

Neuropsychiatric Comorbidities in a Small Cohort of Adolescents: A Single Centre Study

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Abstract: Headache is one of the most common somatic complaints in children and adolescents. The prevalence is estimated to be 10–20% in the school-age population. Until puberty, it hasn't been seen gender differences (with a slight male predominance), at a later stage it has been noted an increase among females with a ratio of 2.5:1, except that lasts into adulthood. Prevalence of migraine in the pediatric population ranges from 3,3% to 21,4% and it increases from childhood to adolescence. In children and adolescents, headache and migraine are commonly associated with various diseases, such as psychiatric and neurological comorbidity, in particular depression and anxiety, epilepsy, sleep disorders, ADHD. We collected 11 cases of adolescents (14-17 years) all referring to our adult Centre for Headache from January 2019 to October 2020, 9 girls (81%) and 2 boys (19%), ranging from 14 to 17 years. 7/11 (63%) were diagnosed for migraine, 4/11 (33%) for tension-type headache. 4/11 (33%) complained of more than 4 episodes/months. Three patients (2 girls and a boy) were diagnosed with panic attack disorder, 1/11 with major depression disorders, 1/11 with borderline personality disorder (in all of them psychiatric treatment and psychotherapy were promptly started). A 14 years-old young girl received diagnosis of medication overuse headache. In conclusion we performed a small study whose data seem to be coherent with those previously reported in literature. We remark the importance of considering possible neuropsychiatric comorbidities associated with headache in order to assure best treatment of both.

Keywords: Neuropsychiatric, Comorbidities, ADHD.

INTRODUCTION

Headache is one of the most common somatic complaints in children and adolescents [Perquin, C.W. *et al.*, 2000]. The prevalence is estimated to be 10–20% in the school-age population, with progressive increase with age, up to values about 27–32% at the age of 13–14 years (considering monthly crisis), 87–94% (considering the presence of headache at least once a year) [Perquin, C.W. *et al.*, 2000]. Until puberty, it hasn't been seen gender differences (with a slight male predominance), at a later stage it has been noted an increase among females with a ratio of 2.5:1, except that lasts into adulthood [Guidetti, V. *et al.*, 2005; Guidetti, V. *et al.*, 2012]. Prevalence of migraine in the pediatric population ranges from 3,3% to 21,4% and it increases from childhood to adolescence [Bellini, B. *et al.*, 2013]. Tension-type headache (TTH) (prevalence of 20–25%) is the most common cause of primary headache, followed by migraine (prevalence of 8%) [Guidetti, V. *et al.*, 2012]. TTH and migraine were identified as second and third most common diseases all over the world [Abu-Arafeh, I. *et al.*, 2010], and furthermore they are associated with a great number of comorbidities such as anxiety, mood disorder, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), etc. [Bellini, B. *et al.*, 2013; Minen, M.T. *et al.*, 2016]. Although some authors suggested that fundamental cause of migraine in children is largely genetic [Gelfand, A. A. *et al.*, 2015], [Arruda, M.A. *et al.*, 2015] showed in a large

sample of Brazilian children that patients with migraine are at an increased risk of having emotional symptoms, conduct problems, hyperactivity, peer problems, and total difficulties in psychosocial adjustment [Arruda, M.A. *et al.*, 2015].

Furthermore it is widely recognized that headache patients with comorbidity made a greater use of health services, and they have a poor health perception than headache patients without comorbidity [Minen, M.T. *et al.*, 2016; Kalaydjian, A. *et al.*, 2008; Minen, M.T. *et al.*, 2014]. Indeed studies about health-related quality of life (HRQOL) in migraine patients found a poor HRQOL, further reduced when individual had another disorder in comorbidity, especially a mood disorder [Brna, P. *et al.*, 2008; Lipton, R.B. *et al.*, 2000].

