Chapter 8
Comorbidity in Paediatric Headaches

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Abstract Headache and migraine may be associated with a broad variety of comorbid disorders in children and adolescents. In this chapter, we review evidence from population-based and clinic-based studies including somatic as well as psychiatric disorders.

Keywords Headache • Migraine • Comorbidity • Asthma • Allergy • Cardiovascular disorders • Stroke • Epilepsy • Learning disabilities • Sleep disorders • Attention deficit hyperactivity disorder • Tourette syndrome • Depression • Anxiety

8.1 Introduction

Headache and migraine in children and adolescents show an estimated overall mean prevalence of 54.4 and 9.1 % and cause significant burden [1, 2]. Accordingly adequate treatment is mandatory [3–5]. Managing headache in young patients requires a comprehensive view of the problem, not focusing on headache itself but also considering comorbidity, psychosocial aspects and the patients' environments affecting headache frequency [3, 5]. In this chapter, we will review the comorbidity of headache and migraine in children and adolescents and summarize the scientific evidence.

'Comorbidity' is a general medical term that implies an association, more than casual, but probably not causal, between an index disease and one or more coexisting physical or psychiatric disorders [6]. The epidemiology of the comorbidities in children and adolescents with recurrent headache is largely unknown. The majority of the reports on comorbidities are based on observations within headache centres

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and thus have a referral bias. They do provide an estimate of these conditions in patients with frequent or disabling headaches. The pathophysiology of the comorbidities should be expected to be similar to adults with the same conditions. For many of these conditions the exact interrelationship is not known and may be due to a general biological stressor that can be broadly applied, while others may have a more defined aetiology.

8.2 Asthma and Atopic Disorders

Asthma and related allergic disorders including sinusitis are a common problem in children and adolescents. Approximately, 9 % of children and adolescents have asthma, and this increases to 32 % for any allergic condition [7]. Migraine itself has a neuroinflammatory component, and it could be expected that in patients with immunologic or inflammatory conditions, there may be an increased risk of migraine. In two population-based studies from the USA [8, 9], asthma and hay fever were more common in children with headache than in those without headache and asthma, as well as seasonal allergies were more common in adolescents with migraine than in those with 'nonspecific headache'. Two clinic-based studies showed conflicting results. In one study there was no association between primary headaches and atopic disorders [10], whereas in another study, the risk of atopic disorders was significantly increased in migraine compared to tension-type headache (TTH) and in migraine with aura compared to migraine without aura and TTH [11].

The underlying aetiology of a possible comorbidity of migraine and atopic disorders might be due to an inflammatory disorder or due to the stress of two chronic conditions and therefore be a generic comorbid response. Regarding pharmacological treatment of migraine in patients with comorbid asthma or atopic disorders, the risk of sensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) must be considered, and beta-blockers should not be used for migraine prophylaxis to avoid exacerbation of asthma.

8.3 Cardiovascular Disease

In adults there may be a relationship between cardiovascular disease and migraine. This has not been well described in children. As many of the cardiovascular syndromes in children are due to congenital heart defects, there may be a degree of compensation by the time the patients begin to express their migraine. The correlation between migraine and patent foramen ovale (PFO) is debatable. In a review published in 2008 [12], the authors identified 134 articles and included 18 which met a priori selection criteria. The estimated strength of association between PFO and migraine, reflected by summary odds ratios (ORs), was 5.13 [95 % confidence interval (CI) = 4.67–5.59], and between PFO and migraine with aura, the OR was

3.21 (95 % CI = 2.38–4.17). The grade of evidence was low. The association between migraine and PFO was OR 2.54 (95 % CI = 2.01–3.08). The grade of evidence was low to moderate. Six studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence. In a review from 2016 [13] including the only two studies in children [14, 15], the authors suggest to close the debate on PFO and migraine and they emphasize the low quality of the studies. According to this review, in patients with PFO, the prevalence of migraine ranged between 16 and 64 %, and in patients with migraine, the prevalence of PFO ranged between 15 and 90 %. Observational studies that examined the effect of PFO closure on migraine showed a wide range of outcomes and all three randomized controlled trials failed to meet the primary endpoint. The authors conclude that 'there is no good quality evidence to support a link between migraine and PFO and, that patients and providers should adhere to guidelines-recommended pharmacological, physical, and behavioural therapy for patients with migraine, even if a PFO is identified on echocardiography'.

