; 23: 206-213.
 - 20) SONG TJ, CHO SJ, KIM WJ, YANG KI, YUN CH, CHU MK. Anxiety and depression in tension-type headache: a population-based study. *PLoS One* 2016; 11: e0165316.
 - 21) ARRUDA MA, BIGAL ME. Behavioral and emotional symptoms and primary headaches in children: a population-based study. *Cephalalgia* 2012; 14: 1093-1100.
 - 22) WANG SJ, JUANG KD, FUH JL, LU SR. Psychiatric comorbidity and suicide risk in adolescents with chronic daily headache. *Neurol* 2007; 14: 1468-1473.
 - 23) WANG SJ, FUH JL, JUANG KD, LU SR. Migraine and suicidal ideation in adolescents aged 13 to 15 years. *Neurol* 2009; 14: 1146-1152.
 - 24) PARISI P. Migraine and suicidal ideation in adolescents aged 13 to 15 years. *Neurology* 2009; 14: 1713.
 - 25) SLATER SK, KASHIKAR-ZUCK SM, ALLEN JR, LECATES SL, KABBOUCHE MA, O'BRIEN HL, HERSHEY AD, POWERS SW. Psychiatric comorbidity in pediatric chronic daily headache. *Cephalalgia* 2012; 14: 1116-1122.
 - 26) MERIKANGAS KR, ANGST J, ISLER H. Migraine and psychopathology: result of the Zurich cohort study on young adults. *Arc Gen Psych* 1990; 47: 849-885.
 - 27) BLAAUW BA, DYB G, HAGEN K, HOLMEN TL, LINDE M, WENTZEL-LARSEN T, ZWART JA. Anxiety, depression and behavioral problems among adolescents with recurrent headache: the Young-HUNT study. *J Headache Pain* 2014; 15: 38.
 - 28) KOWAL A, PRITCHARD D. Psychological characteristics of children who suffer from headache: a research note. *J Child Psychol Psychiatry* 1990; 14: 637-649.
 - 29) LAURELL K, LARSSON B, EEG-OLOFSSON O. Headache in schoolchildren: association with other pain, family history and psychosocial factors. *Pain* 2005; 14: 150-158.
 - 30) BELLINI B, ARRUDA M, CESCUT A, SAULLE C, PERSICO A, CAROTENUTO M, GATTA M, NACINOVICH R, PIAZZA FP, TERMINE C, TOZZI E, LUCCHESI F, GUIDETTI V. Headache and comorbidity in children and adolescents. *J Headache Pain* 2013; 14: 79.
 - 31) CUNNINGHAM SJ, MCGRATH PJ, FERGUSON HB, HUMPREYS P, D'ASTOUS J, JE L, GOODMAN JT, FIRESTONE P. Personality and behavioral characteristics in pediatric migraine. *Headache* 1987; 14: 16-20.
 - 32) ANTONACI F, NAPPI G, GALLI F, MANZONI GC, CALABRESI P, COSTA A. Migraine and psychiatric comorbidity: a review of clinical findings. *J Headache Pain* 2011; 14: 115-125.
 - 33) GALLI F, CANZANO L, SCALISI TG, GUIDETTI V. Psychiatric disorders and headache familial recurrence: a study on 200 children and their parents. *J Headache Pain* 2009; 14: 187-197.
 - 34) OELKERS-AX R, RESCH F. Headache in children and psychiatric problems. *Psychiatric Times* 2004; 21: 1-2.
 - 35) GONDA X, RIHMER Z, JUHASZ G, ZSOMBOK T, BAGDY G. High anxiety and migraine are associated with a allele of the 5 HTTLPR gene polymorphism. *Psychiatry Res* 2007; 14: 261-266.
 - 36) DYB G, STENSLAND S, ZWART JA. Psychiatric comorbidity in childhood and adolescence headache. *Curr Pain Headache Rep* 2015; 19: 5.
 - 37) KELLY M, STRELZIK J, LANGDON R, DISABELLA M. Pediatric headache: overview. *Curr Opin Pediatr* 2018; 30: 748-754.
 - 38) HOLROYD KA, O'DONNELL FJ, STENSLAND M, LIPCHIK GL, CORDINGLEY GE, GARLSON BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001; 285: 2208-2215.
 - 39) NARDI B, FRANCESCONI G, CATENA-DELL'OSSO M, BELLANTUONO C. Adolescent depression: clinical features and therapeutic strategies. *Eur Rev Med Pharmacol Sci* 2013; 17: 1546-1551.
 - 40) JUANG KD, YANG CY. Psychiatric comorbidity of chronic daily headache: focus on traumatic experiences in childhood, post-traumatic stress disorder and suicidality. *Curr Pain Headache Rep* 2014; 18: 405.