Most important psychiatric comorbidities in adolescents with headache are:

Suicide

Suicide is one of the most common causes of death among adolescents [Kyu, H.H. *et al.*, 2016]. Horton has coined the term “suicide headache” because the severity of headache attacks can lead patients to consider suicide. Indeed several studies showed a great prevalence of suicide attempts, suicidal ideation, and intentional self-harm in adults with headache [Aly, Z. *et al.*, 2016]. Wang, *et al.*, in 2007 investigated the prevalence and

correlates of comorbid psychiatric disorders and suicidal risk in community-based adolescents with chronic daily headache (CDH) [Wang, S.J. *et al.*, 2007]. They identified and recruited 122 adolescents with CDH from a non-referral student sample. An in-person psychiatric interview was performed with each subject with CDH to assess depressive and anxiety disorders and suicidal risk based on the Mini-International Neuropsychiatric Interview–Kid (MINI-Kid) [15]. Among a total of 121 subjects who finished the psychiatric interview fifty-seven subjects (47%) had ≥ 1 assessed psychiatric comorbidity with major depression (21%) and panic disorder (19%) as the two most common diagnoses and current suicidal risk was assessed as high (score ≥ 10) in 20% of subjects. Female gender and older age were associated with depressive disorders. Presence of migraine was associated with psychiatric comorbidities. The associations with psychiatric disorders were stronger for migraine with aura than for migraine without aura. Migraine with aura also independently predicted a high suicidal risk (score ≥ 10) [Wang, S.J. *et al.*, 2007].

Learning Disabilities

Several studies showed the burden of pediatric headache on quality of life and its impact on school [Wöber-Bingöl, Ç. *et al.*, 2014]. Learning disabilities affect about 24.7% of children and adolescent with headache [Genizi, J. *et al.*, 2013]. A previous study reported that children with migraine were absent from school activities, did not perform household tasks, and did not participate in leisure activities for 23.9 days, during the last 3 months, because of migraine. The loss of school days due to headache affects school performance, and it is one of the major causes of learning disabilities [Ferracini, G.N. *et al.*, 2014].

Depression

As well as headache, depression is a widespread problem in children, especially among teenagers. Internalizing disorders, just as depression and anxiety, are most frequently associated with primary headaches, and it has been noted that such symptoms are much more common in patients diagnosed with migraine, rather than in people without any pathology [Gesztelyi, G. *et al.*, 2005].

Many researches have studied depressive symptoms in children and adolescents with headache or the incidence of depression in headache population. For example, Blaauw and colleagues noted that children with chronic daily headache had higher depression scores than the

headache-free population [Blaauw, B.A. *et al.*, 2014]. Moreover, children with chronic migraine were more anxious and more depressed than those with chronic tension-type headache, whereas there were no differences between children with episodic migraine and chronic headache. The strong association between chronic migraine and depressive symptoms in children and adolescents is well recognized in literature [Arita, J.H. *et al.*, 2013].

Pavone. *et al.*, (2012) studied the frequency of some comorbidities in primary headaches in childhood. They enrolled two hundred and eighty children (175 males and 105 females), aged 4 to 14 years, affected by primary headaches. In direct interviews, parents and children gave information about the association of their headaches with different conditions. The Authors found a significant association of primary headache with anxiety and depression [Pavone, P. *et al.*, 2012].

Post-Traumatic Stress Disorder (PTSD)

Experiences or the exposition to personal violence, sexual abuse, natural disaster, chronic disease, or other traumatic events can lead to post-traumatic stress disorder (PTSD) [Javidi, H. *et al.*, 2012; Nooner, K.B. *et al.*, 2012]. PTSD has a high prevalence rate among children and adolescents, and it can change according to different traumatic events. Many studies have evaluated somatic symptoms among children with PTSD, and headache is quite common. For example, Zhang and colleagues found that somatic symptoms were frequent in children and adolescents after the Lushan earthquake in China [Zhang, J. *et al.*, 2015]. About 41.7% of children and adolescents suffered from headache 6 months after the earthquake. Generally, childhood adversities may contribute to greater risk of the development of headache and, in particular, chronic daily headache in young adolescents. Many theories suggest the implication of serotonergic, autonomic nervous system, and HPA axis dysfunction underlying both PTSD and migraine [Juang, K.D. *et al.*, 2014]. Also in anxiety disorders, these systems are involved, explaining the high comorbidity rates between anxiety and both migraine and PTSD. The hypothalamic-pituitary-adrenal axis (HPA axis) controls multiple biological, affective, behavioral, and cognitive responses to stress, and its dysregulation may be one mechanism through which stress impacts health. According to these evidences [Lupien, S.J. *et al.*, 2009], Kuhlman and colleagues studied the relationship between trauma and HPA axis activation, and they found different

axis activations according to various types of trauma (exposure to non-intentional trauma, physical abuse, and emotional abuse) [Kuhlman, K.R. *et al.*, 2015].