With respect to other cardiac comorbidities, Jacobs et al. [6] identified in their review only one over other potential findings, i.e. QTc prolongation during a migraine attack in three of 13 children seen in an emergency department [16].

8.4 Stroke

An increased risk for stroke in teenage girls and young women with probable migraine with aura has been noticed, particularly for those who smoke or use oral contraceptives, compared with women who do not have migraines.

In 2007, a study by MacClellan et al. assessed the link between probable migraine with visual aura (PMVA) and probable migraine without visual aura with ischemic stroke among groups of women [17]. Using data from a population-based, case-control study, they studied 386 women aged 15–49 years with first ischemic stroke and 614 age- and ethnicity-matched controls. Based on their responses to a questionnaire on headache symptoms, subjects were classified as having no migraine, probable migraine without visual aura or probable migraine with visual aura(PMVA) according to various factors including headache characteristics and various clinical features. The results showed that young women with PMVA had 1.5 greater odds of ischemic stroke (95 % CI = 1.1–2.0); the risk was highest in those with no history of hypertension, diabetes or myocardial infarction compared to women with no migraine. Women with PMVA who were current cigarette smokers and current users of oral contraceptives had 7.0-fold higher odds of stroke (95 % CI = 1.3–22.8) than did women with PMVA who were non-smokers and not users of oral contraceptives. Women with onset of PMVA within the previous year had 6.9-fold higher adjusted odds of stroke (95 % CI = 2.3–21.2) compared to women with no history of migraine. Their conclusion was that PMVA was associated with an increased risk of stroke, particularly among young women and teenage girls without other medical conditions associated with stroke. Behavioural risk factors, specifically smoking

and oral contraceptive use, markedly increased the risk of PMVA, as did recent onset of PMVA. PMVA may be a risk factor for stroke or these patients may be genetically predisposed for both, with the migraine or the stroke being a comorbidity.

In 2015, Gelfand et al. published the first population-based study on the association between migraine and stroke in children and adolescents [18]. The authors included more than 1.5 million subjects aged 2–17 years. All of them were members of a health care delivery system that provides care to approximately 30 % of the population of northern California. Children and adolescents were classified as having migraine, if they had an ICD-9 code for migraine from any encounter, if migraine was mentioned in a significant health problem list or if pharmacy records showed a prescription of a migraine-specific medication. A stroke had occurred in eight of 88,164 migraineurs and in 80 of 1.3 million children and adolescents without headache. The ischemic stroke incidence rate was 0.9/100,000 person-years in migraineurs and 0.4/100,000 person-years in children and adolescents without headache. This difference was statistically not significant (incidence rate ratio (IR) 2.0, 95 % CI0.8–5.2). Similarly, the hemorrhagic stroke incidence rate (0.5/100,000 person-years in migraineurs and 0.9/100,000 person-years in subjects without headache) did not show a statistically significant difference between migraineurs and subjects without headache (IR 0.6, 95 % CI 0.2–2.0). In contrast, a post hoc analysis of adolescents aged 12–17 years showed an increased risk of ischemic stroke among those with migraine (IR 3.4, 95 % CI 1.2–9.5). Further studies are needed to confirm this finding.

8.5 Epilepsy

In a population-based study, the prevalence of epilepsy was higher in children with headache than in headache-free children epilepsy (OR, 2.02; 95 % CI, 1.04–3.94) [8]. In a clinic-based study of paediatric epilepsy patients, it has been observed that a larger than expected proportion of these patients and their families have a history of migraine. This relationship appeared to be even higher for children who had migraine with aura [19]. Migraine and epilepsy are related with each other in various ways and share aspects of genetics, pathophysiology, semiology and treatment [20]. Winawer and Connors found a shared genetic susceptibility to migraine with aura in many types of nonacquired focal and generalized epilepsies [21]. Furthermore linkage studies in families with rolandic epilepsy and other types of epilepsy showed associations with genes related to familial hemiplegic migraine [19]. The precise mechanisms underlying the association of migraine and epilepsy remain unclear. Several studies have suggested an excessive neocortical hyperexcitability together with similar molecular and genetic substrates [20]. In epilepsy, neocortical hyperexcitability, abnormal hypersynchronous electrical discharges in neuronal cells and subsequent alterations of ion metabolism

lead to recurrent seizures. In migraine, however, cortical spreading depression, rather than hypersynchronous discharges the basis for migraine aura and the trigger for headache [20].

Regarding the differential diagnosis of migraine aura and occipital epilepsy, it was suggested that elementary visual hallucinations cannot be anything else but visual seizures. They were found to be entirely different from migraine visual aura in colour, shape, size, location, movement, duration and development. In distinction, migraine visual aura with or without headache usually starts with predominantly flickering black and white, linear and zigzag patterns in the centre of the visual field, gradually expanding over minutes toward the periphery of the hemifield and often leaving a scotoma [20].

According to the beta version of the third edition of the International Classification of Headache Disorders (ICHD-3 beta) [22], headache related to epileptic seizures may be classified as migraine aura-triggered seizure (ICHD-3 beta 1.4.4), hemicrania epileptica (ICHD-3 beta 7.6.1) and post-ictal headache (ICHD-3 beta 7.6.2) with the latter being by far the most common [20].

Antiepileptic drugs (AEDs) which have been demonstrated to be safe and effective in the treatment of migraine include in particular divalproate and topiramate. The choice of AED in comorbid epilepsy and migraine should be guided by the underlying epilepsy syndrome and should consider a medication with prospective migraine preventive properties. The goals of treatment vary; for migraine the aim is reduction in frequency by at least 50 % and treatment is administered for 4–6 months, whereas for epilepsy the goal is seizure freedom for 2 years. Thus the epilepsy treatment dictates the duration of AED use.

8.6 Obesity

Obesity is an area of growing concern in children and adolescents. Worldwide the incidence of obesity in childhood and adolescence is increasing. In obese children, there is an effect on both headache frequency and disability [6, 8, 23]. Pathophysiologically, serotonin, orexin, adiponectin and leptin have been suggested to have roles in both feeding and migraine [24]. The increased risk of headache and migraine related to obesity needs to be addressed in the overall treatment plan, as it appears that those children who can lower their BMI percentile have a greater improvement than those who don't lose weight [24].

In a prospective study investigating the impact of a weight loss treatment on headache in 135 obese adolescent migraineurs participating in a 12-month programme including dietary education, physical training and behavioural treatment, the authors assessed decreases in weight, body mass index (BMI), waist circumference, headache frequency and intensity, use of acute medications and disability. Both lower baseline BMI and amount of weight loss were associated with better outcomes [25].

8.7 Sleep Disorders

Disturbances in sleep can have both a biological and a behavioural basis. Sleep deprivation is one of the most common triggers of migraine in children and adolescents. This is complicated by the biological changes affecting sleep that occur during puberty, causing adolescents to have delayed sleep onset, which is hormonally controlled, in conflict with many school systems that require these children to wake earlier than is biologically natural.

Headaches may occur during sleep; they may be related to certain sleep stages or they may be noticed on awakening. Nocturnal headaches can be a result of disrupted sleep or may cause sleep disruption. However, headaches wakening a child from sleep may also be red flag and call for further diagnostic workup including magnetic resonance imaging. In addition, there may be specific sleep disturbances in children and adolescents [24]. Children who suffer from headache may have a high rate of sleep difficulties, such as insufficient sleep, co-sleeping with parents, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares and fatigue during the day [24]. Migraine in children and adolescents was related to sleepwalking, bedwetting, pavor nocturnus and restless legs syndrome [24, 26]. Epidemiologic studies on the relation of headache and migraine to sleep disturbances in children and adolescents are lacking.