Anxiety and Headache

Anxiety and depressive disorders are among the most common forms of psychopathology affecting children and adolescents. Anxiety disorders prevalence rates are approximating 15–20% in the general population [Beesdo, K. *et al.*, 2009]. Children with headache often complain internalizing symptoms, and the most frequent are anxiety symptoms. According to Machnes-Maayan and colleagues [Machnes-Maayan, D. *et al.*, 2014], anxiety is present in 68.8% in children with tension-type headache and in 56.3% in children with migraine, compared to 9.1% in children without any pathology.

Also social phobia can coexist with headache [APA, 2013]. This specific phobia is characterized by extreme anxiety and fear of embarrassment during social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. It seems that chronic migraine is strongly associated with high social anxiety score, whereas there are no differences between episodic migraine and population without migraine [Masruha, M.R. *et al.*, 2012; Cappucci, S. *et al.*, 2015]. Anxiety and internalizing symptoms can be linked to fear of pain that could contribute to the maintenance and exacerbation of chronic pain. Higher anxiety sensitivity can lead to a higher fear of pain and consequently to an increased likelihood of headache chronicity. The association between headache and anxiety is not

well known yet, but several theorists highlight the commonality of mechanisms that underlie anxiety and chronic pain, such as serotonergic dysfunction, hormonal influences, dysregulation of the hypothalamic-pituitary-adrenal axis, and/or psychological factors like interoceptive conditioning, fear of pain, anxiety sensitivity, and avoidance behavior [Masruha, M.R. *et al.*, 2012; Cappucci, S. *et al.*, 2015; Laurell, K. *et al.*, 2004].

We collected 11 cases of adolescents (14-17 years) all referring to our adult Centre for Headache from January 2019 to October 2020, in order to assess the presence of psychiatric comorbidities.

METHODS

We collected n= 11 cases of adolescents all referring to our adult Centre for Headache from January 2019 to October 2020, 9 girls (81%) and 2 boys (19%), ranging from 14 to 17 years of age (mean age 16.3 ±0.92). all Caucasian, all originary from Valcamonica (Brescia) a large valley located in the province of Brescia (Lombardy, in northern Italy), and all with both parents originating from Valcamonica with a population of about 100.000 inhabitants (font: Istituto nazionale di STATistica January 2018), without marriages between relatives. All of them started secondary high school but two of them (18.2%) retired. 2/11 (18.2%) are smokers but none of them admitted drug use. 3/9 girls (33.3%), all suffering from migraine without aura, referred of using of assuming oral contraceptives. Only 2/11 (18.2%) practiced some sports.

Demographic and familial data have been collected in table 1.

Table 1: demographic and familial data

Case	Age	Gender	Familiar history for headache	Smoke	School	BMI	Contraceptive therapy	Sport activity (not including gymnastic at school)
1	17	F	no	no	SHS	normal	no	no
2	17	F	no	yes	A	normal	no	no
3	17	F	no	no	SHS	normal	no	yes
4	17	M	no	no	SHS	normal	-	yes
5	17	F	yes	no	SHS	normal	yes	no
6	17	F	yes	no	SHS	normal	yes	no
7	17	F	yes	yes	SHS	normal	no	no
8	17	M	yes	no	SHS	UW	-	no
9	16	F	yes	no	SHS	normal	yes	no
10	14	F	no	no	SHS	normal	no	no
11	17	F	no	no	A	normal	no	no

A= abandoned, BMI: body mass index. SHS: secondary high school. UW: underweighted.

6/11 (54.5%) were diagnosed for migraine of which 5 (84) without aura, and one with visual aura (16%); 4/11 (33%) for tension-type headache. A 14 years- old young girl received diagnosis of medication overuse headache (excessive intake of Nonsteroidal anti-inflammatory drug in a month confirmed by her mother). 5/11 (45.4%) complained of more than 4 episodes/months (we

considered n=4 as cutoff for evaluating prophylactic therapy for headache). None of our girls referred menstrual related -or pure menstrual headache (see figures 2-3) and none of the patients presented diagnostic symptoms and signs suggestive for trigeminal autonomic cephalgias (TACs) or other primary or secondary forms of headache.