With respect to treatment education and lifestyle modification, including sleep hygiene has been suggested, and sleep conditions should be screened obligatorily in children and adolescents with migraine in order to improve patient management and to choose the most appropriate treatment [27].

8.8 Learning Disabilities

The term learning disabilities (LD) comprises difficulties in a broad range of academic and functional skills such as listening, speaking, reading, writing, reasoning, mathematics, coordination, spatial adaptation and memorization. These difficulties can occur alone or in varying combinations and can range from mild to severe. The causes of LD are not well understood, and sometimes there is no apparent cause. In some cases LD are related to heredity, problems during pregnancy and birth, head injuries, malnutrition, toxic exposure or behavioural or social factors [28]. By using data from the National Survey of Children's Health, the overall lifetime prevalence of LD in US children in 2003 was calculated to be 9.7 %(95 % CI = 9.4–10.1), meaning that an estimated 6 million US children aged below 18 years had LD at some stage in their life [29]. From experience in a tertiary headache centre, LD are more frequently seen in children with migraine. In an epidemiologic study, LD were more frequently reported in children with frequent or severe headaches (OR, 1.59; 95 % CI = 1.26–2.02) [8]. Although LD are considered to be lifelong disorders, academic skills themselves can be improved with targeted interventions. Practice is a particularly important component in developing competence. Specialized instructions are

designed to make improvements in the weak areas. In addition, adjustments and equipment such as electronic dictionaries or word spellers are intended to accommodate or help compensate for the disabilities. In children with migraine experiencing a significant increase in attack frequency afterschool entry, LD should be considered as an underlying cause, even though evidence from controlled trials is lacking.

8.9 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in children. Eight to twelve percent of children are affected worldwide. The onset is before 7 years of age. ADHD is characterized by a persistent pattern of inattention, hyperactivity and impulsiveness. At least half of children with the disorder will have impairing symptoms in adulthood. Twin, adoption and molecular genetic studies show ADHD to be highly heritable, and other findings have recorded obstetric complications and psychosocial adversity as predisposing risk factors [29]. In an epidemiologic study [8] including subjects aged 4–18 years, the prevalence of attention deficit disorder was significantly higher in individuals with frequent or severe headache (OR, 2.02; 95 % CI = 1.56–2.64). In contrast, other studies found an association between migraine and hyperactivity symptoms, but not with symptoms of inattention. Studies showing an association of childhood migraine with inattention symptoms were questioned because of methodological limitations [24]. In one study, ADHD was more common in patients with tension-type headache than in migraineurs, but this was not confirmed in other studies [6]. With respect to the management of children and adolescents with recurrent headaches, physicians should be aware of symptoms of ADHD, as they might have a negative impact on frequency or severity of comorbid migraine or TTH.

8.10 Gilles de la Tourette Syndrome

Tourette syndrome (TS) is one of the most common childhood genetic movement disorders, with a reported frequency in children as high as 3 %. The condition is characterized by motor and phonic tics that fluctuate in distribution, severity and frequency. TS is associated with attention deficit with or without hyperactivity, obsessive-compulsive traits and other neurobehavioral comorbidities, such as poor impulse control, self-injurious behaviour, anxiety and mood disorders. The frequency of migraine headache in a clinic sample of TS subjects including 62 children and 38 adults was nearly fourfold more than the frequency of migraines reported in the general population [30]. In a prospective questionnaire-based study [31], the incidence of migraine was four times higher, and the incidence of TTH was five times higher in children with TS than in the age-matched general population.