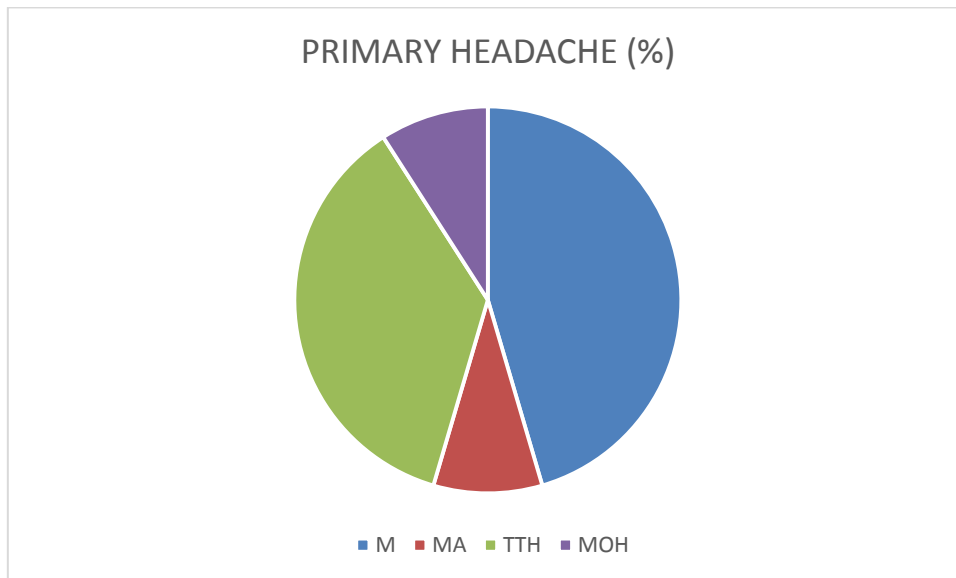


Figure 1: M= migraine, MA= migraine with aura, TTH= tension-type headache, MOH= medical overuse headache

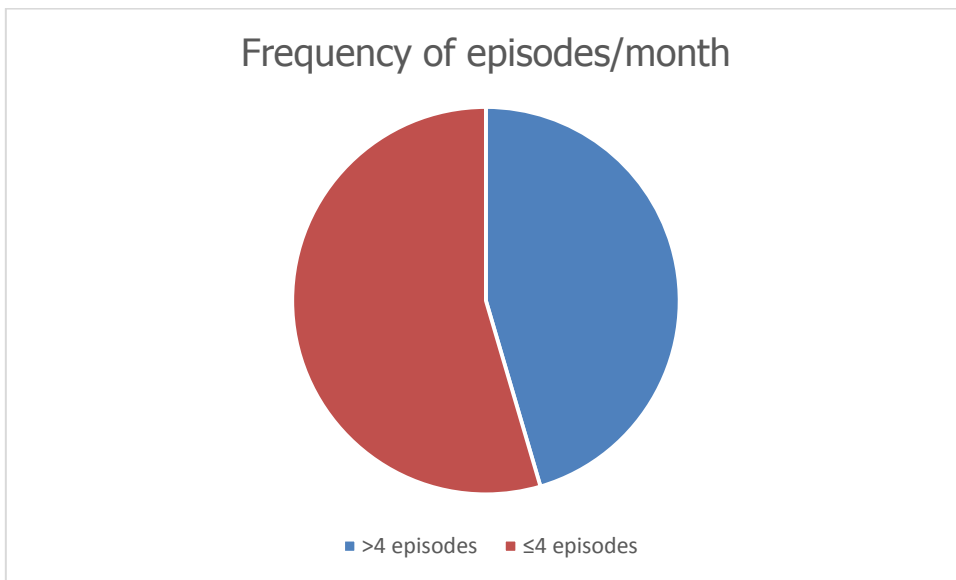


Figure 2: frequency of episodes/months.

Only in a girl magnetic brain magnetic resonance resulted altered (hypothalamic hamartoma associated with isolated trigone dilatation and fusion of the vestibule and Lateral-semicircular canal (LSCC) with precocious puberty, scoliosis, hypercortisolism but normal neurocognitive development and absence of dacristic, gelastic seizures or elements indicative for Pallister Hall

syndrome or neurocognitive development disorders.

Among the adolescents nobody among them referred of learning disabilities or was diagnosed for Attention Deficit Hyperactivity Disorder but two of them, both suffering from panic disorders, admitted many problems involving relationship

with teachers and classmates with consequent “hate for school” while 2/11 affected with to major depressive disorders (MDD) and borderline personality disorder both abandoned high secondary school. All the others referred an average school performance.