8.11 Depression and Anxiety Disorders

Depression is a common disorder in children and adolescents. A lifetime prevalence of serious depression is found in approximately 5 % of subjects younger than 18 years of age. The prevalence of depression increases with age, especially after the onset of puberty. There is no gender-related difference in children. Onset of puberty, however, is associated with a marked increase in the rate of depression among females, with a female-to-male ratio of 2:1. The prevalence of depression may be higher in children with other psychiatric disorders, such as ADHD or anxiety disorders, and in those with general medical conditions such as diabetes, asthma or cancer. Anxiety disorders comprise generalized anxiety disorder, panic disorder, phobias, obsessive-compulsive disorder, post-traumatic stress disorder and separation anxiety.

The comorbidity of migraine and psychiatric disorders has been investigated frequently and carefully in adults [32]. In contrast, there is far less evidence in children and adolescents [24, 33–35]. In 2008, Amouroux and Rousseau-Salvador [33] reviewed studies on the relation between migraine, anxiety and depression and selected those specifying the diagnostic criteria of migraine and using validated measures for anxiety and depression. Of 11 articles, 10 used a control group matched for age and sex. Only three of the studies used a representative sample of the general population. The studies included do not provide conclusive findings for the comorbidity of migraine, anxiety and depression in children. The majority of the studies with clinical populations show slightly higher scores on at least one of the anxiety or depression scales in the migraine group as compared to the control group. However, in all 11 studies, the average score on the anxiety and depression scales in children with migraine did not reach a pathological level, according to the norms established by the validated scales. Findings point to above-average levels of anxiety or depression, rather than diagnosed psychopathologies. None of the three studies carried out in the general population revealed differences between the anxiety and depression scores in children with migraine as opposed to children in the control group. In recent a review, Gelfand et al. concluded that the majority of children and adolescents with migraine do not have a comorbid psychiatric disorder and they point out that depression was associated with chronic migraine in one study [35].

Longitudinal studies suggest that psychiatric disorders in children and adolescents have an impact on pre-existing primary headaches and increase the risk of subsequent development of recurrent headache. In a clinic-based follow-up study, Guidetti et al. [36] assessed the relation between migraine, tension-type headache and various psychiatric disorders including anxiety disorders, sleep disorders, adjustment disorder, elimination disorders, eating disorders, mood disorders and school disorders. Generalized anxiety disorder was the most frequent psychiatric diagnosis, and anxiety disorder at baseline was related to enduring headache and migraine. In an epidemiologic study on ‘functionally impairing headache’, Pine et al. [37] found headache to be twice as common in depressed adolescents than in non-depressed adolescents. Major depression in adolescents, without current or past

headache, prospectively predicted the new onset of headaches in young adulthood. Among adolescents without a history of chronic impairing headache, those with current major depression faced a nearly tenfold increased risk of developing such headaches at some time during the next 7 years. Similarly, results from the Young HUNT follow-up study suggest that symptoms of anxiety and depression in early adolescence may be associated with subsequent occurrence of recurrent headache and the authors suggest that early identification of depression and anxiety in young headache patients may lead to improved headache management [38].

Studying the relationship between migraine and suicidal ideation in a non-referred sample of adolescents, Wang et al. [39] found that suicidal ideation was reported more frequently by subjects with migraine compared to non-migraine subjects (16.1 % vs 6.2 %; OR 2.9; 95 % CI = 2.3–3.6; $p = 0.001$). After controlling for depression score and sociodemographic characteristics, the association remained for migraine with aura (adjusted OR 1.79; 95 % CI = 1.07–2.99; $p = 0.025$) and high headache frequency (>7 days/month; adjusted OR 1.69; 95 % CI = 1.12–2.56; $p = 0.013$) but not for migraine without aura or probable migraine.

8.12 Conclusions

Recurrent headache and migraine in childhood and adolescence may be associated with and influenced by various comorbidities. Evidence is still limited. Statistically significant associations between migraine and other disorders were found more often in clinic-based than in population-based studies. Considering possible comorbid disorders in the management of headache and migraine is a prerequisite for establishing effective treatment strategies.

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