Cases with Neuropsychiatric Involvement

Case 2: a 17 years-old girl was initially diagnosed at the age of 16 for migraine without aura (fronto-temporal pain with episodes of nausea and vomit, for which she used to assume NSAIDs if needed). Her brain magnetic resonance resulted negative. She developed a borderline personality disorder (BPD) for which she attempted suicide (defenestration) with consequent politrauma and compartmental syndrome at left lower limb. She abandoned high school and she was evaluated from both psichiaticians and neurologists due to functional neurological disorders (psychogenic seizures, psychogenic hemiparesis, lower limb weakness, persistent headache). Many attempts of treatment with neuroleptics and mood stabilizers failed, such as psychotherapy, due to absence of compliance and discontinuity in assumption of drugs both for headache and BPS. Her boyfriend, a 50 years- old Caucasian man, suffered from the same disorder.

Case 8: a 17 years - old caucasian boy with panic attack disorder. He presented many difficulties at school due to referred problems with many teachers and conflictual relationship with his parents who didn't accept his homosexuality. He presented with chronic migraine (more than 15 episodes in a month) and therapy for attacks was limited due to many drugs intolerances (NSAIDs). His medical history was positive for bronchial asthma. He was evaluated and also in-hospitalized due to chronic TTH. Amytriptilline, duloxetine and sertraline were administered by psichiaticians due to persistent anxiety and depressive mood. He also performed psychotherapy. His problems both psychiatric and headache partially improved at the end of high school.

Case 9: a 16 years-old Caucasian girl suffered from chronic migraine headache without aura and recurrent panic attacks, especially at school (associated with social phobia). She referred persistent frontal and bilateral temporal pulsating pain with recurrent episodes of nausea, phonophobia, photophobia, dizziness, for which she referred persistent difficulty to concentrate and study and for which she referred many problems at school (she used to stay at home about 3-4 days in

a month due to headache) for which she was going to retire. She was treated with amytriptillin as prophylaxis, then with Selective serotonin reuptake inhibitor (SSRI) such as fluoxetine and sertraline according to psychiatrists, such as with behavioral psychotherapy. Her headache slightly improved and now she has decided to continue to study until diploma (and then to attend the college and become a teacher).

Case 11: a 17 years-old Caucasian girl started to suffer from chronic migraine without aura from the age of 14, associated with major depression for which she retired from school. She was followed by psychologist and also by psychiatrist without great benefit and treated with sertraline and amytriptillin. She also abandoned neurological follow up after a couple of evaluations.

DISCUSSION

We analyzed a small cohort of adolescents referring to an adult –center for treatment of headache. We can conclude that results obtained are superimposable to that obtained in literature. First of all our small cohort was composed by women (82%). These data are comparable with those found in other studies who found a greater prevalence in young girl than in boys (even if the opposite occurs before puberty) [Laurell, K. *et al.*, 2004; Sillanpää, M, 1983].

A 1995 review by Silberstein and colleagues extensively summarized existing literature regarding relationships between primary headache disorders and personality traits, focusing on personality measures with well-established validity. They concluded that migraineurs often endorse higher levels of neuroticism, or susceptibility to experience negative affect, than non-migraineurs, in both population-based studies and among samples of convenience [Silberstein, S.D. *et al.*, 1995]. Arguing for a need for further research, they highlighted that most studies on personality and migraine did not control for headache frequency or disability, psychiatric comorbidity, and substance use, and that prior conclusions about rigid, obsessive personality traits might have resulted from selection bias. In the decades since the Silberstein. *et al.* review, numerous studies have attempted to identify personality traits that differentiate migraineurs from those without headache, as well as from those with other headache diagnoses. The previously identified link between neuroticism and migraine has been replicated with some attention to

limitations of earlier studies [Silberstein, S.D. *et al.*, 1995].

Even if we reported a small sample of patients we can confirm the correlation between migraine and psychiatric disorders, already evaluated in literature [Bellini, B. *et al.*, 2013]. Particularly according to literature the case that we reported of borderline personality disorder was a female, presented about 2-3 episodes of headache in month, scarcely responsive even due to scarce/absent compliance and inadequate family background [Rothrock, J. *et al.*, 2007].

In contrast to children and adults, less is known about the association between major depressive disorder, generalized anxiety disorder, and migraine in older adolescents and college-age individuals. Some studies, combining children and adolescents, have shown an association, with others failing to do so [Dindo, L.N. *et al.*, 2017]. In our case we found a clear relationship with a young girl affected with major depressive disorder with negative familial history for both migraine and psychiatric diseases. MDD and migraine are thought to share some common etiopathological pathways related to psychosocial stress, poor lifestyle habits, avoidance behavior, and biological mechanisms, as well. In the case of our patients psychiatrists found an avoidance behavior (for which also she decided to retire from school and avoid friendships and social relations) together with important psychosocial stress, who was scarcely responsive to pharmacologic treatment.

We observed that two of three patients suffering from panic attack disorders responded to SSRI with benefit on both DAP and headache.

In our small cohort boys seemed to suffer more from tension-type headache. We considered that all of them spent a good part of their afternoons studying without practicing sport activities. 2 of them presented more than 4 episodes in a month and particularly one (who also suffered from panic attacks) experienced more than 15 attacks in a month.

We evaluated that 9/11 of our patients didn't practice any sport activity. According to Bailey [Bailey, R, 2006], participants in physical education and sports experience several benefits. For instance, Talbot [Talbot, M, 2001] asserted that involvement in sports can help children develop respect for their body as well as respect for others. He also stated that sport participation contributes to positive development of mind and

body leading to higher self-confidence, and self-esteem [Talbot, M, 2001]. Global burden of 2016 showed that globally more than 80% of school-going adolescents aged 11–17 years did not meet current recommendations for daily physical activity, compromising their current and future health [Guthold, R. *et al.*, 2020]. Various studies indicated that depression and anxiety symptoms were reduced amongst adolescents when practicing physical activity; an increase in physical activity of about 1 h a week was associated with an 8% decrease in the odds of depressive symptoms in both boys and girls [Rothon, C. *et al.*, 2010]. In a multi-level mixed effects model more frequent physical activity and participation in sport were both found to independently contribute to greater well-being and lower levels of anxiety and depressive symptoms in both sexes [McMahon, E.M. *et al.*, 2017]. The results of most recent epidemiological studies are consistent to show an inverse association between physical exercise and migraine, but it is quite challenging to establish whether physical inactivity may be the cause or the consequence of migraine, since migraine is a well-established disabling condition that may actually limit social and physical capabilities [Lippi, G. *et al.*, 2018]. Overall, a general reduction of frequency, severity and duration of migraine attacks has been observed after the exercise intervention periods, and this has also been frequently associated with a considerable improvement of the quality of life of the affected subject [Lippi, G. *et al.*, 2018]. Consequently we suggested to perform regular sport activity to all our patients (8/11 =72.8% declared to spend more than three hours in a day watching television or playing with videogames or on social media).

In collaboration with psychiatrists we suggested also to all adolescents suffering from migraine and mental diseases that behavioral interventions could provide a treatment option that can enhance or if necessary, replace pharmacotherapy [Faedda, N. *et al.*, 2016]. In fact we think that, according to literature, medications should generally not be prescribed alone but rather in combination with non-pharmacological therapies. Behavioral therapy help maximize long-term therapeutic benefit and ensure compliance with pharmacological treatment, which has been proven a significant problem with headache patients [Faedda, N. *et al.*, 2016]. Unfortunately many adolescents didn't show a high compliance for behavioral therapy and abandoned it. Psychiatrists experienced also some problems with relatives and parents of these

adolescents, who were afraid of social stigma and drug addiction and refused to allow their sons to continue follow up at psychosocial center.

Finally we considered the case of our young girl already affected with chronic migraine with MOH. Studies concerning the etiopathogenesis of MOH in adults are far from being abundant, but studies exploring the same topic in children and adolescents are even fewer [Moavero, R. et al., 2020; Chiappedi, M. et al., 2014]. In this particular case we have to consider the role of familial background of the patient (a very anxious mother who administered her NSAIDs every time she reported headache and easy accessibility for her to drugs that she could take without informing parents). Pakalnis. et al., confirmed the need to study other factors that could contribute to medication overuse, including accessibility of over-the-counter analgesics, perceived over-the-counter drug safety by parents and/or guardians, and also the increasing direct-to-consumer advertising [Pakalnis, A. et al., 2007]. This is relevant also in the actual context, where many adolescents decide what to take without consulting parents and/or a physician.

CONCLUSIONS AND REMARKS

We think that it is very important to recognize precociously possible psychiatric comorbidities in adolescents with diagnosis of headache first of all in order to improve their quality of life, social and scholar functioning but also because treating psychiatric disorders mean treat and improve also headache. A strict alliance with parents, relative, educational institution, psychiatrists and psychologist should be performed in order to care for them, follow them up, ensure compliance in the care pathways (constant drugs intake avoiding abuse, diligence in medical checks).

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